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申請實體審查：無 申請專利範圍項數：94 項 圖式數：20 共 729 頁

(54)名稱

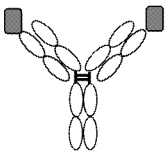
抗 PD-1 抗體減弱之 IL-2 免疫結合物及其用途

(57)摘要

本發明揭示免疫特異性結合至人類計劃性細胞死亡蛋白-1 (hPD-1)之經修飾之人類介白素-2 (hIL-2)蛋白質、人類抗體分子或其抗原結合片段，及包含其之免疫結合物。

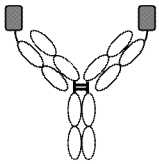
Disclosed herein are modified human interleukin-2 (hIL-2) proteins, human antibody molecules, or antigen-binding fragments thereof, that immunospecifically bind to human programmed cell death protein-1 (hPD-1), and immunoconjugates comprising the same.

指定代表圖：



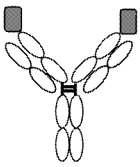
hIL-2 N端輕鏈df

【圖1A】



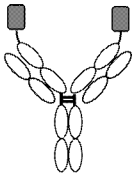
hIL-2 N端輕鏈L6融合物

【圖1B】



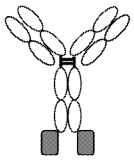
hIL-2 N端重鏈df

【圖1C】



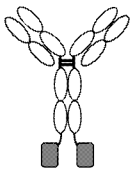
hIL-2 N端重鏈L6融合物

【圖1D】



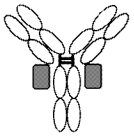
hIL-2 C端重鏈df

【圖1E】



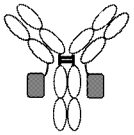
hIL-2 C端重鏈L6融合物

【圖1F】



hIL-2 C端輕鏈df

【圖1G】



hIL-2 C端輕鏈L6融合物

【圖1H】



hIL-2

L6

202415442

【發明摘要】

【中文發明名稱】

抗PD-1抗體減弱之IL-2免疫結合物及其用途

【英文發明名稱】

ANTI-PD-1 ANTIBODY-ATTENUATED IL-2 IMMUNOCONJUGATES AND USES THEREOF

【中文】

本發明揭示免疫特異性結合至人類計劃性細胞死亡蛋白-1 (hPD-1)之經修飾之人類介白素-2 (hIL-2)蛋白質、人類抗體分子或其抗原結合片段，及包含其之免疫結合物。

【英文】

Disclosed herein are modified human interleukin-2 (hIL-2) proteins, human antibody molecules, or antigen-binding fragments thereof, that immunospecifically bind to human programmed cell death protein-1 (hPD-1), and immunoconjugates comprising the same.

【指定代表圖】

圖1A至圖1H

【代表圖之符號簡單說明】

無

【發明說明書】

【中文發明名稱】

抗PD-1抗體減弱之IL-2免疫結合物及其用途

【英文發明名稱】

ANTI-PD-1 ANTIBODY-ATTENUATED IL-2 IMMUNOCONJUGATES AND USES THEREOF

【技術領域】

【0001】 本文揭示免疫特異性結合至人類計劃性細胞死亡蛋白-1 (human programmed cell death protein-1；hPD-1)之經修飾之人類介白素-2 (human interleukin-2；hIL-2)蛋白質、人類抗體分子或其抗原結合片段，及包含該等經修飾之人類介白素-2 (hIL-2)蛋白質、人類抗體分子或其抗原結合片段之免疫結合物。

【先前技術】

【0002】 人類IL-2 (hIL-2)為一種1型四α-螺旋束、醣基化細胞介素，其由CD4+ T細胞及CD8+ T細胞產生。自分泌及旁分泌IL-2信號傳導經由包含IL-2Rα (CD25)、IL-2Rβ (CD122)及IL-2Rγ (CD132)之高親和力三聚體受體複合物，或包含IL-2Rβ (CD122)及IL-2Rγ (CD132)之中等親和力二聚體受體複合物的接合而發生。IL-2具有雙重相對及多效性作用，因為其可刺激T細胞增殖以產生T細胞效應子、T細胞記憶體及經活化之NK細胞，且亦可刺激抑制性調節T細胞以用於維持免疫穩態。低劑量IL-2主要刺激調節T細胞以及一些T效應子及NK細胞，而高劑量IL-2廣泛刺激細胞毒性T細胞、T效應子及NK細胞以及調節T細胞。然而，IL-2在治療自體免疫疾病及作為癌症免疫療法中之使用受到與IL-2之投與相關之脫靶

效應及毒性的限制。

【發明內容】

【0003】 本文揭示經修飾之人類介白素-2 (hIL-2)蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代，其中相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質對高親和力hIL-2受體及中等親和力hIL-2受體兩者展現降低之效力。

【0004】 本文亦揭示經修飾之人類介白素-2 (hIL-2)蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代及在胺基酸位置38處之R38E取代。

【0005】 本文亦揭示免疫特異性結合至人類計劃性細胞死亡蛋白-1 (hPD-1)之人類抗體分子或其抗原結合片段，其中人類抗體分子或其抗原結合片段包含：

a) 包含SEQ ID NO: 418之胺基酸序列的重鏈互補決定區1 (heavy chain complementarity determining region 1；CDR1)、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3；

b) 包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈CDR1、包含

SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3；

c) 包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3；或

d) 包含SEQ ID NO: 406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序列的輕鏈CDR3。

【0006】 本文亦揭示免疫結合物，該等免疫結合物包含：

(a) 經修飾之hIL-2蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代；及

(b) 免疫特異性結合至hPD-1之人類抗體分子或其抗原結合片段，其中人類抗體分子或其抗原結合片段包含：

(i) 包含SEQ ID NO: 418之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3；

(ii) 包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3；

(iii) 包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3；或

(iv) 包含SEQ ID NO: 406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序列的輕鏈CDR3。

【0007】 亦揭示包含本文中所揭示之經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段，或免疫結合物中之任一者的醫藥組合物。

【0008】 本文亦揭示聚核苷酸，其包含編碼本文中所揭示之經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段，或免疫結合物中之任一者的核酸序列，以及包含該等聚核苷酸之載體及包含該等載體之經轉型之細胞。

【0009】 本文揭示治療個體中之疾病或病症的方法，該方法包含向個體投與治療有效量之本文中所揭示之免疫結合物或醫藥組合物中之任一

者，由此治療該疾病或病症。

【0010】 亦揭示本文中所揭示之免疫結合物或醫藥組合物中之任一者在製備用於治療疾病之藥物中之用途，及本文中所揭示之免疫結合物或醫藥組合物中之任一者用於治療疾病或病症之用途。

【圖式簡單說明】

【0011】 當結合附圖閱讀時，進一步理解發明內容以及以下實施方式。出於說明所揭示之經修飾之hIL-2蛋白質、抗hPD-1抗體或其抗原結合片段及免疫結合物之目的，圖式中展示經修飾之hIL-2蛋白質、抗hPD-1抗體或其抗原結合片段及免疫結合物之例示性實施例；然而，經修飾之hIL-2蛋白質、抗hPD-1抗體或其抗原結合片段及免疫結合物不限於所揭示之特定實施例。在圖式中：

【0012】 **圖1A**、**圖1B**、**圖1C**、**圖1D**、**圖1E**、**圖1F**、**圖1G**及**圖1H**繪示經本文實例1中所描述之例示性抗體-hIL-2免疫結合物。未減弱之人類IL-2細胞介素(灰色矩形)直接(df)或經由L6連接子(L6)融合至抗體之兩個重鏈或兩個κ輕鏈之N端或C端。

【0013】 **圖2A**、**圖2B**、**圖2C**、**圖2D**、**圖2E**、**圖2F**、**圖2G**及**圖2H**繪示具有hCD25 (1-164)胞外域之例示性抗體-hIL-2免疫結合物，該胞外域經設計以干擾免疫結合物之hIL-2結合至人類IL-2Rα。對於N端變異體，人類CD25/IL-2Rα胞外域(黑色三角形)係經由L20連接子(淺灰色線)融合至未減弱之hIL-2細胞介素(灰色矩形)。隨後，未減弱之hIL-2細胞介素直接融合(df)至抗體或藉由L6連接子融合至抗體。對於C端變異體，hCD25/IL-2Rα胞外域部分直接融合(df)至抗體或使用L6連接子融合至抗體，隨後使用L20連接子融合至未減弱之hIL-2細胞介素。

【0014】 **圖3**繪示含有CD25/IL-2Rα胞外域部分之例示性1H3-hIgG1-L6-hIL-2免疫結合物。hCD25/IL-2Rα胞外域部分係經由L6連接子融合至各重鏈之C端處的1H3-hIgG1-L6-hIL-2，隨後經由L20連接子融合至hIL-2細胞介素部分(減弱之hIL-2)，該hIL-2細胞介素部分含有經預測調節與經實例2中所描述之CD122/IL-2Rβ之結合的取代。

【0015】 **圖4A**、**圖4B**、**圖4C**及**圖4D**展示在暴露於抗hPD-1抗體之前，在存在飽和濃度之抗hPD-1 #1-mIgG2b-N297A及抗hPD-1 #2-mIgG2b-N297A (10 μM)之情況下分析抗hPD-1抗體2H7-hIgG4、C51E6-5-hIgG4及A2-hIgG4與Jurkat細胞上之人類PD-1受體之結合之實驗的結果。

【0016】 **圖5**繪示用L6連接子(L6) (左側)或直接融合物(df) (右側)之例示性抗hPD-1減弱之hIL-2免疫結合物。在Fc域中具有或不具有L235E (LE)或L235A/G237A (LAGA)修飾的情況下，包含hIgG4或hIgG1 Fc域之抗hPD-1抗體在抗體重鏈之C端融合至減弱之hIL-2細胞介素。在hIL-2細胞介素中引入各種取代以用於減弱效力。

【0017】 **圖6A**及**圖6B**展示競爭分析法之結果，其證實在存在飽和濃度之抗hPD-1減弱之hIL-2免疫結合物(280 nM)之情況下，抗hPD-1 #1-mIgG2b-N297A (**圖6A**)或抗hPD-1 #2-mIgG2b-N297A (**圖6B**)結合至Jurkat細胞上之抗hPD-1受體。

【0018】 **圖7**展示競爭分析法之結果，其證實使用PD-1/PD-L1阻斷生物分析法(Blockade Bioassay)，抗hPD-1減弱之hIL-2免疫結合物2H7-hIgG4-df-hIL-2 (D20A/R38E)、C51E6-5-L6-hIgG4-hIL-2 (D20A/R38E)及A2-hIgG4-df-hIL-2 (D20A/R38E)並不抑制人類PD-L1與人類PD-1受體之

結合。

【0019】 **圖8**展示實驗之結果，該實驗分析投與媒劑、抗PD-1抗體替代物(抗mPD-1 RMP1-14 mIgG2b-N297A及抗mPD-1 RMP1-30 mIgG2b-N297A)，及抗PD-1減弱之hIL-2免疫結合物替代物(抗mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)或抗mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R))對經實例18中所描述之C57BL/6小鼠中已建立之皮下MC38同基因型腫瘤之生長的作用。在第1天開始，每週兩次以5 mg/kg腹膜內給藥測試藥劑持續4週。圖上之點表示每組平均10隻小鼠之平均腫瘤體積。

【0020】 **圖9A**、**圖9B**及**圖9C**繪示經實施以測定抗hPD-1減弱之hIL-2免疫結合物替代物抗mPD-1 RMP1-30 mIgG2ba-N297A-hIL-2 (F42K/Y45R/V69R)在MC38鼠類結腸腺癌模型中之功效之研究的結果。**圖9A**描繪在第一劑量之測試藥劑(以5 mg/kg在第1天、第4天及第8天之3次劑量)後的8天內，每3至4天所量測之平均皮下腫瘤體積(mm^3)。腫瘤生長曲線表示每組平均15隻動物。**圖9B**概述在第9天藉由流式細胞分析技術(flow cytometry)對腫瘤進行免疫表現型分型之結果，展示不同$CD8^+$ T細胞亞群之比例作為總$CD8^+$ T細胞平均絕對計數之分率。**圖9C**繪示在第9天之免疫表現型分型結果，其證實在暴露於免疫結合物替代物後，$CD8^+$效應記憶T細胞顯著擴增且腫瘤中之調節T細胞(個細胞/微升)有減少之趨勢。

【0021】 **圖10**展示來自分析暴露於抗hPD-1減弱之hIL-2免疫結合物之NOD-*Prkdc*^{em26Cd52}*IL-2rg*^{em26Cd22}/NjuCrl (NCG)小鼠中的移植物抗宿主病(Graft vs Host Disease)加速之實驗的結果，如藉由NCG-PBMC模型中

顯著之體重降低所證實。

【0022】 **圖11A**及**圖11B**展示分析NCG-PBMC模型中經2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)處理之NOD-*Prkdc*^{em26Cd52}*IL-2rg*^{em26Cd22}/NjuCrl (NCG)小鼠的血液CD8$^+$效應記憶T細胞(**圖11A**)及CD4$^+$效應記憶T細胞(**圖11B**)之劑量依賴型擴增(細胞/毫升)之實驗的結果。

【0023】 **圖12**展示NCG-PBMC模型中經2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 處理之NOD-*Prkdc*^{em26Cd52}*IL-2rg*^{em26Cd22}/NjuCrl (NCG)小鼠之血液調節T細胞以細胞/毫升計之減少。

【0024】 **圖13A**及**圖13B**展示在暴露之前，在存在飽和濃度之抗hPD-1 #1-mIgG2b-N297A及抗hPD-1 #2-mIgG2b-N297A (10 μM)之情況下，H7-632-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) (指定為「H7-767」) (**圖13B**)持續結合至Jurkat細胞上之人類PD-1受體。

【0025】 **圖14A**及**圖14B**為展示如藉由表面電漿子共振(surface plasmon resonance；SPR)所評估，由固定至CM5感測器晶片之H7-767所捕獲的重組人類PD-1之結合，隨後(**圖14A**) H7-767、KEYTRUDA®或OPDIVO®或(**圖14B**) PD-L1或PD-L2之結合的圖。

【0026】 **圖15**證實，使用hPD-1/hPD-L1阻斷生物分析法，H7-632-hIgG1-LAGA及H7-767並不抑制人類PD-L1與人類PD-1受體之結合。

【0027】 **圖16A**、**圖16B**、**圖16C**及**圖16D**為展示如藉由流式細胞分析技術所評定，在暴露於抗hPD-1減弱之hIL-2免疫結合物之前，在存在飽和濃度之抗hPD-1 #1-mIgG2b-N297A及抗hPD-1 #2-mIgG2b-N297A (10 μM)之情況下，抗hPD-1減弱之hIL-2免疫結合物2H7-hIgG4-df-hIL-2 (D20A/R38E)、C51E6-5-hIgG4-df-hIL-2 (D20A/R38E)及A2-hIgG4-df-

hIL-2 (D20A/R38E)與Jurkat細胞上之人類PD-1受體之結合的圖。

【0028】 **圖17**為展示如藉由流式細胞分析技術所評定，2H7-hIgG4-df-hIL-2 (D20A/R38E) 、 C51E6-5-hIgG4-df-hIL-2 (D20A/R38E) 、 A2-hIgG4-df-hIL-2 (D20A/R38E)及不相關之抗體對照1H3-hIgG4-df-hIL-2 (D20A/R38E)與以重組方式表現石蟹獼猴(cynomolgus) PD-1之HEK-293T細胞之結合的圖。

【0029】 **圖18A**、**圖18B**、**圖18C**及**圖18D**展示在存在抗hPD-1 #1或抗hPD-1 #2之情況下，抗hPD-1減弱之hIL-2免疫結合物2H7-hIgG4-df-hIL-2 (D20A/R38E) 、 C51E6-5-hIgG4-df-hIL-2 (D20A/R38E) 及 A2-hIgG4-df-hIL-2 (D20A/R38E)之拮抗劑活性。**圖18A**及**圖18B**展示在存在固定濃度之抗hPD-1減弱之hIL-2免疫結合物的情況下來自抗hPD-1 #1或抗hPD-1 #2之滴定的結果。**圖18C**及**圖18D**展示來自相反實驗之結果，該實驗中抗hPD-1減弱之hIL-2免疫結合物係藉由固定濃度之100 nM抗hPD-1 #1 (**圖18C**)或100 nM抗hPD-1 #2 (**圖18D**)滴定。

【0030】 **圖19**展示投與包括抗小鼠PD-1/減弱之IL-2免疫結合物替代物的各種測試藥劑對C57BL/6小鼠中已建立之皮下MC38同基因型腫瘤之生長的作用。各生長曲線表示每個治療組十隻小鼠之平均腫瘤體積。

【0031】 **圖20**展示與來自**圖19**中所繪示之MC38原發性腫瘤研究的小鼠(先前用抗mPD-1-hIL-2 F42K/Y45R/V69R給藥且證實已建立之原發性腫瘤的完全長期消退)相比，MC38腫瘤細胞在腫瘤未經治療之小鼠中生長之能力。將來自兩個群組(每組10隻小鼠)之動物在與原發性腫瘤之位置為對側的左側腹部皮下植入5×10^5個MC38腫瘤細胞。先前暴露於替代藥劑抗mPD-1-hIL-2 F42K/Y45R/V69R之小鼠由於其已產生持久免疫性而

不展現腫瘤生長，而相應未經治療之小鼠對照組展現腫瘤在小鼠腹部中之典型生長。

【實施方式】

相關申請案之交互參照

【0032】 本申請案主張於2022年6月16日申請之美國臨時申請案第63/352,842號、於2023年1月26日申請之美國臨時申請案第63/481,630號及於2023年5月17日申請之美國臨時申請案第63/502,746號之優先權，其各者之揭示內容以全文引用之方式併入本文中。

序列表

【0033】 本申請案含有序列表，該序列表特此以XML格式以電子方式提交且以全文引用之方式併入本文中。該XML複本創建於2023年6月5日，命名為102085.021703_Sequence Listing.xml且大小為696,000位元組。

【0034】 所揭示之經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物可藉由參考以下結合附圖進行之實施方式而更容易地理解，該等附圖形成本發明之一部分。應理解，所揭示之經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物不限於本文中所描述及/或展示之經特定修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物，且本文中所使用之術語僅出於作為實例描述特定實施例之目的且不意欲限制所主張之經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物。

【0035】 除非另外特定說明，否則任何關於可能機制或作用模式或改良原因之描述僅意謂為說明性的，且所揭示之經修飾之hIL-2蛋白質、

人類抗體分子或其抗原結合片段及免疫結合物不受任何此類建議機制或作用模式或改良原因之正確性或不正確性限制。

【0036】 在本文通篇中，描述係指經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物，以及使用經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物之方法。在本發明描述或主張與經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物相關之特徵或實施例的情況下，此類特徵或實施例同樣適用於使用經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物之方法。同樣地，在本發明描述或主張與使用經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物之方法相關的特徵或實施例的情況下，此類特徵或實施例同樣適用於經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物。

【0037】 在本文中敍述或確立數值範圍之情況下，該範圍包括其端點及該範圍內之所有個別整數及分數，且亦包括其中由此等端點以及內部整數及分數之所有各種可能組合形成的較窄範圍中之各者，以形成在所陳述範圍內之值的較大群組之子群組，其程度如同明確敍述此等較窄範圍中之各者一般。在數值範圍在本文中陳述為大於所陳述值的情況下，該範圍仍然有限且在其上端上由在本文揭示內容之上下文內可操作的值限定。在數值範圍在本文中陳述為小於所陳述值的情況下，該範圍在其下端上仍然由非零值限定。不意欲經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物之範疇受限於在定義範圍時所敍述之特定值。所有範圍均為包括性及可組合的。

【0038】 當藉由在前面使用「約」，以近似值表示值時，應理解特

定值形成另一實施例。除非上下文另外明確指示，否則提及特定數值至少包括該特定值。術語「約」在用於提及數值範圍、截止值或特定值時用於指示所敍述之值可自所列舉之值改變至多高達10%。因此，術語「約」用於涵蓋給定值之± 10%或更小之差異、± 5%或更小之差異、± 1%或更小之差異、± 0.5%或更小之差異或± 0.1%或更小之差異。

【0039】 應瞭解，在單獨實施例之上下文中，本文中出於清楚起見而描述的所揭示之經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物之某些特徵亦可以組合形式提供於單一實施例中。反之，出於簡潔起見而在單一實施例之上下文中描述的所揭示之經修飾之hIL-2蛋白質、人類抗體分子或其抗原結合片段及免疫結合物之各種特徵亦可分別或以任何子組合形式提供。

【0040】 如本文中所使用，單數形式「一(a)」、「一(an)」及「該(the)」包括複數形式。

【0041】 在本說明書及申請專利範圍通篇中使用與本說明書之態樣相關的各種術語。除非另外指示，否則此類術語將提供其在此項技術中之普通含義。其他特別定義之術語應以符合本文中所提供之定義的方式進行解釋。

【0042】 術語「包含」意欲包括由術語「基本上由……組成」及「由……組成」所涵蓋之實例；類似地，術語「基本上由……組成」意欲包括由術語「由……組成」所涵蓋之實例。

【0043】 術語「抗體分子」意謂具有廣泛意義且包括全長免疫球蛋白分子及其抗原結合片段。

【0044】 免疫球蛋白可分配成五個主要類別，即IgA、IgD、IgE、

IgG及IgM，其視重鏈恆定域胺基酸序列而定。IgA及IgG進一步細分類為同型IgA1、IgA2、IgG1、IgG2、IgG3及IgG4。任何脊椎動物物種之抗體輕鏈可基於其恆定域之胺基酸序列分配為兩種明顯不同類型(亦即κ (kappa)及λ (lambda))之一。

【0045】「抗原結合片段」係指免疫球蛋白分子之一部分，其保留親本全長抗體(亦即「其抗原結合片段」)之抗原結合特性。例示性抗原結合片段可具有：重鏈互補決定區(CDR) 1、2及/或3；輕鏈CDR 1、2及/或3；重鏈可變區(VH)；輕鏈可變區(VL)；及其組合。抗原結合片段包括：Fab片段；由VL、VH、恆定輕鏈(CL)及恆定重鏈1 (CH1)域組成之單價片段；$F(ab)_2$片段；包含由鉸鏈區處之二硫橋鍵連接之兩個Fab片段的二價片段；由VH及CH1域組成之Fd片段；由抗體之單臂的VL及VH域組成之Fv片段；及單域抗體(dAb)片段(Ward等人, Nature 341:544-546, 1989)，其係由VH域或VL域組成。VH及VL域可經由合成連接子工程改造並連接在一起以形成各種類型之單鏈抗體設計，其中VH/VL域在分子內成對，或在VH及VL域由單獨單鏈抗體構築體表現時的情況下在分子間成對，以形成單價抗原結合部位，諸如描述於例如國際專利公開案第WO1998/44001號、第WO1988/01649號、第WO1994/13804號及第WO1992/01047號中之單鏈Fv (scFv)或雙功能抗體。此等抗體片段係使用熟習此項技術者熟知之技術獲得，且以與全長抗體相同之方式來篩選供使用之片段。

【0046】片語「免疫特異性結合」係指所揭示之抗體分子優先與其標靶(就抗hPD-1抗體分子而言為hPD-1)結合而不在含有分子之混合群體的樣品中優先結合其他分子的能力。免疫特異性結合hPD-1之抗體分子實

質上不含具有不同抗原特異性之其他抗體(例如，抗hPD-1抗體實質上不含特異性地結合除hPD-1以外之抗原的抗體)。然而，免疫特異性結合hPD-1之抗體分子可與其他抗原，諸如hPD-1之異種同源物(包括長尾獼猴(*Macaca fascicularis*) (石蟹獼猴(cynomolgus monkey)) PD-1)具有交叉反應性。本文中所揭示之抗體分子能夠免疫特異性結合天然產生之hPD-1及在哺乳動物或原核細胞中以重組方式產生之PD-1兩者。

【0047】 抗體可變區係由間雜有三個「抗原結合部位」之四個「構架」區組成。使用各種術語定義抗原結合部位：(i)互補決定區(CDR)，三種在VH中(HCDR1、HCDR2、HCDR3)，三種在VL中(LCDR1、LCDR2、LCDR3)係基於序列可變性(Wu及Kabat J Exp Med 132:211-50, 1970；Kabat等人, Sequences of Proteins of Immunological Interest,第5版Public Health Service, National Institutes of Health, Bethesda, Md., 1991)；及(ii)「高變區」(「HVR」或「HV」)，三種在VH中(H1、H2、H3)及三種在VL中(L1、L2、L3)係指抗體可變域之區域，該等抗體可變域在如藉由Chothia及Lesk (Chothia及Lesk Mol Biol 196:901-17, 1987)所定義之結構上為高變的。CDR之AbM定義亦廣泛使用；其為Kabat與Chothia編號方案之間的折中方案，且之所以如此命名係因為其係由Oxford Molecular之AbM抗體模型化軟體(Rees, A.R., Searle, S.M.J., Henry, A.H.及Pedersen, J.T. (1996) In Sternberg M.J.E. (編), Protein Structure Prediction. Oxford University Press, Oxford, 141-172)使用。其他術語包括「IMGT-CDR」(Lefranc等人, Dev Comparat Immunol 27:55-77, 2003)及「特異性決定殘基利用率(Specificity Determining Residue Usage)」(SDRU) (Almagro Mol Recognit 17:132-43, 2004)。國際免疫遺

傳學(International ImMunoGeneTics，IMGT)資料庫(http://www_imgt_org)提供抗原結合部位之標準化編號及定義。CDR、HV與IMGT描述之間的對應關係描述於Lefranc等人，Dev Comparat Immunol 27:55-77, 2003中。

【0048】「構架」或「構架序列」係除了定義為抗原結合部位之可變區序列以外的其餘可變區序列。由於抗原結合部位可由經上文所描述之各種術語定義，因此構架之確切胺基酸序列視如何定義抗原結合部位而定。

【0049】「人類抗體」、「完全人類抗體」及類似術語係指具有重鏈及輕鏈可變區之抗體，其中構架及抗原結合部位兩者均衍生自人類來源之序列。若抗體含有恆定區，則恆定區亦衍生自人類來源之序列。若抗體之可變區獲自使用人類生殖系免疫球蛋白或經重排之免疫球蛋白基因的系統，則人類抗體包含「衍生自」人類來源之序列的重鏈及/或輕鏈可變區。此類系統包括在噬菌體上呈現之人類免疫球蛋白基因庫，及攜帶經本文所描述之人類免疫球蛋白基因座的基因轉殖之非人類動物，諸如小鼠或雞。當與人類生殖系或經重排之免疫球蛋白序列相比時，由於例如天然存在之體細胞突變或可變域(構架及抗原結合部位)或恆定域中之取代的有意引入，「人類抗體」可含有胺基酸差異。通常，「人類抗體」在胺基酸序列上與由人類生殖系或經重排之免疫球蛋白基因編碼之胺基酸序列至少約80%、81%、82%、83%、84%、85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或100%一致。在一些情況下，「人類抗體」可含有衍生自人類構架序列分析之共識構架序列，例如經Knappik等人, J Mol Biol 296:57-86, 2000所描述，或併入

至在噬菌體上呈現之人類免疫球蛋白基因庫中之合成HCDR3，經例如Shi等人, J Mol Biol 397:385-96, 2010及國際專利公開案第WO2009/085462號所描述。其中抗原結合部位衍生自非人類物種之抗體不包括於「人類抗體」之定義中。

【0050】 人類抗體雖然衍生自人類免疫球蛋白序列，但可使用諸如噬菌體呈現併入合成CDR及/或合成構架之系統產生，或可經歷活體外誘變以在可變區或恆定區或兩者中改良抗體特性，從而在活體內產生不天然存在於人類抗體生殖系譜系內之抗體。

【0051】 「重組抗體」包括藉由重組方式製備、表現、產生或分離之所有抗體，諸如：自對於人類免疫球蛋白基因而言為轉基因或轉染色體的動物(例如小鼠)或自其製備之融合瘤(下文進一步描述)分離之抗體；自經轉型以表現抗體之宿主細胞分離之抗體；自重組、組合抗體庫分離之抗體；及藉由涉及人類免疫球蛋白基因序列與其他DNA序列之剪接的任何其他方式製備、表現、產生或分離之抗體，或使用Fab臂交換在活體外產生之抗體。

【0052】 「單株抗體」係指單一分子組成之抗體分子之群體。單株抗體組合物對特定抗原決定基顯示單一結合特異性及親和力，或在雙特異性單株抗體之情況下，對兩種不同抗原決定基顯示雙重結合特異性。因此，除可能熟知之改變，諸如自抗體重鏈移除C端離胺酸以外，單株抗體係指在各重鏈及各輕鏈中具有單一胺基酸組成之抗體群體。單株抗體在抗體群體內可具有異質醣基化。單株抗體可為單特異性或多特異性，或單價、二價或多價的。雙特異性抗體包括於術語單株抗體中。

【0053】 「抗原決定基」係指抗體特異性結合之抗原之一部分。抗

原決定基通常係由諸如胺基酸或多醣側鏈之部分的化學活性(諸如極性、非極性或疏水性)表面基團組成，且可具有特定三維結構特徵，以及荷質比特徵。抗原決定基可包含形成構形空間單元之相鄰及/或不相鄰胺基酸。對於不相鄰抗原決定基，來自抗原之線性序列之不同部分的胺基酸經由蛋白質分子之摺疊而在3維空間中緊密臨近。

【0054】「變異體」係指與參考多肽或參考聚核苷酸相差一或多種修飾(例如取代、插入或缺失)之多肽或聚核苷酸。如本文中所使用，術語「突變」意謂對多肽或聚核苷酸進行之一或多種有意取代。

【0055】「治療(Treat)」、「治療(treatment)」及類似術語係指治療性治療及預防性或防治性措施兩者，且包括降低症狀之嚴重程度及/或出現率，消除症狀及/或症狀之潛在病因，降低症狀及/或其潛在病因之出現率或可能性，及改善或修復由疾病或病症直接或間接引起之損傷。「治療(Treatment)」亦包括與在未接受治療之個體的預計存活期相比延長之存活期。所治療之個體包括患有疾病或病症者之個體以及易於患疾病或病症之個體或需要預防體內疾病或病症之個體。

【0056】如本文中所使用，「向個體投與」及類似術語指示將所揭示之經修飾之hIL-2蛋白質、免疫結合物或醫藥組合物注射至個體中，從而使得個體身體之靶細胞、組織或片段與所揭示之經修飾之hIL-2蛋白質或包含該等經修飾之hIL-2蛋白質的免疫結合物接觸的程序。

【0057】片語「治療有效量」係指可有效達成特定生物或治療結果(諸如(但不限於)本文中所揭示、描述或例示之生物或治療結果)的經本文所描述之經修飾之hIL-2蛋白質、免疫結合物或醫藥組合物的量。治療有效量可根據諸如個體之疾病病狀、年齡、性別及體重之因素，及經修飾之

hIL-2蛋白質、免疫結合物或醫藥組合物在個體中引起所需反應之能力而變化。治療有效量之例示性指標包括例如患者健康改善、疾病症狀減輕、疾病症狀之進展停滯或減緩，及/或疾病症狀不存在。

【0058】 如本文中所使用，術語「個體」欲意謂任何動物，尤其哺乳動物。因此，方法適用於人類及非人類動物，但最佳用於人類。「個體」及「患者」在本文中可互換地使用。

【0059】 免疫結合物及融合蛋白在本文中可互換地使用。

經修飾之人類介白素-2 (hIL-2)蛋白質

【0060】 本文揭示經修飾之hIL-2蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代，其中相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質對高親和力hIL-2受體及中等親和力hIL-2受體兩者展現降低之效力。所揭示之經修飾之hIL-2蛋白質在本文中亦稱為「減弱」之hIL-2。

【0061】 在胺基酸位置20處之適合之取代包括例如D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代中之任一者。

【0062】 在胺基酸位置38處之適合之取代包括例如R38E、R38N、R38G、R38H、R38I、R38L、R38M、R38F、R38P、R38S、R38T、R38W、R38Y、R38V、R38A、R38Q、R38D或R38K取代中之任一者。

【0063】 在一些實施例中，D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代中之任一者可與R38E取代組合。

【0064】 經修飾之hIL-2蛋白質可包含SEQ ID NO: 134至150、

307、344、607至611、614、617或620中之任一者的胺基酸序列。經修飾之hIL-2蛋白質可包含SEQ ID NO: 134至150、307、344、608、611、614或620中之任一者的胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 134之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 135之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 136之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 137之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 138之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 139之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 140之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 141之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 142之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 143之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 144之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 145之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 146之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 147之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 148之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 149之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 150之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 307之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 344之胺基酸序列。在一些實施例中，經修

飾之hIL-2蛋白質包含SEQ ID NO: 607之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 608之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 609之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 610之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 611之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 614之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 617之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 620之胺基酸序列。胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質可進一步包含T3A取代及/或C125A取代。在一些實施例中，胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含T3A取代。在一些實施例中，胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含C125A取代。在一些實施例中，胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含T3A取代及C125A取代。

【0065】 經修飾之hIL-2蛋白質可包含D20A取代及R38E取代。

【0066】 經本文所描述，術語「降低之效力」及相關術語(諸如「效力降低」或IL-2活性之「減弱」)係指在IL-2依賴性分析法中，藉由相對於未經修飾之hIL-2之EC_{50}值增加的EC_{50}值所測定，經修飾之hIL-2之效力降低。經本文所描述，經修飾之hIL-2之效力降低將針對高親和力及中等親和力IL-2受體兩者。用於確定效力之IL-2依賴性分析法可為經工程改造

之人類紅白血病TF1 (TF1+IL-2Rβ)或經本文所描述之人類自然殺手NK-92細胞增殖分析法。在一個實施例中，用於確定效力之IL-2依賴性分析法為經工程改造之人類紅白血病TF1 (TF1+IL-2Rβ)細胞增殖分析法。在另一實施例中，用於測定效力之IL-2依賴性分析法為人類自然殺手NK-92細胞增殖分析法。用於測定效力之其他IL-2依賴性分析法亦可為經本文所描述之TF1+IL-2Rβ或人類自然殺手NK-92 pSTAT5分析法。未經修飾之hIL-2可為原核生物表現之hIL-2，諸如Proleukin® (其具有除C125S取代以外用於移除未結合之半胱胺酸的天然人類IL-2胺基酸序列，且其在殘基T3上不攜帶正常人類碳水化合物表現)，或未經修飾之hIL-2可為具有SEQ ID NO: 345之胺基酸序列或具有C125S取代之SEQ ID NO: 345之胺基酸序列的hIL-2，其在哺乳動物細胞株(諸如CHO或HEK細胞株)中表現。

【0067】 經修飾之hIL-2蛋白質可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之取代。適合之取代包括例如T3A。在一些實施例中，經修飾之hIL-2蛋白質包含T3A取代、D20A取代及R38E取代。在一些態樣中，經修飾之hIL-2蛋白質包含SEQ ID NO: 216之胺基酸序列。

【0068】 或者，經修飾之hIL-2蛋白質可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列的胺基酸位置3之缺失。在一些實施例中，經修飾之hIL-2蛋白質包含胺基酸1至3之缺失、D20A取代及R38E取代。在一些態樣中，經修飾之hIL-2蛋白質包含SEQ ID NO: 218之胺基酸序列。

【0069】 經修飾之hIL-2蛋白質可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。在

胺基酸位置125處之取代可為C125A。在一些實施例中，經修飾之hIL-2蛋白質包含D20A取代、R38E取代及C125A取代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 215之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含T3A取代、D20A取代、R38E取代及C125A取代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 217之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含胺基酸1至3之缺失、D20A取代、R38E取代及C125A取代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 219之胺基酸序列。

【0070】 相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現大於約10,000倍之效力降低。對於本文中所描述之經修飾之hIL-2蛋白質，hIL-2對高親和力hIL-2受體之效力降低更大可為可能及可接受的，但由於細胞增殖分析法條件之限制，此類降低可能無法用本文中所描述之方法定量。

【0071】 另外，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對中等親和力IL-2受體(hIL-2Rβγ)展現至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對中等親和力IL-2受體(hIL-2Rβγ)展現大於約

10,000倍之效力降低。

【0072】 相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現至多約10,000倍之效力降低，且對中等親和力IL-2受體(hIL-2Rβγ)展現至多約10,000倍之效力降低，例如如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現大於約10,000倍之效力降低，且對中等親和力IL-2受體(hIL-2Rβγ)展現大於約10,000倍之效力降低。

【0073】 如本文中所證實，經修飾之hIL-2蛋白質可融合至抗PD-1抗體或其抗原結合片段。hIL-2蛋白質可在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、抗原結合片段之N端或抗原結合片段之C端處融合至抗PD-1抗體或其抗原結合片段。在一些實施例中，經修飾之hIL-2蛋白質係藉由肽鍵直接融合至抗PD-1抗體或其抗原結合片段。經修飾之hIL-2蛋白質可例如藉由肽鍵直接融合至抗PD-1抗體重鏈之C端胺基酸殘基。在一些實施例中，經修飾之hIL-2蛋白質係經由連接子融合至抗PD-1抗體或其抗原結合片段。

【0074】 經修飾之hIL-2蛋白質與抗體或其抗原結合片段之融合可拯救經修飾之hIL-2蛋白質結合且活化表現PD-1之細胞(諸如T細胞且尤其腫瘤浸潤性淋巴細胞)上之人類中等親和力IL-2受體之能力。在一些實施例中，融合至抗體或其抗原結合片段之hIL-2蛋白質對表現PD-1之細胞上之中等親和力IL-2受體展現效力，該效力與野生型hIL-2對中等親和力IL-2受體之效力類似。

【0075】 經修飾之hIL-2蛋白質與抗體或其抗原結合片段之融合可

用於將IL-2信號傳導選擇性地遞送至表現抗體或其抗原結合片段之PD-1標靶的細胞。在不受理論束縛之情況下，咸信將經修飾之hIL-2蛋白質靶向特定細胞群體可顯著增強IL-2之治療作用(例如抗腫瘤免疫性)而無脫靶全身性毒性。

【0076】 本文亦揭示經修飾之人類介白素-2 (hIL-2)蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代及在胺基酸位置38處之R38E取代。

【0077】 經修飾之hIL-2蛋白質可包含SEQ ID NO: 307、607至611、614、617或620中之任一者的胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 307之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 607之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 608之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 609之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 610之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 611之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 614之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 617之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 620之胺基酸序列。胺基酸序列SEQ ID NO: 307、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質可進一步包含T3A取代及/或C125A取代。在一些實施例中，胺基酸序列SEQ ID NO: 307、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含T3A

取代。在一些實施例中，胺基酸序列SEQ ID NO: 307、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含C125A取代。在一些實施例中，胺基酸序列SEQ ID NO: 307、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含T3A取代及C125A取代。

【0078】 經修飾之hIL-2蛋白質可包含D20A取代及R38E取代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 149之胺基酸序列。

【0079】 經修飾之hIL-2蛋白質可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之取代。適合之取代包括例如T3A。在一些實施例中，經修飾之hIL-2蛋白質包含T3A取代、D20A取代及R38E取代。在一些態樣中，經修飾之hIL-2蛋白質包含SEQ ID NO: 216之胺基酸序列。

【0080】 或者，經修飾之hIL-2蛋白質可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列的胺基酸位置3之缺失。在一些實施例中，經修飾之hIL-2蛋白質包含胺基酸1至3之缺失、D20A取代及R38E取代。在一些態樣中，經修飾之hIL-2蛋白質包含SEQ ID NO: 218之胺基酸序列。

【0081】 經修飾之hIL-2蛋白質可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。在胺基酸位置125處之取代可為C125A。在一些實施例中，經修飾之hIL-2蛋白質包含D20A取代、R38E取代及C125A取代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 215之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含T3A取代、D20A取代、R38E取代及C125A取

代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 217之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含胺基酸1至3之缺失、D20A取代、R38E取代及C125A取代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 219之胺基酸序列。

【0082】 相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現大於約10,000倍之效力降低。對於本文中所描述之經修飾之hIL-2蛋白質，hIL-2對高親和力hIL-2受體之效力降低更大可為可能及可接受的，但由於細胞增殖分析法條件之限制，此類降低可能無法用本文中所描述之方法定量。

【0083】 另外，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對中等親和力IL-2受體(hIL-2Rβγ)展現至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對中等親和力IL-2受體(hIL-2Rβγ)展現大於約10,000倍之效力降低。

【0084】 相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現至多約10,000倍之效力降低，且對中等親和力IL-2受體(hIL-2Rβγ)展現至多約10,000倍之效力降低，例如如在本文

中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現大於約10,000倍之效力降低，且對中等親和力IL-2受體(hIL-2Rβγ)展現大於約10,000倍之效力降低。

【0085】 如本文中所證實，經修飾之hIL-2蛋白質可融合至抗PD-1抗體或其抗原結合片段。hIL-2蛋白質可在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、抗原結合片段之N端或抗原結合片段之C端處融合至抗PD-1抗體或其抗原結合片段。在一些實施例中，經修飾之hIL-2蛋白質係藉由肽鍵直接融合至抗PD-1抗體或其抗原結合片段。經修飾之hIL-2蛋白質可例如藉由肽鍵直接融合至抗PD-1抗體重鏈之C端胺基酸殘基。在一些實施例中，經修飾之hIL-2蛋白質係經由連接子融合至抗PD-1抗體或其抗原結合片段。

【0086】 經修飾之hIL-2蛋白質與抗體或其抗原結合片段之融合可拯救經修飾之hIL-2蛋白質結合且活化表現PD-1之細胞(諸如T細胞且尤其腫瘤浸潤性淋巴細胞)上之人類中等親和力IL-2受體之能力。在一些實施例中，融合至抗體或其抗原結合片段之hIL-2蛋白質對表現PD-1之細胞上之中等親和力IL-2受體展現效力，該效力與野生型hIL-2對中等親和力IL-2受體之效力類似。

【0087】 經修飾之hIL-2蛋白質與抗體或其抗原結合片段之融合可用於將IL-2信號傳導選擇性地遞送至表現抗體或其抗原結合片段之PD-1標靶的細胞。在不受理論束縛之情況下，咸信將經修飾之hIL-2蛋白質靶向特定細胞群體可顯著增強IL-2之治療作用(例如抗腫瘤免疫性)而無脫靶全身性毒性。

人類抗人類計劃性細胞死亡蛋白-1 (hPD-1)抗體

【0088】本文揭示免疫特異性結合至hPD-1之人類抗體分子或其抗原結合片段，其中人類抗體分子或其抗原結合片段包含：

a) 包含SEQ ID NO: 418之胺基酸序列的重鏈互補決定區1 (CDR1)、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3；

b) 包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3；

c) 包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3；或

d) 包含SEQ ID NO: 406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序列的輕鏈CDR3。

【0089】在一些實施例中，人類抗體分子或其抗原結合片段包含有包含SEQ ID NO: 418之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3 (在本文中稱為「H7-632」)。

【0090】在一些實施例中，人類抗體分子或其抗原結合片段包含有包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3 (在本文中稱為「2H7」)。

【0091】在一些實施例中，人類抗體分子或其抗原結合片段包含有包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3 (在本文中稱為「C51E6-5」)。

【0092】在一些實施例中，人類抗體分子或其抗原結合片段包含有包含SEQ ID NO: 406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序

列的輕鏈CDR3 (在本文中稱為「A2」)。

【0093】 所揭示之人類抗體分子或其抗原結合片段可展現以下活性中之一或多者：

• 結合至PD-1而不抑制PD-L1結合至PD-1；

• 在存在臨床中所使用之標準照護(standard-of-care)抗PD-1抗體(例如KEYTRUDA®及OPDIVO®)之情況下結合至PD-1；

• 對PD-1具有高度選擇性且不免疫特異性結合其他相關B7家族成員；及

• 結合至經活化之人類T細胞上之PD-1 (在流式細胞分析技術結合分析法中EC_{50}約0.1至0.2 nM)。

【0094】 人類抗體分子或其抗原結合片段可包含有包含SEQ ID NO: 416之胺基酸序列的重鏈可變區及包含SEQ ID NO: 417之胺基酸序列的輕鏈可變區(在本文中稱為「H7-632」)。

【0095】 人類抗體分子或其抗原結合片段可包含有包含SEQ ID NO: 384之胺基酸序列的重鏈可變區及包含SEQ ID NO: 385之胺基酸序列的輕鏈可變區(在本文中稱為「2H7」)。

【0096】 人類抗體分子或其抗原結合片段可包含有包含SEQ ID NO: 394之胺基酸序列的重鏈可變區及包含SEQ ID NO: 395之胺基酸序列的輕鏈可變區(在本文中稱為「C51E6-5」)。

【0097】 人類抗體分子或其抗原結合片段可包含有包含SEQ ID NO: 404之胺基酸序列的重鏈可變區及包含SEQ ID NO: 405之胺基酸序列的輕鏈可變區(在本文中稱為「A2」)。

【0098】 人類抗體分子或其抗原結合片段可包含人類IgG1重鏈恆定

區。

【0099】 人類抗體分子或其抗原結合片段在恆定區內可具有取代或缺失以最小化Fc介導之免疫效應功能，諸如FcγRIIIA介導之抗體依賴性細胞介導之細胞毒性(antibody-dependent cell-mediated cytotoxicity；ADCC)、FcγRI及FcγRIIa依賴性抗體依賴性細胞吞噬作用(antibody-dependent cellular phagocytosis；ADCP)及C1q結合介導之補體依賴性細胞毒性(complement-dependent cytotoxicity；CDC)。在一些實施例中，人類抗體分子包含L235A取代基，其中胺基酸編號係根據EU編號。在一些實施例中，人類抗體分子包含G237A取代，其中胺基酸編號係根據EU編號。在一些實施例中，人類抗體分子包含L235A及G237A取代，其中胺基酸編號係根據EU編號。

【0100】 人類抗體分子或其抗原結合片段可包含有包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415之胺基酸序列的輕鏈(在本文中稱為「H7-632-hIgG1-LAGA」)。

【0101】 人類抗體分子或其抗原結合片段可包含有包含SEQ ID NO:424之胺基酸序列的重鏈及包含SEQ ID NO:425之胺基酸序列的輕鏈(在本文中稱為「2H7-hIgG4」)。

【0102】 人類抗體分子或其抗原結合片段可包含有包含SEQ ID NO: 426之胺基酸序列的重鏈及包含SEQ ID NO: 427之胺基酸序列的輕鏈(在本文中稱為「C51E6-5-hIgG4」)。

【0103】 人類抗體分子或其抗原結合片段可包含有包含SEQ ID NO: 428之胺基酸序列的重鏈及包含SEQ ID NO: 429之胺基酸序列的輕鏈(在本文中稱為「A2-hIgG4」)。

【0104】 人類抗體分子或其抗原結合片段可融合至經修飾之hIL-2蛋白質，該經修飾之hIL-2蛋白質包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代。人類抗體分子或其抗原結合片段可融合至本文中所揭示之經修飾之hIL-2蛋白質中之任一者。

【0105】 當未融合至抗體分子或其抗原結合片段時，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力hIL-2受體及對中等親和力hIL-2受體兩者展現降低之效力。

【0106】 在經修飾之hIL-2的胺基酸位置20處之適合之取代包括例如D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代中之任一者。

【0107】 在經修飾之hIL-2蛋白質的胺基酸位置38處之適合之取代包括例如R38E、R38N、R38G、R38H、R38I、R38L、R38M、R38F、R38P、R38S、R38T、R38W、R38Y、R38V、R38A、R38Q、R38D或R38K取代中之任一者。

【0108】 在一些實施例中，D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代中之任一者可與R38E取代組合。

【0109】 經修飾之hIL-2蛋白質可包含SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的胺基酸序列。經修飾之hIL-2蛋白質可包含SEQ ID NO: 134至150、307、344、608、611、614或620中之任一者的胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 134之胺基酸序列。在一些實施例中，經修飾之hIL-

2蛋白質包含SEQ ID NO: 135之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 136之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 137之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 138之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 139之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 140之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 141之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 142之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 143之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 144之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 145之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 146之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 147之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 148之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 149之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 150之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 307之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 344之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 607之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 608之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 609之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 610之胺基酸序列。在一

些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 611之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 614之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 617之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 620之胺基酸序列。胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質可進一步包含T3A取代及/或C125A取代。在一些實施例中，胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含T3A取代。在一些實施例中，胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含C125A取代。在一些實施例中，胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含T3A取代及C125A取代。

【0110】 經修飾之hIL-2蛋白質可包含D20A取代及R38E取代。

【0111】 經修飾之hIL-2蛋白質可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之取代。適合之取代包括例如T3A。在一些實施例中，經修飾之hIL-2蛋白質包含T3A取代、D20A取代及R38E取代。在一些態樣中，經修飾之hIL-2蛋白質包含SEQ ID NO: 216之胺基酸序列。

【0112】 或者，經修飾之hIL-2蛋白質可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列的胺基酸位置3之缺失。在一些實施例中，經修飾之hIL-2蛋白質包含胺基酸1至3之缺失、D20A取代及R38E取代。在一些態樣中，經修飾之hIL-2蛋白質包含SEQ ID NO: 218之

胺基酸序列。

【0113】 經修飾之hIL-2蛋白質可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。在胺基酸位置125處之取代可為C125A。在一些實施例中，經修飾之hIL-2蛋白質包含D20A取代、R38E取代及C125A取代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 215之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含T3A取代、D20A取代、R38E取代及C125A取代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 217之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含胺基酸1至3之缺失、D20A取代、R38E取代及C125A取代。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 219之胺基酸序列。

【0114】 當未融合至人類抗體分子或其抗原結合片段時，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，當未融合至人類抗體分子或其抗原結合片段時，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現大於約10,000倍之效力降低。對於本文中所描述之經修飾之hIL-2蛋白質，hIL-2對高親和力hIL-2受體之效力降低更大可為可能及可接受的，但由於細胞增殖分析法條件之限制，此類降低可能無法用本文中所描述之方法定量。

【0115】 另外，當未融合至人類抗體分子或其抗原結合片段時，相

對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對中等親和力IL-2受體(hIL-2Rβγ)展現至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，當未融合至人類抗體分子或其抗原結合片段時，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對中等親和力IL-2受體(hIL-2Rβγ)展現大於約10,000倍之效力降低。

【0116】 當未融合至人類抗體分子或其抗原結合片段時，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現至多約10,000倍之效力降低，且對中等親和力IL-2受體(hIL-2Rβγ)展現至多約10,000倍之效力降低，例如如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。當未融合至人類抗體分子或其抗原結合片段時，相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質可對高親和力IL-2受體(hIL-2Rαβγ)展現大於約10,000倍之效力降低，且對中等親和力IL-2受體(hIL-2Rβγ)展現大於約10,000倍之效力降低。

【0117】 經修飾之hIL-2蛋白質與抗體或其抗原結合片段之融合可拯救經修飾之hIL-2蛋白質結合且活化表現PD-1之細胞(諸如T細胞且尤其腫瘤浸潤性淋巴細胞)上之人類中等親和力IL-2受體之能力。在一些實施例中，融合至抗體或其抗原結合片段之hIL-2蛋白質對表現PD-1之細胞上之中等親和力IL-2受體展現效力，該效力與野生型hIL-2對中等親和力IL-2受體之效力類似。

【0118】 經修飾之hIL-2蛋白質可在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、抗原結合片段之N端或抗原結合

片段之C端處融合至人類抗體分子或其抗原結合片段。在一些實施例中，hIL-2蛋白質係藉由肽鍵直接融合至抗體或其抗原結合片段。hIL-2可例如藉由肽鍵直接融合至抗體重鏈之C端胺基酸殘基。在一些實施例中，hIL-2蛋白質係經由連接子融合至抗體或其抗原結合片段。

【0119】 人類抗體分子或其抗原結合片段與經修飾之hIL-2蛋白質之融合可用於將IL-2信號傳導選擇性地遞送至表現PD-1之細胞。在不受理論束縛之情況下，咸信將經修飾之hIL-2蛋白質靶向表現PD-1之特定細胞群體可顯著增強IL-2之治療作用(例如抗腫瘤免疫性)，同時減少或最小化脫靶全身性毒性。

免疫結合物

【0120】 本文揭示包含本文中所揭示之經修飾之hIL-2蛋白質中之任一者及本文中所揭示之人類抗體分子或其抗原結合片段中之任一者的免疫結合物。免疫結合物可包含：

(a) 經修飾之hIL-2蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代；及

(b) 免疫特異性結合至hPD-1之人類抗體分子或其抗原結合片段，其中人類抗體分子或其抗原結合片段包含：

(i) 包含SEQ ID NO: 418之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3；

(ii) 包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3；

(iii) 包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3；或

(iv) 包含SEQ ID NO: 406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序列的輕鏈CDR3。

【0121】 在免疫結合物之經修飾之hIL-2部分的胺基酸位置20處的適合之取代包括例如D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代中之任一者。

【0122】 在免疫結合物之經修飾之hIL-2部分的胺基酸位置38處的適合之取代包括例如R38E、R38N、R38G、R38H、R38I、R38L、R38M、R38F、R38P、R38S、R38T、R38W、R38Y、R38V、R38A、R38Q、R38D或R38K取代中之任一者。

【0123】 在一些實施例中，D20A、D20S、D20Q、D20M、D20I、

D20V、D20N、D20G、D20T或D20E取代中之任一者可與R38E取代組合。

【0124】免疫結合物之經修飾之hIL-2蛋白質部分可包含SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的胺基酸序列。免疫結合物之經修飾之hIL-2蛋白質部分可包含SEQ ID NO: 134至150、307、344、608、611、614或620中之任一者的胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 134之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 135之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 136之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 137之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 138之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 139之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 140之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 141之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 142之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 143之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 144之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 145之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 146之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 147之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 148之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 149之胺基酸序列。

在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 150之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 307之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 344之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 607之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 608之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 609之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 610之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 611之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 614之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 617之胺基酸序列。在一些實施例中，經修飾之hIL-2蛋白質包含SEQ ID NO: 620之胺基酸序列。胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質可進一步包含T3A取代及/或C125A取代。在一些實施例中，胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含T3A取代。在一些實施例中，胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含C125A取代。在一些實施例中，胺基酸序列SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的經修飾之hIL-2蛋白質進一步包含T3A取代及C125A取代。

【0125】 免疫結合物之經修飾之hIL-2蛋白質部分可包含D20A取代及R38E取代。

【0126】 免疫結合物之經修飾之hIL-2蛋白質部分可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之取代。適合之取代包括例如T3A。在一些實施例中，免疫結合物之經修飾之hIL-2蛋白質部分包含T3A取代、D20A取代及R38E取代。在一些態樣中，免疫結合物之經修飾之hIL-2蛋白質部分包含SEQ ID NO: 216之胺基酸序列。

【0127】 或者，免疫結合物之經修飾之hIL-2蛋白質部分可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列的胺基酸位置3之缺失。在一些實施例中，免疫結合物之經修飾之hIL-2蛋白質部分包含胺基酸1至3之缺失、D20A取代及R38E取代。在一些態樣中，免疫結合物之經修飾之hIL-2蛋白質部分包含SEQ ID NO: 218之胺基酸序列。

【0128】 免疫結合物之經修飾之hIL-2蛋白質部分可進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。在胺基酸位置125處之取代可為C125A。在一些實施例中，免疫結合物之經修飾之hIL-2蛋白質部分包含D20A取代、R38E取代及C125A取代。在一些實施例中，免疫結合物之經修飾之hIL-2蛋白質部分包含SEQ ID NO: 215之胺基酸序列。在一些實施例中，免疫結合物之經修飾之hIL-2蛋白質部分包含T3A取代、D20A取代、R38E取代及C125A取代。在一些實施例中，免疫結合物之經修飾之hIL-2蛋白質部分包含SEQ ID NO: 217之胺基酸序列。在一些實施例中，免疫結合物之經修飾之hIL-2蛋白質部分包含胺基酸1至3之缺失、D20A取代、R38E取代及C125A取代。在一些實施例中，免疫結合物之經修飾之hIL-2蛋白質部分包含SEQ ID NO: 219之胺基酸序列。

【0129】 相對於未經修飾之hIL-2，免疫結合物之經修飾之hIL-2蛋白質部分可對高親和力IL-2受體(hIL-2Rαβγ)展現至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，相對於未經修飾之hIL-2，免疫結合物之經修飾之hIL-2蛋白質部分可對高親和力IL-2受體(hIL-2Rαβγ)展現大於約10,000倍之效力降低。對於本文中所描述之經修飾之hIL-2蛋白質，hIL-2對高親和力hIL-2受體之效力降低更大可為可能及可接受的，但由於細胞增殖分析條件之限制，此類降低可能無法用本文中所描述之方法定量。

【0130】 另外，相對於未經修飾之hIL-2，免疫結合物之經修飾之hIL-2蛋白質部分可對中等親和力IL-2受體(hIL-2Rβγ)展現至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，相對於未經修飾之hIL-2，免疫結合物之經修飾之hIL-2蛋白質部分可對中等親和力IL-2受體(hIL-2Rβγ)展現大於約10,000倍之效力降低。

【0131】 相對於未經修飾之hIL-2，免疫結合物之經修飾之hIL-2蛋白質部分可對高親和力IL-2受體(hIL-2Rαβγ)展現至多約10,000倍之效力降低，且對中等親和力IL-2受體(hIL-2Rβγ)展現至多約10,000倍之效力降低，例如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。相對於未經修飾之hIL-2，免疫結合物之經修飾之hIL-2蛋白質部分可對高親和力IL-2受體(hIL-2Rαβγ)展現大於約10,000倍之效力降

低，且對中等親和力IL-2受體(hIL-2Rβγ)展現大於約10,000倍之效力降低。

【0132】 免疫結合物之hIL-2蛋白質部分可在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、抗原結合片段之N端或抗原結合片段之C端處融合至抗體或其抗原結合片段。在一些實施例中，免疫結合物之hIL-2蛋白質部分係藉由肽鍵直接融合至人類抗體分子或其抗原結合片段。免疫結合物之hIL-2蛋白質部分可例如藉由肽鍵直接融合至抗體重鏈之C端胺基酸殘基。在一些實施例中，免疫結合物之hIL-2蛋白質部分係經由連接子融合至人類抗體分子或其抗原結合片段。

【0133】 經修飾之hIL-2蛋白質與人類抗體分子或其抗原結合片段之融合可拯救經修飾之hIL-2蛋白質活化中等親和力IL-2受體之能力。在一些實施例中，免疫結合物能夠使中等親和力IL-2受體活化至與中等親和力IL-2受體之野生型hIL-2活化類似之程度。

【0134】 在一些實施例中，免疫結合物之人類抗體分子或其抗原結合片段部分包含有包含SEQ ID NO: 418之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3。

【0135】 在一些實施例中，免疫結合物之人類抗體分子或其抗原結合片段部分包含有包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈

CDR1、包含SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3。

【0136】 在一些實施例中，免疫結合物之人類抗體分子或其抗原結合片段部分包含有包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3。

【0137】 在一些實施例中，免疫結合物之人類抗體分子或其抗原結合片段部分包含有包含SEQ ID NO:406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序列的輕鏈CDR3。

【0138】 免疫結合物之人類抗體分子或其抗原結合片段部分可包含有包含SEQ ID NO: 416之胺基酸序列的重鏈可變區及包含SEQ ID NO: 417之胺基酸序列的輕鏈可變區。

【0139】 免疫結合物之人類抗體分子或其抗原結合片段部分可包含有包含SEQ ID NO: 384之胺基酸序列的重鏈可變區及包含SEQ ID NO: 385之胺基酸序列的輕鏈可變區。

【0140】 免疫結合物之人類抗體分子或其抗原結合片段部分可包含有包含SEQ ID NO: 394之胺基酸序列的重鏈可變區及包含SEQ ID NO: 395之胺基酸序列的輕鏈可變區。

【0141】 免疫結合物之人類抗體分子或其抗原結合片段部分可包含有包含SEQ ID NO: 404之胺基酸序列的重鏈可變區及包含SEQ ID NO: 405之胺基酸序列的輕鏈可變區。

【0142】 免疫結合物之人類抗體分子或其抗原結合片段部分可包含IgG1重鏈恆定區。

【0143】 免疫結合物之人類抗體分子或其抗原結合片段部分在恆定區內可具有取代或缺失以最小化Fc介導之免疫效應功能，諸如FcγRIIIA介導之抗體依賴性細胞介導之細胞毒性(ADCC)、FcγRI及FcγRIIa依賴性抗體依賴性細胞吞噬作用(ADCP)及C1q結合介導之補體依賴性細胞毒性(CDC)。在一些實施例中，免疫結合物之人類抗體分子部分包含L235A取代，其中胺基酸編號係根據EU編號。在一些實施例中，免疫結合物之人類抗體分子部分包含G237A取代，其中胺基酸編號係根據EU編號。在一些實施例中，免疫結合物之人類抗體分子部分包含L235A及G237A取代，其中胺基酸編號係根據EU編號。

【0144】 免疫結合物之人類抗體分子或其抗原結合片段部分可包含有包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415之胺基酸序列的輕鏈。

【0145】 免疫結合物之人類抗體分子或其抗原結合片段部分可包含有包含SEQ ID NO: 424之胺基酸序列的重鏈及包含SEQ ID NO: 425之胺基酸序列的輕鏈。

【0146】 免疫結合物之人類抗體分子或其抗原結合片段部分可包含有包含SEQ ID NO: 426之胺基酸序列的重鏈及包含SEQ ID NO: 427之胺基酸序列的輕鏈。

【0147】 免疫結合物之人類抗體分子或其抗原結合片段部分可包含有包含SEQ ID NO: 428之胺基酸序列的重鏈及包含SEQ ID NO: 429之胺基酸序列的輕鏈。

【0148】 免疫結合物可具有以下特性中之一或多者：

• 結合至PD-1但不抑制PD-L1結合至PD-1；

• 在存在臨床中所使用之標準照護抗PD-1抗體(例如KEYTRUDA®及OPDIVO®)之情況下結合至PD-1；

• 對PD-1具有高度選擇性且不免疫特異性結合其他相關B7家族成員；

• 結合經活化之人類T細胞上之PD-1 (在流式結合分析法中EC_{50}約0.1至0.2 nM)；

• 相對於未經修飾之hIL-2，對高親和力IL-2受體(hIL-2Rαβγ)具有至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如在本文中所描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，相對於未經修飾之hIL-2，免疫結合物之經修飾之hIL-2蛋白質部分可對高親和力IL-2受體(hIL-2Rαβγ)展現大於約10,000倍之效力降低。對於本文中所描述之經修飾之hIL-2蛋白質，hIL-2對高親和力hIL-2受體之效力降低更大可為可能及可接受的，但由於細胞增殖分析條件之限制，此類降低可能無法用本文中所描述之方法定量；

• 相對於未經修飾之hIL-2，對中等親和力IL-2受體(hIL-2Rβγ)具有至少約200倍、至少約500倍、至少約1,000倍、至少約2,000倍、至少約5,000倍、至少約6,500倍或至少約10,000倍之效力降低，例如在本文中所

描述之hIL-2依賴性細胞增殖分析法中藉由比較EC_{50}值所定量。在一些實施例中，相對於未經修飾之hIL-2，免疫結合物之經修飾之hIL-2蛋白質部分可對中等親和力IL-2受體(hIL-2Rβγ)展現大於約10,000倍之效力降低；

• 在GvHD動物模型中拯救及擴增表現PD-1之人類記憶T細胞亞群；及

• 在1及10 mg/kg之單次劑量之後，對石蟹獼猴之體重、血液化學或血液學參數具有極小影響或無影響。

【0149】 在一些實施例中，免疫結合物包含經修飾之hIL-2蛋白質，其包含融合至人類抗hPD-1抗體之抗體重鏈之C端的T3A取代、R38E取代、D20A取代及C125A取代，該人類抗hPD-1抗體包含具有L235A取代及G237A取代之人類IgG1構架。在一些實施例中，免疫結合物包含有包含SEQ ID NO: 415之胺基酸序列的輕鏈及包含SEQ ID NO: 532之胺基酸序列的重鏈-hIL-2蛋白質融合物。

【0150】 所揭示之免疫結合物可選擇性地遞送IL-2信號傳導至表現PD-1之T細胞。免疫結合物之人類抗體分子或其抗原結合片段部分僅用於遞送經修飾之hIL-2至表現PD-1之細胞且不阻斷PD-1受體功能，如同典型之抗PD-1抑制劑抗體(諸如OPDIVO®及KEYTRUDA®)一樣。本文中所揭示之免疫結合物的主要作用機制係經由IL-2之T細胞選擇性活性實現。人類PD-1受體主要表現於具有強腫瘤反應性之小部分T細胞亞群上。在不受理論束縛之情況下，咸信將免疫結合物之經修飾之hIL-2蛋白質部分靶向此T細胞群體可顯著增強抗腫瘤免疫性，同時減少或最小化由缺乏PD-1表現之細胞群體介導之脫靶全身性IL-2介導之毒性。

醫藥組合物、聚核苷酸、載體及細胞

【0151】本文揭示醫藥組合物，其包含本文中所揭示之經修飾之hIL-2蛋白質中之任一者、本文中所揭示之人類抗體分子或其抗原結合片段中之任一者，或本文中所揭示之免疫結合物中之任一者。在一些實施例中，醫藥組合物包含本文中所揭示之經修飾之hIL-2蛋白質中之任一者。在一些實施例中，醫藥組合物包含本文中所揭示之人類抗體分子或其抗原結合片段中之任一者。在一些實施例中，醫藥組合物包含本文中所揭示之免疫結合物中之任一者。

【0152】本文揭示聚核苷酸，其包含編碼本文中所揭示之經修飾之hIL-2蛋白質中之任一者、本文中所揭示之人類抗體分子或其抗原結合片段中之任一者，或本文中所揭示之免疫結合物中之任一者的核酸序列。在一些實施例中，聚核苷酸包含編碼本文中所揭示之經修飾之hIL-2蛋白質中之任一者的核酸序列。在一些實施例中，聚核苷酸包含編碼本文中所揭示之人類抗體分子或其抗原結合片段中之任一者的核酸序列。在一些實施例中，聚核苷酸包含編碼本文中所揭示之免疫結合物中之任一者的核酸序列。

【0153】本文揭示包含聚核苷酸之載體，該聚核苷酸包含編碼本文中所揭示之經修飾之hIL-2蛋白質中之任一者、本文中所揭示之人類抗體分子或其抗原結合片段中之任一者，或本文中所揭示之免疫結合物中之任一者的核酸序列。在一些實施例中，載體包含聚核苷酸，該聚核苷酸包含編碼本文中所揭示之經修飾之hIL-2蛋白質中之任一者的核酸序列。在一些實施例中，載體包含聚核苷酸，該聚核苷酸包含編碼本文中所揭示之人類抗體分子或其抗原結合片段中之任一者的核酸序列。在一些實施例中，載體包含聚核苷酸，該聚核苷酸包含編碼本文中所揭示之免疫結合物中之

任一者的核酸序列。

【0154】 本文亦揭示包含本文中所揭示之載體中之任一者的經轉型之細胞。

治療方法及用途

【0155】 本文揭示治療個體中之疾病或病症的方法，該方法包含向個體投與治療有效量之本文中所揭示之免疫結合物或醫藥組合物中之任一者，由此治療該疾病。

【0156】 亦揭示本文中所揭示之免疫結合物或醫藥組合物中之任一者的用途，其係用以製備用於治療疾病之藥物。亦揭示本文中所描述之免疫結合物或醫藥組合物中之任一者的用途，其係用於治療疾病或病症。

【0157】 所揭示之免疫結合物及醫藥組合物可用於治療其中個體之免疫系統之刺激將有益之疾病或病症。在一些實施例中，個體之免疫反應不足或有缺陷，且所揭示之免疫結合物及醫藥組合物刺激個體之免疫反應。免疫結合物之抗體部分可用以藉由例如與表現於免疫細胞表面上之抗原結合來導引經修飾之hIL-2蛋白質至個體之免疫細胞。在所揭示之經修飾之hIL-2蛋白質-人類抗hPD-1抗體免疫結合物之情況下，舉例而言，免疫結合物之抗PD-1抗體(或其抗原結合片段)部分可結合表現於T細胞上之PD-1，由此遞送經修飾之hIL-2蛋白質至T細胞。將經修飾之IL-2蛋白靶向特定細胞可顯著增強IL-2蛋白之治療功效而無由缺乏抗原表現之細胞群體所介導之脫靶全身性毒性。所揭示之方法及用途可用於治療例如癌症、自體免疫疾病及發炎疾病，以及慢性感染及感染性疾病。例示性癌症包括膀胱癌、腦癌、頭頸癌、胰臟癌、肺癌、非小細胞肺癌、乳癌、卵巢癌、子宮癌、宮頸癌、子宮內膜癌、食道癌、結腸癌、結腸直腸癌、直腸癌、

胃癌、前列腺癌、血液癌、皮膚癌、黑色素瘤、鱗狀細胞癌瘤、骨癌及腎臟癌。例示性自體免疫疾病及發炎疾病包括全身性紅斑狼瘡(systemic lupus erythematosus；SLE)、1型糖尿病、類風濕性關節炎、僵直性脊椎炎、牛皮癬、白塞氏病(Behcet's disease)、伴有多血管炎之肉芽腫、高安氏病(Takayasu's disease)、克羅恩氏病(Crohn's disease)、潰瘍性結腸炎、自體免疫肝炎、硬化性膽管炎、修格蘭氏症候群(Sjoren's syndrome)、斑禿(alopecia areata)及發炎性肌病。例示性感染性疾病包括HIV及B型肝炎。

【0158】 在一些實施例中，疾病為癌症。方法及用途可包含向個體投與治療有效量之本文中所揭示之經修飾之hIL-2蛋白質-抗體結合物中之任一者，由此治療癌症。在一些態樣中，癌症為黑色素瘤。在一些態樣中，癌症為非小細胞肺癌。

實例

【0159】 提供以下實例以進一步描述本文中所揭示之一些實施例。實例意欲說明而非限制所揭示之實施例。

一般方法

方案A.用於抗hPD-1抗體或抗hPD-1抗體減弱之hIL-2融合物與人類PD-1之結合的流式細胞分析技術篩選

【0160】 為了測試與hPD-1之結合，抗體及抗體減弱之hIL-2融合蛋白之特徵在於完全滴定曲線。Jurkat細胞株經哺乳動物載體轉染，該哺乳動物載體編碼人類PD-1 (SEQ ID NO: 346)之胺基酸1至185以穩定表現人類PD-1之胞外域及跨膜域之一部分，且此經轉染之細胞株係用於測定抗hPD-1抗體之結合。洗滌Jurkat + hPD-1細胞並在FACS緩衝液(PBS，

0.2%加熱滅活之胎牛血清(Fetal Bovine Serum))中將其以100,000個細胞/孔添加至96孔盤中。將細胞在4℃下用1:50稀釋度之人類FcR阻斷劑(Miltenyi)阻斷10分鐘並用FACS緩衝液洗滌。

【0161】 抗體或抗體減弱之hIL-2免疫結合物(融合蛋白)在FACS緩衝液中連續稀釋六倍以得到8點曲線，且在冰上以100 μL體積添加至表現人類PD-1之Jurkat細胞中持續1小時。洗滌細胞且再懸浮於含有1:40稀釋度之別藻藍蛋白(Allophycocyanin)結合之抗人類IgG Fc單株抗體的FACS緩衝液中。將細胞再次洗滌，再懸浮於含有1:1000稀釋度之Sytox Green (Thermo Fisher)的FACS緩衝液中，且在BD FACS Canto II，BD Celesta或BD Fortessa (BD Biosciences)流式細胞儀上進行流式細胞分析。使用FlowJo軟體版本10計算幾何平均螢光強度(geometric mean fluorescent intensity；gMFI)。使用GraphPad Prism 7軟體，自所滴定濃度中之別藻藍蛋白信號之gMFI計算半數最大有效濃度(EC_{50})值。

方案B.用於抗hPD-1抗體或抗hPD-1抗體減弱之hIL-2融合物與人類PD-1之結合的流式細胞分析技術競爭篩選

【0162】 對抗體及抗體減弱之hIL-2融合蛋白在存在飽和濃度之抗hPD-1 #1-mIgG2b-N297A (包含納武單抗(nivolumab) (殖株5C4)之重鏈及輕鏈可變區序列之序列，經美國專利公開案第US 2009/0217401A1號中所描述，在鼠類IgG2b-N297A背景上格式化) (SEQ ID NO: 348及349)或抗hPD-1 #2-mIgG2b-N297A (包含帕博利珠單抗(pembrolizumab) (殖株109A-H/K09A-L-11)之重鏈及輕鏈可變區序列之序列，經國際公開案第WO2008/156712A1號中所描述，在鼠類IgG2b-N297A背景上格式化) (SEQ ID NO: 350及351)之情況下結合人類PD-1之能力進行測試。

【0163】抗體或抗體減弱之hIL-2融合蛋白在存在及不存在飽和量之10 μM抗hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A的情況下連續稀釋六倍以得到8點滴定曲線。簡言之，洗滌穩定表現hPD-1之Jurkat細胞(經上文方案A中所描述)且再懸浮於含有1:50稀釋度之人類FcR阻斷試劑的FACS緩衝液中。在4℃下培育細胞10分鐘並洗滌。隨後將細胞再懸浮於100 μL體積中，其中抗hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N287A在FACS緩衝液中稀釋至10 μM，且在4℃下培育該等細胞一小時。洗滌細胞且使其與連續稀釋六倍之測試抗體或抗體減弱之hIL-2融合蛋白在4℃下以100 μL體積一起培育一小時以得到8點曲線。為了偵測結合之測試抗hPD-1抗體或抗hPD-1減弱之hIL-2融合蛋白，再次洗滌細胞且在冰上與1:40稀釋度之別藻藍蛋白結合之抗人類IgG Fc單株抗體一起培育45分鐘。洗滌細胞且再懸浮於含有1:1000稀釋度之Sytox Green (Thermo Fisher)之FACS緩衝液中。為了產生比較，穩定表現人類PD-1之Jurkat細胞僅與經滴定之測試抗體或抗體減弱之hIL-2融合蛋白(不含抗hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A)一起培育，且隨後與1:40稀釋度之別藻藍蛋白結合之抗人類IgG Fc二級抗體一起培育。作為對照，將抗hPD-1 #1及抗hPD-1 #2選殖至hIgG4構架中且在添加及不添加抗hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A之情況下評估。在BD Canto II，BD Celesta或BD Fortessa (BD Biosciences)流式細胞儀上進行流式細胞分析技術且使用FlowJo軟體版本10計算gMFI。使用GraphPad Prism 7軟體，自所滴定濃度中之別藻藍蛋白信號之gMFI計算EC_{50}值。

方案C.用於非拮抗劑抗hPD-1抗體或抗hPD-1抗體減弱之hIL-2融合物之表

徵的基於細胞之篩選

【0164】 表徵人類PD-1抗體及抗hPD-1減弱之hIL-2融合蛋白阻斷hPD-1結合至配位體hPD-L1 (SEQ ID NO: 584)之能力。使用基於活體外細胞之人類PD-1/PD-L1阻斷生物分析法(Promega，目錄號J1255)，將抗hPD-1抗體及抗hPD-1減弱之hIL-2融合蛋白表徵為拮抗劑或非拮抗劑。此共培養分析法利用兩種細胞株：FCγR11b人工抗原呈現細胞/中國卵巢倉鼠(Chinese Ovary Hamster) K1 (aAPC/CHO-K1)及Jurkat效應細胞。aAPC/CHO K1細胞穩定表現人類PD-L1配位體及細胞表面蛋白質兩者以活化同源T細胞受體(TCR)，而Jurkat效應細胞在活化T細胞反應元件之核因子(Nuclear Factor of Activated T cells response element；NFAT-RE)的控制下表現hPD-1及螢光素酶報導子。當此等細胞在存在非拮抗性抗體之情況下共培養時，hPD-1/hPD-L1相互作用抑制TCR信號傳導且未偵測到發光。在存在拮抗hPD-1與hPD-L1 (SEQ ID NO: 584)之相互作用之抗體的情況下，破壞抑制信號且偵測到發光。

【0165】 根據製造商之說明書進行解凍及使用(thaw-and-use)分析法。簡而言之，首先解凍aAPC/CHO-K1細胞且在37℃下在5% CO_2培育箱中以30,000個細胞/孔接種於平底96孔盤中18小時。在細胞貼附之後，移除培養基且將200 nM或1000 nM測試抗體或抗體減弱之hIL-2融合蛋白在40 μL分析法緩衝液(RPMI 1640培養基+ 1% FBS)中稀釋且添加至aAPC/CHO-K1細胞中。靶向鎖孔帽貝血氰蛋白(Keyhole Limpet Hemocyanin；KLH)殖株C3 (SEQ ID NO: 585及586)之人類IgG4同型對照單株抗體係用作陰性對照。以24,000個細胞/孔，以40 μL體積添加表現hPD-1之Jurkat效應細胞。所測試之固定抗體之最終濃度為100 nM或500

nM。在一些實施例中，在此共培養分析法中測試一系列濃度之抗hPD-1或抗hPD-1減弱之hIL-2融合蛋白，其中最高濃度在500 nM之五倍滴定系列中(圖7)。

【0166】 在37℃下在5% CO_2培育箱中培育共培養分析法額外18至20小時。為了讀出發光信號，使盤達到室溫且將80 μL Bio-Glo™試劑添加至各孔中。在室溫下於暗處培育盤15分鐘，且在Victor X光度計(Perkin Elmer)上讀出發光。對每三個相對發光單位(Relative luminescence unit；RLU)取平均值且使用GraphPad Prism 7軟體繪製圖表。

方案D.測試hIL-2變異體之減弱之活體外磷酸化STAT5分析法

【0167】 使用磷酸化STAT5分析法來表徵抗體減弱之hIL-2融合蛋白的hIL-2受體活化活性之減弱程度。在hIL-2反應性人類自然殺手NK-92細胞及經工程改造之人類紅白血病TF1細胞兩者中測試變異體。NK-92細胞株在生理程度下天然表現高親和力hIL-2受體(IL-2Rαβγ)，而天然表現IL-2Rγ (SEQ ID NO: 352)之TF1細胞株經工程改造亦穩定表現用於表現中等親和力hIL-2受體複合物(IL-2Rβγ)之人類CD122 (IL-2Rβ) (SEQ ID NO: 353)。此TF1+IL-2Rβ穩定細胞株不表現IL-2Rα (SEQ ID NO: 354)。NK-92及TF1+IL-2Rβ細胞株兩者係用於評估IL-2效力在呈固定濃度篩選及完全滴定曲線形式之基於此等細胞之效力分析法中之減弱程度。

【0168】 為了進行固定濃度篩選，將100,000個NK-92細胞或TF1+IL-2Rβ細胞接種於50 μL缺乏人類IL-2細胞介素之新鮮生長培養基之96孔中，且在37℃下在CO_2培育箱中培育隔夜。在15至16小時之後，將人類IL-2饑餓細胞用25.7 nM重組hIL-2 (表示為rhIL-2) (SEQ ID NO: 345)或測試抗體減弱之hIL-2融合蛋白處理以進行NK-92細胞分析法，或用33.3

nM hIL-2或測試hIL-2變異體處理以進行TF1+IL-2Rβ細胞分析法。在37℃、5% CO_2下培育細胞10分鐘。在37℃下用Cytofix緩衝液(BD Biosciences)固定細胞10分鐘且隨後用Perm Buffer III (BD Biosciences)在冰上處理30分鐘之後進行滲透。在室溫下於暗處用Alexa Fluor-647結合之抗Stat5抗體(BD Biosciences)以每個樣品0.5 μL對細胞進行染色固定及滲透45分鐘之後，偵測到hIL-2依賴性Stat5磷酸化。洗滌細胞且在BD Pharmingen緩衝液(BD Biosciences)中稀釋試劑。在FACS-Celesta細胞計數器(BD Biosciences)上獲取經染色之細胞且使用FlowJo軟體版本10.7.2進行分析。在群組中進行分析法，但使用各盤之rhIL-2標準化。在範圍為1200 nM至7 pM之8點、6倍連續滴定曲線中評估所選擇之抗體減弱之hIL-2融合蛋白在NK-92及TF1+IL-2Rβ細胞株兩者上之減弱程度。用與上文所描述之方法相同的方式進行pStat5曲線之程序。使用GraphPad Prism 7軟體，自所滴定濃度中之幾何平均螢光強度(gMFI)計算EC_{50}值。藉由變異體之EC_{50}值除以hIL-2之EC_{50}來計算相對於rhIL-2之活性倍數變化。

方案E.測試抗體減弱之hIL-2融合蛋白之減弱的基於活體外細胞之增殖分析法

【0169】 亦在hIL-2依賴性細胞增殖分析法中測試抗體減弱之hIL-2融合蛋白的減弱之hIL-2活性。將懸浮於50 μL無hIL-2細胞介素之新鮮生長培養基中之10,000個NK-92細胞(表現高親和力受體hIL-2Rαβγ)或TF1+IL-2Rβ細胞(表現中等親和力受體hIL-2Rβγ)接種於96孔U形底細胞培養盤之每個孔中。將具有996 nM之最高濃度的抗體減弱之hIL-2融合蛋白的八點，6倍連續滴定稀釋於新鮮培養基中且覆蓋於孔中之細胞上。在37℃下在5% CO_2培育箱中培育細胞，TF1+IL-2Rβ細胞為3天或NK-92細

胞為4天。為了量測增殖，將Cell-Titer-Glo (Promega)添加至孔中，在室溫下培育10分鐘且使用VictorX多標記盤讀取器(Perkin Elmer)每孔讀出發光0.1秒。使用GraphPad Prism 7軟體，自所滴定濃度中之相對發光單位(RLU)計算EC_{50}值。藉由變異體之EC_{50}值除以hIL-2之EC_{50}來計算相對於rhIL-2之活性倍數變化。在群組中進行分析法，但使用各盤之rhIL-2 EC_{50}值標準化。

實例1：抗體減弱之hIL-2融合蛋白變異體之最佳化及其對中等及高親和力hIL-2受體複合物之hIL-2活性之測定

【0170】為了測定抗體減弱之hIL-2融合蛋白之最佳結構，使未減弱之hIL-2在抗體可變區中以如圖1中所示之各種方式融合至指定為1H3-hIgG1 (SEQ ID NO: 379、SEQ ID NO: 374)之抗DNA酶I抗體(殖株1H3)。變化形式包括經由表示為hIL-2 N端輕鏈df (SEQ ID NO: 379、SEQ ID NO: 356)、hIL-2 N端重鏈df (SEQ ID NO: 358、SEQ ID NO: 374)之直接融合物(direct fusion；df)或表示為hIL-2 N端輕鏈L6融合物(SEQ ID NO: 379、SEQ ID NO: 357)及hIL-2 N端重鏈L6融合物(SEQ ID NO: 359、SEQ ID NO: 374)之六胺基酸連接子(L6) (SEQ ID NO: 355)，在人類抗DNA酶I抗體(殖株1H3)免疫球蛋白hIgG1重鏈或人類κ輕鏈之N端處融合之hIL-2。亦產生其中hIL-2部分係經由df或L6融合至重鏈及輕鏈兩者之C端的變化形式且將其表示為hIL-2 C端重鏈df (SEQ ID NO: 360、SEQ ID NO: 374)、hIL-2 C端重鏈L6融合物(SEQ ID NO: 361、SEQ ID: 374)、hIL-2 C端輕鏈df (SEQ ID NO: 379、SEQ ID NO: 362)、hIL-2 C端輕鏈L6融合物(SEQ ID NO: 379、SEQ ID NO: 363)。產生其他變化形式，其中CD25/IL-2Rα胞外域(胺基酸1至164) (SEQ ID NO: 126)融合至重

鏈或κ輕鏈之N端或C端以干擾IL-2與CD25之IL-2受體的結合(圖2)。在此等構築體中，人類CD25胞外域(胺基酸1至164) (SEQ ID NO: 126)係經由20胺基酸連接子(L20) (SEQ ID NO: 364)融合至人類IL-2，其接著直接融合或經由L6連接子(SEQ ID NO: 355)融合至N端處之1H3-hIgG1重鏈或輕鏈：hCD25-L20-hIL-2 N端重鏈df (SEQ ID NO: 365、SEQ ID NO: 374)、hCD25-L20-hIL-2 N端重鏈L6融合物(SEQ ID NO: 366、SEQ ID NO: 374)、hCD25-L20-hIL-2 N端輕鏈df (SEQ ID NO: 379、SEQ ID NO: 367)、hCD25-L20-hIL-2 N端輕鏈L6融合物(SEQ ID NO: 379、SEQ ID NO: 368)。最後，產生其中CD25/IL-2Rα胞外域部分(SEQ ID NO: 126)融合至重鏈及κ輕鏈之C端的一組最終變異體：hCD25-L20-hIL-2 C端重鏈df (SEQ ID NO: 369、SEQ ID NO: 374)、hCD25-L20-hIL-2 C端重鏈L6融合物(SEQ ID NO: 370、SEQ ID NO: 374)、hCD25-L20-hIL-2 C端輕鏈df (SEQ ID NO: 379、SEQ ID NO: 371)、hCD25-L20-hIL-2 C端輕鏈L6融合物(SEQ ID NO: 379、SEQ ID NO:372)。使用標準技術來產生、表現及蛋白A (Protein-A)純化此等抗體-hIL-2融合蛋白。在基於活體外細胞之磷酸化STAT5分析法中使用經方案D中所描述之8點、6倍連續滴定來評估上文所描述之16種N端或C端及連接子變異體。

【0171】 表1概述使用藉由FlowJo版本10軟體所計算之幾何平均螢光強度(gMFI)，在8點、6倍連續滴定曲線上計算之EC_{50}。亦計算各變異體相對於rhIL-2之倍數變化作為與rhIL-2陽性對照之活性相比的減弱程度之量測。一些EC_{50}值無法藉由GraphPad Prism 7軟體來計算且標記為未計算(Not Calculated；NC)；然而，基於劑量-滴定曲線，此等變異體不存在減弱。

【0172】 當與表現高親和力hIL-2受體(NK-92)或中等親和力hIL-2受體(TF1+IL-2Rβ)之細胞株上的rhIL-2相比較時，hIL-2部分與免疫球蛋白重鏈之N端或C端的融合未引起IL-2活性降低。當與在IL-2與抗體組分之間使用六胺基酸連接子(L6)的融合相比較時，hIL-2與融合蛋白之抗體組分的直接融合(df)未引起IL-2活性發生變化。類似地，當與rhIL-2相比較時，IL-2組分與抗體組分之重鏈或輕鏈的融合未引起IL-2活性發生變化。預測其中hCD25/hIL-2Rα部分係融合至hIL-2之所有N端或C端及連接子融合蛋白變異體展現融合蛋白與細胞上之hIL-2受體之CD25的結合減少。在實驗上，此等構築體對高親和力IL-2受體(NK-92)展現強烈減弱之hIL-2活性(至少45倍)且對中等hIL-2受體(TF1+IL-2Rβ)展現強烈減弱之hIL-2活性(18倍)。

表1. pSTAT5 EC_{50}及融合蛋白域變異體上之倍數變化

融合蛋白之HC或LC組分	HC及LC SEQ ID NO:	pSTAT5 EC_{50} (NK-92)	相對於rhIL-2之倍數變化 (NK-92)	基於劑量-滴定曲線之減弱 (NK-92)	pSTAT5 EC_{50} (TF1+IL-2Rβ)	相對於rhIL-2之倍數變化 (TF1+IL-2Rβ)	基於劑量-滴定曲線之減弱 (TF1+IL-2Rβ)
hIL-2 N端重鏈df	358, 374	<0.1 [a]	1[a]	未減弱	1.11	2	未減弱
hIL-2 N端重鏈L6融合物	359, 374	NC [a]	NC[a]	未減弱	0.19	0	未減弱
hIL-2 N端輕鏈df	379, 356	<0.1 [a]	1[a]	未減弱	0.52	1	未減弱
hIL-2 N端輕鏈L6融合物	379, 357	<0.1 [a]	0[a]	未減弱	0.13	0	未減弱
hIL-2 C端重鏈df	360, 374	<0.1[a]	0[a]	未減弱	<0.1	0	未減弱
hIL-2 C端重鏈L6融合物	361, 374	NC[a]	NC[a]	未減弱	<0.1	0	未減弱
hIL-2 C端輕鏈df	379, 362	NC[a]	NC[a]	未減弱	1.15	1	未減弱
hIL-2 C端輕鏈L6融合物	379, 363	<0.1[a]	0[a]	未減弱	0.25	0	未減弱
hCD25-L20-hIL-2 N端重鏈df	365, 374	7.42	1052	減弱	190.50 [a]	314[a]	減弱
hCD25-L20-hIL-2 N端重鏈L6融合物	366, 374	2.24	318	減弱	10.70	18	減弱

hCD25-L20-hIL-2 N端輕鏈df	379, 367	106.80	15149	減弱	328.50[a]	542[a]	減弱
hCD25-L20-hIL-2 N端輕鏈L6融合物	379, 368	4.45	631	減弱	27.88	46	減弱
hCD25-L20-hIL-2 C端重鏈df	369, 374	1.89	149	減弱	93.89[a]	104[a]	減弱
hCD25-L20-hIL-2 C端重鏈L6融合物	370, 374	6.09	479	減弱	90.53[a]	101[a]	減弱
hCD25-L20-hIL-2 C端輕鏈df	379, 371	0.58	45	減弱	156.90[a]	174[a]	減弱
hCD25-L20-hIL-2 C端輕鏈L6融合物	379, 372	1.76	138	減弱	221.90[a]	247[a]	減弱

NC=未計算；[a] =倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

實例2：抗體減弱之hIL-2融合蛋白變異體產生及其與重組人類CD25及/或人類CD122之結合動力學之測定

【0173】 由於各種N端或C端免疫球蛋白重鏈融合蛋白中之hIL-2活性未減少，因此指定為「1H3-hIgG1-L6-hIL-2」之hIL-2 C端重鏈L6融合物(SEQ ID NO: 361、374)係用作在hIL-2部分中具有取代之抗體減弱之hIL-2融合蛋白變異體的基礎構築體。將單、雙及/或多個胺基酸取代引入人類IL-2之所選殘基中，以便研究此等殘基在人類CD25/IL-2Rα及/或人類CD122/IL-2Rβ或CD132/IL-2Rγ (人類IL-2R次單元)之識別中發揮的作用。產生超過三百種在hIL-2部分中具有取代之抗體減弱之hIL-2融合蛋白變異體且在6輪中進行評估。首先使用基於流式細胞分析技術之磷酸化STAT5 (pSTAT5)分析法，在IL-2依賴性細胞株(NK-92及TF1+IL-2Rβ)上以及在劑量-滴定曲線中以固定濃度篩選此等變異體。磷酸化STAT5為IL-2活性之下游信號且用作IL-2效力之快照量測。亦進行IL-2依賴性細胞增殖分析法以量測在3至4天之時段內的IL-2活性。用於減弱之hIL-2選擇的準則包括：(1) IL-2對NK-92及TF1+IL-2Rβ細胞株兩者之效力降低，其中

對兩種細胞株之促效劑活性大於50%；及(2)中至高生產良率。

【0174】 人類抗DNA酶I抗體-hIL-2融合蛋白係藉由經由L6連接子使人類IL-2或人類IL-2變異體(SEQ ID NO: 1至344、377、378及575)與人類抗DNA酶I抗體(殖株1H3，具有人類IgG1同型)重鏈之C端融合來產生，該等人類抗DNA酶I抗體-hIL-2融合蛋白與hIgG1輕鏈(1H3-hκ LC；SEQ ID NO: 374)組合以產生1H3-hIgG1-L6-hIL-2融合蛋白(提供於表28中)。小鼠抗黃熱病病毒(yellow fever virus)抗體-hIL-2融合蛋白亦藉由經由L6連接子使人類IL-2變異體與具有降低免疫效應功能之D265A取代的小鼠抗黃熱病病毒抗體(殖株2D12，具有小鼠IgG1同型)重鏈之C端融合來產生，該等小鼠抗黃熱病病毒抗體-hIL-2融合蛋白與2D12-mIgG1輕鏈(2D12-mκ LC；SEQ ID NO: 376)組合以產生2D12-mIgG1-D265A-L6-hIL-2融合蛋白(提供於表28中)。此等小鼠抗黃熱病病毒抗體-hIL-2融合蛋白中之一些在人類IgG1恆定區上格式化且以與上文所描述使用相同之方式產生，該等小鼠抗黃熱病病毒抗體-hIL-2融合蛋白與2D12-hκ輕鏈(2D12-hκ LC；SEQ ID NO: 573)組合。IL-2胺基酸取代之迭代進行六輪(指定為第1至6組)。使用標準技術來產生、表現及蛋白A純化1H3-hIgG1-L6-hIL-2、2D12-mIgG1-D265A-L6-hIL-2及2D12-hIgG1-L6-hIL-2融合蛋白。

【0175】 第1組僅含有初始系列之2D12-mIgG1-D265A-L6-hIL-2或2D12-hIgG1-L6-hIL-2融合蛋白，其包含人類IL-2中之取代或取代之組合，該等取代經預測僅參與與IL-2受體次單元CD25/IL-2Rα、CD122/IL-2Rβ或CD132/IL-2Rγ中之一者的結合。此組中之融合蛋白包括以下對IL-2之取代，該等取代經預測調節與CD25/IL-2Rα之結合：F42K (SEQ ID NO: 1)、V69A (SEQ ID NO: 2)、V69E (SEQ ID NO: 3)、V69F (SEQ ID

NO: 4)、V69G (SEQ ID NO: 5)、V69H (SEQ ID NO: 6)、V69I (SEQ ID NO: 7)、V69K (SEQ ID NO: 8)、V69L (SEQ ID NO: 9)、V69M (SEQ ID NO: 10)、V69Q (SEQ ID NO: 11)、V69S (SEQ ID NO: 12)、V69T (SEQ ID NO: 13)、V69W (SEQ ID NO: 14)、V69Y (SEQ ID NO: 15)、V69R (SEQ ID NO: 581)、(F42K/F44K) (SEQ ID NO: 16)、(F44K/Y45R) (SEQ ID NO: 17)、(F42K/V69R) (SEQ ID NO: 18)、(Y45R/V69R) (SEQ ID NO: 19)、(F42K/F44K/Y45R) (SEQ ID NO: 20)、(F42A/Y45A/L72G) (SEQ ID NO: 574)、(R38A/F42K/Y45R) (SEQ ID NO: 21)、(R38E/F42K/Y45R) (SEQ ID NO: 22)、(K43E/F42K/Y45R) (SEQ ID NO: 23)、(K43T/F42K/Y45R) (SEQ ID NO: 24)、(F42K/Y45R/E62A) (SEQ ID NO: 25)、(P65R/F42K/Y45R) (SEQ ID NO: 26)、(P65S/F42K/Y45R) (SEQ ID NO: 27)、(V69A/F42K/Y45R) (SEQ ID NO: 28)、(V69D/F42K/Y45R) (SEQ ID NO: 29)或(V69R/F42K/Y45R) (SEQ ID NO: 30)。此組中之取代包括以下經預測調節與CD122/IL-2Rβ之結合的取代：D20A (SEQ ID NO: 31)、D20N (SEQ ID NO: 32)、D20K (SEQ ID NO: 33)、N88A (SEQ ID NO: 34)、N88G (SEQ ID NO: 35)、N88H (SEQ ID NO: 36)、N88K (SEQ ID NO: 37)、(D20A/D84A) (SEQ ID NO: 38)、(D20A/E15A) (SEQ ID NO: 39)、(D20A/E95A) (SEQ ID NO: 40)、(D20A/N88A) (SEQ ID NO: 41)、(D20A/S87A) (SEQ ID NO: 42)、(D84A/N88A) (SEQ ID NO: 43)、(E15A/N88A) (SEQ ID NO: 44)或(S87A/N88A) (SEQ ID NO: 45)。第1組亦包括以下對IL-2之取代，該等取代經預測調節IL-2與CD132/IL-2-Rγ之結合：Q126L (SEQ ID NO: 377)或Q126E (SEQ ID NO: 378)。未預測第1組中所研究之IL-2取代調節與IL-

2受體次單元中之多於一者的結合。

【0176】 第2組含有一系列1H3-hIgG1-L6-hIL-2融合蛋白，其包含人類IL-2中之一或多種取代，該一或多種取代經預測僅參與CD25/IL-2Rα結合。此組中之融合蛋白包括以下對IL-2之取代，該等取代經預測調節與CD25/IL-2Rα之結合：R38A (SEQ ID NO: 46)、R38D (SEQ ID NO: 47)、R38E (SEQ ID NO: 48)、R38Q (SEQ ID NO: 49)、F42R (SEQ ID NO: 50)、F42A (SEQ ID NO: 51)、F42D (SEQ ID NO: 52)、F42H (SEQ ID NO: 53)、K43A (SEQ ID NO: 54)、K43E (SEQ ID NO: 55)、K43Q (SEQ ID NO: 56)、Y45A (SEQ ID NO: 57)、Y45K (SEQ ID NO: 58)、Y45S (SEQ ID NO: 59)、Y45R (SEQ ID NO: 60)、E61A (SEQ ID NO: 61)、E61R (SEQ ID NO: 62)、E61K (SEQ ID NO: 63)、E62A (SEQ ID NO: 64)、E62R (SEQ ID NO: 65)、E62K (SEQ ID NO: 66)、E62Y (SEQ ID NO: 67)、E68Y (SEQ ID NO: 68)、E68A (SEQ ID NO: 69)、E68K (SEQ ID NO: 70)、E68R (SEQ ID NO: 71)、E68L (SEQ ID NO: 72)、L72Y (SEQ ID NO: 73)、L72R (SEQ ID NO: 74)、L72A (SEQ ID NO: 75)、L72D (SEQ ID NO: 76)、L72H (SEQ ID NO: 77)、L72F (SEQ ID NO: 78)、(R38D/E61R) (SEQ ID NO: 79)、(R38D/E61R/K43E) (SEQ ID NO: 80)或(T3A/F42A/Y45A/L72G/C125A) (SEQ ID NO: 81)。將取代T3A引入至IL-2胺基酸序列中以移除人類IL-2上經預測之O連接之醣基化部位(參見例如國際公開案第WO2012/107417號)且將取代C125A引入至IL-2胺基酸序列中以移除未成對之半胱胺酸殘基(參見例如國際公開案第WO2018/184964號)。未預測第2組中所研究之IL-2取代調節IL-2與CD132/IL-2-Rγ之結合，亦未預測此等取代調節與IL-2受體次單元中之多

於一者的結合。

【0177】第3組含有一系列1H3-hIgG1-L6-hIL-2融合蛋白，其包含人類IL-2中之一或多種取代，該一或多種取代經預測僅參與CD122/IL-2Rβ結合。此組中之融合蛋白包括以下對IL-2之取代，該等取代經預測調節與CD122/IL-2Rβ之結合：E15A (SEQ ID NO: 82)、E15R (SEQ ID NO: 83)、E15K (SEQ ID NO: 84)、H16A (SEQ ID NO: 85)、H16Y (SEQ ID NO: 86)、H16E (SEQ ID NO: 87)、L19A (SEQ ID NO: 88)、D20I (SEQ ID NO: 89)、D20S (SEQ ID NO: 90)、D20H (SEQ ID NO: 91)、D20T (SEQ ID NO: 92)、D20W (SEQ ID NO: 93)、D20Y (SEQ ID NO: 94)、D20R (SEQ ID NO: 95)、D20F (SEQ ID NO: 96)、R81A (SEQ ID NO: 97)、D84A (SEQ ID NO: 98)、D84R (SEQ ID NO: 99)、D84K (SEQ ID NO: 100)、S87A (SEQ ID NO: 101)、N88Y (SEQ ID NO: 102)、N88D (SEQ ID NO: 103)、N88R (SEQ ID NO: 104)、N88E (SEQ ID NO: 105)、N88F (SEQ ID NO: 106)、N88I (SEQ ID NO: 107)、I92A (SEQ ID NO: 108)、I92Y (SEQ ID NO: 109)、I92S (SEQ ID NO: 110)、I92F (SEQ ID NO: 111)、I92R (SEQ ID NO: 112)、I92D (SEQ ID NO: 113)、I92E (SEQ ID NO: 114)、E95A (SEQ ID NO: 115)、E95R (SEQ ID NO: 116)、E95K (SEQ ID NO: 117)、(D20Y/H16E) (SEQ ID NO: 118)、(D20Y/H16A) (SEQ ID NO: 119)、(D20Y/H16Y) (SEQ ID NO: 120)、(D20Y/I92A) (SEQ ID NO: 121)、(D20Y/I92S) (SEQ ID NO: 122)、(D20Y/I92R) (SEQ ID NO: 123)、(D20Y/E95R) (SEQ ID NO: 124)或(D20Y/E95A) (SEQ ID NO: 125)。

【0178】第4組含有一系列融合蛋白，其含有融合至CD25/IL-2Rα

胞外域部分(SEQ ID NO: 126)之1H3-hIgG1-L6-hIL-2 HC、20胺基酸連接子(L20) (SEQ ID NO: 364)及人類IL-2變異體，該人類IL-2變異體包含對經預測參與與CD122/IL-2Rβ之結合的殘基之一或多種取代。此組中之融合蛋白包括以下對IL-2之取代，該等取代經預測調節與CD122/IL-2Rβ之結合：E15A (SEQ ID NO: 82)、D20I (SEQ ID NO: 89)、D20S (SEQ ID NO: 90)、D20H (SEQ ID NO: 91)、D20W (SEQ ID NO: 93)、D20Y (SEQ ID NO: 94)、D20R (SEQ ID NO: 95)、D20F (SEQ ID NO: 96)、D84K (SEQ ID NO: 100)、S87A (SEQ ID NO: 101)、N88Y (SEQ ID NO: 102)、N88D (SEQ ID NO: 103)、N88R (SEQ ID NO: 104)、N88E (SEQ ID NO: 105)、N88F (SEQ ID NO: 106)、N88I (SEQ ID NO: 107)、I92A (SEQ ID NO: 108)、E95A (SEQ ID NO: 115)或E95K (SEQ ID NO: 117)。此組中之抗體減弱之hIL-2融合蛋白表示為1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2。

【0179】 第5組含有一系列1H3-hIgG1-L6-hIL-2，其包含IL-2中之取代之組合，該等取代經預測參與IL-2與CD25/IL-2Rα及與CD122/IL-2Rβ或CD132/IL-2Rγ之結合。另外，一些變異體在hIL-2部分之N端的前三個胺基酸中具有缺失(Δ1-3APT)。第5組中之融合蛋白包括以下對IL-2之取代，該等取代經預測調節IL-2與CD25/IL-2Rα及與CD122/IL-2Rβ之結合：(F42D/D20A) (SEQ ID NO: 127)、(F42R/D20A) (SEQ ID NO: 128)、(F42K/D20A) (SEQ ID NO: 129)、(F42A/D20A) (SEQ ID NO: 130)、(F42H/D20A) (SEQ ID NO: 131)、(Y45R/D20A) (SEQ ID NO: 132)、(Y45K/D20A) (SEQ ID NO: 133)、(R38N/D20A) (SEQ ID NO: 134)、(R38G/D20A) (SEQ ID NO: 135)、(R38H/D20A) (SEQ ID NO:

136)、(R38I/D20A) (SEQ ID NO: 137)、(R38L/D20A) (SEQ ID NO: 138)、(R38M/D20A) (SEQ ID NO: 139)、(R38F/D20A) (SEQ ID NO: 140)、(R38P/D20A) (SEQ ID NO: 141)、(R38S/D20A) (SEQ ID NO: 142)、(R38T/D20A) (SEQ ID NO: 143)、(R38W/D20A) (SEQ ID NO: 144)、(R38Y/D20A) (SEQ ID NO: 145)、(R38V/D20A) (SEQ ID NO: 146)、(R38A/D20A) (SEQ ID NO: 147)、(R38Q/D20A) (SEQ ID NO: 148)、(D20A/R38E) (SEQ ID NO: 149)、(R38D/D20A) (SEQ ID NO: 150)、(K43E/D20A) (SEQ ID NO: 151)、(E61A/D20A) (SEQ ID NO: 152)、(E62A/D20A) (SEQ ID NO: 153)、(E62Y/D20A) (SEQ ID NO: 154)、(L72D/D20A) (SEQ ID NO: 155)、(L72H/D20A) (SEQ ID NO: 156)、(L72R/D20A) (SEQ ID NO: 157)、(F42D/I92D) (SEQ ID NO: 158)、(F42R/I92D) (SEQ ID NO: 159)、(F42H/I92D) (SEQ ID NO: 160)、(F42A/I92D) (SEQ ID NO: 161)、(H16A/F42A) (SEQ ID NO: 575)、(K43E/I92D) (SEQ ID NO: 162)、(Y45R/I92D) (SEQ ID NO: 163)、(Y45K/I92D) (SEQ ID NO: 164)、(E62A/I92D) (SEQ ID NO: 165)、(E62Y/I92D) (SEQ ID NO: 166)、(L72D/I92D) (SEQ ID NO: 167)、(L72H/I92D) (SEQ ID NO: 168)、(L72R/I92D) (SEQ ID NO: 169)、(R38D/I92D) (SEQ ID NO: 170)、(R38E/I92D) (SEQ ID NO: 171)、(R38Q/I92D) (SEQ ID NO: 172)、(R38A/I92D) (SEQ ID NO: 173)、(R38E/N88R) (SEQ ID NO: 174)、(R38E/D84R) (SEQ ID NO: 175)、(R38E/D84K) (SEQ ID NO: 176)、(F42A/Y45R/D20A) (SEQ ID NO: 177)、(F42H/Y45R/D20A) (SEQ ID NO: 178)、(R38D/E61R/D20A) (SEQ ID NO: 179)、(R38E/E61R/D20A) (SEQ ID NO: 180)、

(R38Q/E61R/D20A) (SEQ ID NO: 181)、(R38A/E61R/D20A) (SEQ ID NO: 182)、(R38A/D20A/E95A) (SEQ ID NO: 183)、(D20A/E95A/R38D) (SEQ ID NO: 184)、(D20A/ E95A/R38E) (SEQ ID NO: 185)、(D20A/E95A/R38Q) (SEQ ID NO: 186)、(D20A/E95A/F42R) (SEQ ID NO: 187)、(D20A/E95A/F42A) (SEQ ID NO: 188)、(D20A/E95A/F42D) (SEQ ID NO: 189)、(D20A/E95A/F42H) (SEQ ID NO: 190)、(D20A/E95A/F42K) (SEQ ID NO: 191)、(D20A/E95A/K43A) (SEQ ID NO: 192)、(D20A/E95A/K43E) (SEQ ID NO: 193)、(D20A/E95A/K43Q) (SEQ ID NO: 194)、(D20A/E95A/Y45A) (SEQ ID NO: 195)、(D20A/E95A/Y45K) (SEQ ID NO: 196)、(D20A/E95A/Y45S) (SEQ ID NO: 197)、(D20A/E95A/Y45R) (SEQ ID NO: 198)、(D20A/E95A/E61A) (SEQ ID NO: 199)、(D20A/E95A/E62A) (SEQ ID NO: 200)、(D20A/E95A/E62R) (SEQ ID NO: 201)、(D20A/E95A/E62K) (SEQ ID NO: 202)、(D20A/E95A/E62Y) (SEQ ID NO: 203)、(D20A/E95A/E68Y) (SEQ ID NO: 204)、(D20A/E95A/E68A) (SEQ ID NO: 205)、(D20A/E95A/E68L) (SEQ ID NO: 206)、(D20A/E95A/L72Y) (SEQ ID NO: 207)、(D20A/E95A/L72R) (SEQ ID NO: 208)、(D20A/E95A/L72A) (SEQ ID NO: 209)、(D20A/E95A/L72D) (SEQ ID NO: 210)、(D20A/E95A/L72H) (SEQ ID NO: 211)、(D20A/E95A/L72F) (SEQ ID NO: 212)、(F42K/Y45R/D20A/S87A) (SEQ ID NO: 213)、(F42K/Y45R/D20A/E95A) (SEQ ID NO: 214)、(D20A/R38E/C125A) (SEQ ID NO: 215)、(T3A/D20A/R38E) (SEQ ID NO: 216)、(T3A/D20A/R38E/C125A) (SEQ ID NO: 217)、(Δ1-3APT/D20A/R38E)

(SEQ ID NO: 218)或(Δ1-3APT/D20A/R38E/C125A) (SEQ ID NO: 219)。第5組中之融合蛋白包括以下對IL-2之取代，該等取代經預測調節IL-2與CD25/IL-2Rα及與CD132/IL-2R之結合：(R38E/Q22A) (SEQ ID NO: 220)、(R38E/T123A) (SEQ ID NO: 221)、(R38E/I129A) (SEQ ID NO: 222)、(R38E/S130A) (SEQ ID NO: 223)、(R38E/Q126A) (SEQ ID NO: 224)、(R38E/Q126D) (SEQ ID NO: 225)、(R38E/Q126V) (SEQ ID NO: 226)、(R38E/Q22A/S130A) (SEQ ID NO: 227)、(F42K/Y45R/Q126D) (SEQ ID NO: 228)或(D20A/E95A/Q126D) (SEQ ID NO: 229)。其中編號係根據IL-2序列之第5組抗體減弱之hIL-2融合蛋白之hIL-2序列的突變列於SEQ ID NO: 127至229及575中。

【0180】 第6組含有一系列1H3-hIgG1-L6-hIL-2融合蛋白，其包含人類IL-2中之取代之組合，該等取代經預測參與IL-2與CD25/IL-2Rα及與CD122/IL-2Rβ而非與CD132/IL-2Rγ之結合。第6組中之融合蛋白包括IL-2中之取代的以下組合，該等取代經預測調節IL-2與CD25/IL-2Rα及CD122/IL-2Rβ之結合：(D20A/E61R) (SEQ ID NO: 230)、(D20A/E61N) (SEQ ID NO: 231)、(D20A/E61D) (SEQ ID NO: 232)、(D20A/E61Q) (SEQ ID NO: 233)、(D20A/E61G) (SEQ ID NO: 234)、(D20A/E61H) (SEQ ID NO: 235)、(D20A/E61I) (SEQ ID NO: 236)、(D20A/E61L) (SEQ ID NO: 237)、(D20A/E61K) (SEQ ID NO: 238)、(D20A /E61M) (SEQ ID NO: 239)、(D20A/E61F) (SEQ ID NO: 240)、(D20A/E61P) (SEQ ID NO: 241)、(D20A/E61S) (SEQ ID NO: 242)、(D20A/E61T) (SEQ ID NO: 243)、(D20A/E61W) (SEQ ID NO: 244)、(D20A/E61Y) (SEQ ID NO: 245)、(D20A/E61V) (SEQ ID NO: 246)、(D20A/F42N)

(SEQ ID NO: 247)、(D20A/F42Q) (SEQ ID NO: 248)、(D20A/F42E) (SEQ ID NO: 249)、(D20A F42G) (SEQ ID NO: 250)、(D20A/F42I) (SEQ ID NO: 251)、(D20A/F42L) (SEQ ID NO: 252)、(D20A/F42M) (SEQ ID NO: 253)、(D20A/F42P) (SEQ ID NO: 254)、(D20A/F42S) (SEQ ID NO: 255)、(D20A/F42T) (SEQ ID NO: 256)、(D20A /F42W) (SEQ ID NO: 257)、(D20A/F42Y) (SEQ ID NO: 258)、(D20A/F42V) (SEQ ID NO: 259)、(D20A/Y45A) (SEQ ID NO: 260)、(D20A/Y45N) (SEQ ID NO: 261)、(D20A/Y45D) (SEQ ID NO: 262)、(D20A/Y45Q) (SEQ ID NO: 263)、(D20A/Y45E) (SEQ ID NO: 264)、(D20A/Y45G) (SEQ ID NO: 265)、(D20A/Y45H) (SEQ ID NO: 266)、(D20A/Y45I) (SEQ ID NO: 267)、(D20A/Y45L) (SEQ ID NO: 268)、(D20A/Y45M) (SEQ ID NO: 269)、(D20A/Y45F) (SEQ ID NO: 270)、(D20A/Y45P) (SEQ ID NO: 271)、(D20A/Y45S) (SEQ ID NO: 272)、(D20A/Y45T) (SEQ ID NO: 273)、(D20A/Y45W) (SEQ ID NO: 274)、(D20A/Y45V) (SEQ ID NO: 275)、(I92D/F42N) (SEQ ID NO: 276)、(I92D/F42Q) (SEQ ID NO: 277)、(I92D/F42E) (SEQ ID NO: 278)、(I92D/F42G) (SEQ ID NO: 279)、(I92D/F42I) (SEQ ID NO: 280)、(I92D/F42L) (SEQ ID NO: 281)、(I92D/F42K) (SEQ ID NO: 282)、(I92D/F42M) (SEQ ID NO: 283)、(I92D/F42P) (SEQ ID NO: 284)、(I92D/F42S) (SEQ ID NO: 285)、(I92D/F42T) (SEQ ID NO: 286)、(I92D/F42W) (SEQ ID NO: 287)、(I92D/F42Y) (SEQ ID NO: 288)、(I92D/F42V) (SEQ ID NO: 289)、(I92D/Y45A) (SEQ ID NO: 290)、(I92D/Y45N) (SEQ ID NO: 291)、(I92D/Y45D) (SEQ ID NO: 292)、(I92D/Y45Q) (SEQ ID NO:

293)、(I92D/Y45E) (SEQ ID NO: 294)、(I92D/Y45G) (SEQ ID NO: 295)、(I92D/Y45H) (SEQ ID NO: 296)、(I92D/Y45I) (SEQ ID NO: 297)、(I92D/Y45L) (SEQ ID NO: 298)、(I92D/Y45M) (SEQ ID NO: 299)、(I92D/Y45F) (SEQ ID NO: 300)、(I92D/Y45P) (SEQ ID NO: 301)、(I92D/Y45S) (SEQ ID NO: 302)、(I92D/Y45T) (SEQ ID NO: 303)、(I92D/Y45W) (SEQ ID NO: 304)、(I92D/Y45V) (SEQ ID NO: 305)、(R38E/D20H) (SEQ ID NO: 306)、(R38E/D20S) (SEQ ID NO: 307)、(F42A/N88R) (SEQ ID NO: 308)、(F42A/N88D) (SEQ ID NO: 309)、(R38E/D84A) (SEQ ID NO: 310)、(R38E/D84N) (SEQ ID NO: 311)、(R38E/D84Q) (SEQ ID NO: 312)、(R38E/D84E) (SEQ ID NO: 313)、(R38E/D84G) (SEQ ID NO: 314)、(R38E/D84H) (SEQ ID NO: 315)、(R38E/D84I) (SEQ ID NO: 316)、(R38E/D84L) (SEQ ID NO: 317)、(R38E/D84M) (SEQ ID NO: 318)、(R38E/D84F) (SEQ ID NO: 319)、(R38E/D84P) (SEQ ID NO: 320)、(R38E/D84S) (SEQ ID NO: 321)、(R38E/D84T) (SEQ ID NO: 322)、(R38E/D84W) (SEQ ID NO: 323)、(R38E/D84Y) (SEQ ID NO: 324)、(R38E/D84V) (SEQ ID NO: 325)、(R38E/I92A) (SEQ ID NO: 326)、(R38E/I92R) (SEQ ID NO: 327)、(R38E/I92N) (SEQ ID NO: 328)、(R38E/I92Q) (SEQ ID NO: 329)、(R38E/I92E) (SEQ ID NO: 330)、(R38E/I92G) (SEQ ID NO: 331)、(R38E/I92H) (SEQ ID NO: 332)、(R38E/I92L) (SEQ ID NO: 333)、(R38E/I92K) (SEQ ID NO: 334)、(R38E/I92M) (SEQ ID NO: 335)、(R38E/I92F) (SEQ ID NO: 336)、(R38E/I92P) (SEQ ID NO: 337)、(R38E/I92S) (SEQ ID NO: 338)、(R38E/I92T) (SEQ ID NO:

339)、(R38E/I92W) (SEQ ID NO: 340)、(R38E/I92Y) (SEQ ID NO: 341)、(R38E/I92V) (SEQ ID NO: 342)、(R38E/H16E) (SEQ ID NO: 343)或(R38K/D20A) (SEQ ID NO: 344)。其中編號係根據IL-2序列之第6組抗體減弱之hIL-2融合蛋白之hIL-2序列的突變列於SEQ ID NO: 230至344中。

【0181】 使用生物層干涉量測術(bio-layer interferometry；BLI)測定個別重組人類CD25及人類CD122與一些經純化之1H3-hIgG1-L6-hIL-2變異體蛋白之結合動力學。簡言之，在25℃下使用Octet Red96儀器(Pall ForteBio)進行結合實驗。將C端聚組胺酸標記之人類CD25及人類CD122胞外域捕獲於抗His2感測器(Pall ForteBio)上。將負載受體之感測器浸漬於各1H3-hIgG-L6-hIL-2變異體之7點連續3倍稀釋液中，以300 nM之最高濃度開始。1H3-hIgG1-L6-hIL-2融合蛋白經稀釋為分析法緩衝液，該分析法緩衝液係由補充有0.1% BSA、0.02% Tween-20之磷酸鹽緩衝鹽水(PBMS) (pH 7.2)組成。使用10 mM甘胺酸緩衝液(pH 1.7)更新負載之感測器。使用單價模型計算動力學常數。

【0182】 表2記錄74種結合至重組人類CD25或重組人類CD122之免疫球蛋白-hIL-2融合蛋白變異體之締合常數(k_{on})、解離常數(k_{off})及平衡常數(K_D)。

表2. 藉由Octet BLI進行之1H3-hIgG-L6-hIL-2融合蛋白與重組人類CD25或CD122之結合動力學

1H3-hIgG1-L6-hIL-2融合蛋白	**hIL-2變異體之SEQ ID NO**	**由IL-2取代靶向之經預測之受體次單元**	**K_D (M)**	**k_{on} (1/Ms)**	**k_{off} (1/s)**
1H3-hIgG1-L6-hIL-2 WT	345	N/A	3.20E-10	5.90E+05	1.90E-04
1H3-hIgG1-L6-hIL-2 (E15A)	82	CD122	2.04E-09	1.15E+05	2.35E-04
1H3-hIgG1-L6-hIL-2 (E15R)	83	CD122	3.41E-09	9.48E+04	3.23E-04
1H3-hIgG1-L6-hIL-2 (E15K)	84	CD122	1.39E-09	1.71E+05	2.37E-04

1H3-hIgG1-L6-hIL-2 (H16A)	85	CD122	1.68E-09	1.71E+05	2.87E-04
1H3-hIgG1-L6-hIL-2 (H16Y)	86	CD122	1.46E-09	1.50E+05	2.20E-04
1H3-hIgG1-L6-hIL-2 (H16E)	87	CD122	1.40E-09	1.57E+05	2.20E-04
1H3-hIgG1-L6-hIL-2 (L19A)	88	CD122	1.76E-09	2.03E+05	3.57E-04
1H3-hIgG1-L6-hIL-2 (D20I)	89	CD122	1.16E-09	1.70E+05	1.98E-04
1H3-hIgG1-L6-hIL-2 (D20S)	90	CD122	6.24E-10	1.74E+05	1.09E-04
1H3-hIgG1-L6-hIL-2 (D20H)	91	CD122	1.13E-09	1.88E+05	2.12E-04
1H3-hIgG1-L6-hIL-2 (D20W)	93	CD122	1.01E-09	1.87E+05	1.90E-04
1H3-hIgG1-L6-hIL-2 (D20Y)	94	CD122	1.42E-09	1.51E+05	2.14E-04
1H3-hIgG1-L6-hIL-2 (D20R)	95	CD122	1.21E-09	1.44E+05	1.75E-04
1H3-hIgG1-L6-hIL-2 (D20F)	96	CD122	1.57E-09	1.75E+05	2.75E-04
1H3-hIgG1-L6-hIL-2 (R38A)	46	CD25	5.55E-09	1.82E+05	1.01E-03
1H3-hIgG1-L6-hIL-2 (R38D)	47	CD25	1.86E-09	8.84E+05	1.64E-03
1H3-hIgG1-L6-hIL-2 (R38E)	48	CD25	8.74E-09	3.31E+05	2.89E-03
1H3-hIgG1-L6-hIL-2 (R38Q)	49	CD25	6.33E-09	4.83E+05	3.05E-03
1H3-hIgG1-L6-hIL-2 (F42R)	50	CD25	2.63E-09	1.59E+06	4.20E-03
1H3-hIgG1-L6-hIL-2 (F42A)	51	CD25	9.25E-09	9.89E+05	9.15E-03
1H3-hIgG1-L6-hIL-2 (F42D)	52	CD25	4.51E-09	1.70E+06	7.64E-03
1H3-hIgG1-L6-hIL-2 (F42H)	53	CD25	6.84E-09	8.23E+05	5.63E-03
1H3-hIgG1-L6-hIL-2 (K43A)	54	CD25	4.79E-09	2.59E+05	1.24E-03
1H3-hIgG1-L6-hIL-2 (K43E)	55	CD25	5.66E-09	4.52E+05	2.56E-03
1H3-hIgG1-L6-hIL-2 (K43Q)	56	CD25	2.28E-09	4.49E+05	1.02E-03
1H3-hIgG1-L6-hIL-2 (Y45A)	57	CD25	3.66E-09	4.29E+05	1.57E-03
1H3-hIgG1-L6-hIL-2 (Y45K)	58	CD25	9.03E-09	5.22E+05	4.71E-03
1H3-hIgG1-L6-hIL-2 (Y45S)	59	CD25	2.45E-09	5.05E+05	1.24E-03
1H3-hIgG1-L6-hIL-2 (Y45R)	60	CD25	1.96E-09	6.46E+05	1.27E-03
1H3-hIgG1-L6-hIL-2 (E61A)	61	CD25	7.00E-09	3.21E+05	2.25E-03
1H3-hIgG1-L6-hIL-2 (E61R)	62	CD25	8.84E-09	1.22E+06	1.08E-02
1H3-hIgG1-L6-hIL-2 (E61K)	63	CD25	1.56E-08	3.16E+05	4.94E-03
1H3-hIgG1-L6-hIL-2 (E62A)	64	CD25	1.23E-08	3.79E+05	4.67E-03
1H3-hIgG1-L6-hIL-2 (E62R)	65	CD25	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (E62K)	66	CD25	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (E62Y)	67	CD25	1.55E-08	2.91E+05	4.50E-03
1H3-hIgG1-L6-hIL-2 (E68Y)	68	CD25	8.18E-09	1.80E+05	1.47E-03
1H3-hIgG1-L6-hIL-2 (E68A)	69	CD25	4.49E-09	1.45E+05	6.52E-04
1H3-hIgG1-L6-hIL-2 (E68K)	70	CD25	9.63E-09	2.54E+05	2.44E-03
1H3-hIgG1-L6-hIL-2 (E68R)	71	CD25	1.16E-08	2.54E+05	2.96E-03
1H3-hIgG1-L6-hIL-2 (E68L)	72	CD25	8.62E-09	1.02E+05	8.82E-04
1H3-hIgG1-L6-hIL-2 (I92R)	112	CD122	2.54E-09	1.08E+05	2.76E-04
1H3-hIgG1-L6-hIL-2 (I92D)	113	CD122	7.94E-09	4.95E+04	3.93E-04
1H3-hIgG1-L6-hIL-2 (I92E)	114	CD122	2.41E-09	8.54E+04	2.06E-04
1H3-hIgG1-L6-hIL-2 (E95A)	115	CD122	3.11E-09	1.47E+05	4.58E-04
1H3-hIgG1-L6-hIL-2 (E95R)	116	CD122	2.29E-09	1.14E+05	2.61E-04
1H3-hIgG1-L6-hIL-2 (E95K)	117	CD122	3.25E-09	1.25E+05	4.07E-04
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/D20A/S87A)	213	CD25+CD122	3.25E-08	1.24E+05	4.05E-03
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/D20A/E95A)	214	CD25+CD122	未觀測到結合		

1H3-hIgG1-L6-hIL-2 (F42K/Y45R/Q126D)	228	CD25+CD132	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Q126D)	229	CD122+CD132	3.34E-09	4.87E+04	1.62E-04
1H3-hIgG1-L6-hIL-2 (R38D/E61R)	79	CD25	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (R38D/E61R/K43E)	80	CD25	未觀測到結合		

【0183】 表3記錄74種結合至重組人類CD122之1H3-hIgG1-L6-hIL-2融合蛋白之締合常數(k_{on})、解離常數(k_{off})及平衡常數(K_D)。

表3. 藉由Octet BLI進行之1H3-hIgG-L6-hIL-2融合蛋白與重組人類CD122之結合動力學

1H3-hIgG-L6-hIL-2融合蛋白	**hIL-2變異體之SEQ ID NO**	**由IL-2取代靶向之經預測之受體次單元**	**K_D (M)**	**k_{on} (1/Ms)**	**k_{off} (1/s)**
1H3-hIgG1-L6-hIL-2 WT	345[a]	N/A	5.60E-09	7.00E+05	3.90E-03
1H3-hIgG1-L6-hIL-2 (E15A)	82[b]	CD122	8.89E-09	1.75E+05	1.56E-03
1H3-hIgG1-L6-hIL-2 (E15R)	83	CD122	3.69E-09	1.46E+05	5.38E-04
1H3-hIgG1-L6-hIL-2 (E15K)	84	CD122	3.56E-09	2.42E+05	8.62E-04
1H3-hIgG1-L6-hIL-2 (H16A)	85	CD122	1.78E-09	1.55E+06	2.76E-03
1H3-hIgG1-L6-hIL-2 (H16Y)	86	CD122	4.36E-09	9.97E+05	4.35E-03
1H3-hIgG1-L6-hIL-2 (H16E)	87	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (L19A)	88	CD122	1.03E-08	4.72E+05	4.87E-03
1H3-hIgG1-L6-hIL-2 (D20I)	89	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (D20S)	90	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (D20H)	91	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (D20W)	93	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (D20Y)	94	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (D20R)	95	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (D20F)	96	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (R38A)	46	CD25	1.38E-08	2.08E+05	2.87E-03
1H3-hIgG1-L6-hIL-2 (R38D)	47	CD25	2.20E-09	4.28E+05	9.42E-04
1H3-hIgG1-L6-hIL-2 (R38E)	48	CD25	5.81E-09	4.64E+05	2.69E-03
1H3-hIgG1-L6-hIL-2 (R38Q)	49	CD25	1.01E-09	2.81E+05	2.84E-04
1H3-hIgG1-L6-hIL-2 (F42R)	50	CD25	5.47E-09	5.42E+05	2.96E-03
1H3-hIgG1-L6-hIL-2 (F42A)	51	CD25	5.97E-09	4.19E+05	2.50E-03
1H3-hIgG1-L6-hIL-2 (F42D)	52	CD25	1.04E-08	2.38E+05	2.46E-03
1H3-hIgG1-L6-hIL-2 (F42H)	53	CD25	6.33E-09	4.45E+05	2.81E-03
1H3-hIgG1-L6-hIL-2 (K43A)	54	CD25	1.03E-08	2.85E+05	2.94E-03
1H3-hIgG1-L6-hIL-2 (K43E)	55	CD25	5.47E-09	3.65E+05	2.00E-03
1H3-hIgG1-L6-hIL-2 (K43Q)	56	CD25	4.21E-09	5.14E+05	2.17E-03
1H3-hIgG1-L6-hIL-2 (Y45A)	57	CD25	4.93E-09	4.51E+05	2.22E-03

1H3-hIgG1-L6-hIL-2 (Y45K)	58	CD25	6.56E-09	3.55E+05	2.33E-03
1H3-hIgG1-L6-hIL-2 (Y45S)	59	CD25	6.96E-09	5.07E+05	3.53E-03
1H3-hIgG1-L6-hIL-2 (Y45R)	60	CD25	7.58E-09	4.36E+05	3.31E-03
1H3-hIgG1-L6-hIL-2 (E61A)	61	CD25	1.34E-08	3.13E+05	4.18E-03
1H3-hIgG1-L6-hIL-2 (E61R)	62	CD25	1.30E-08	4.56E+05	5.91E-03
1H3-hIgG1-L6-hIL-2 (E61K)	63	CD25	1.56E-08	3.16E+05	4.94E-03
1H3-hIgG1-L6-hIL-2 (E62A)	64	CD25	1.23E-08	3.79E+05	4.67E-03
1H3-hIgG1-L6-hIL-2 (E62R)	65	CD25	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (E62K)	66	CD25	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (E62Y)	67	CD25	1.55E-08	2.91E+05	4.50E-03
1H3-hIgG1-L6-hIL-2 (E68Y)	68	CD25	8.18E-09	1.80E+05	1.47E-03
1H3-hIgG1-L6-hIL-2 (E68A)	69	CD25	4.49E-09	1.45E+05	6.52E-04
1H3-hIgG1-L6-hIL-2 (E68K)	70	CD25	1.05E-08	2.02E+05	2.12E-03
1H3-hIgG1-L6-hIL-2 (E68R)	71	CD25	8.51E-09	2.27E+05	1.93E-03
1H3-hIgG1-L6-hIL-2 (E68L)	72	CD25	2.72E-09	7.79E+04	2.12E-04
1H3-hIgG1-L6-hIL-2 (L72Y)	73	CD25	6.39E-09	1.94E+05	1.24E-03
1H3-hIgG1-L6-hIL-2 (L72R)	74	CD25	1.96E-08	3.07E+04	6.01E-04
1H3-hIgG1-L6-hIL-2 (L72A)	75	CD25	9.08E-09	1.47E+05	1.34E-03
1H3-hIgG1-L6-hIL-2 (L72D)	76	CD25	9.52E-09	1.57E+05	1.50E-03
1H3-hIgG1-L6-hIL-2 (L72H)	77	CD25	9.03E-09	1.65E+05	1.49E-03
1H3-hIgG1-L6-hIL-2 (L72F)	78	CD25	5.04E-09	2.28E+05	1.15E-03
1H3-hIgG1-L6-hIL-2 (R81A)	97	CD122	7.08E-09	2.20E+05	1.56E-03
1H3-hIgG1-L6-hIL-2 (D84A)	98	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (D84R)	99	CD122	1.88E-08	4.73E+05	8.88E-03
1H3-hIgG1-L6-hIL-2 (S87A)	101	CD122	7.09E-09	3.31E+05	2.34E-03
1H3-hIgG1-L6-hIL-2 (N88Y)	102	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (N88D)	103	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (N88R)	104	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (N88E)	105	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (N88F)	106	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (N88I)	107	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (I92A)	108	CD122	3.38E-09	1.95E+06	6.58E-03
1H3-hIgG1-L6-hIL-2 (I92Y)	109	CD122	1.23E-08	4.53E+05	5.57E-03
1H3-hIgG1-L6-hIL-2 (I92S)	110	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (I92F)	111	CD122	5.45E-09	1.03E+05	5.59E-04
1H3-hIgG1-L6-hIL-2 (I92R)	112	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (I92D)	113	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (I92E)	114	CD122	1.62E-09	9.33E+05	1.51E-03
1H3-hIgG1-L6-hIL-2 (E95A)	115	CD122	8.17E-09	2.87E+05	2.35E-03
1H3-hIgG1-L6-hIL-2 (E95R)	116	CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (E95K)	117	CD122	3.81E-09	6.58E+05	2.51E-03
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/D20A/S87A)	213	CD25+CD122	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/D20A/E95A)	214	CD25+CD122	未觀測到結合		

1H3-hIgG1-L6-hIL-2 (F42K/Y45R/Q126D)	228	CD25+CD132	9.16E-09	3.75E+05	3.44E-03
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Q126D)	229	CD122+CD132	未觀測到結合		
1H3-hIgG1-L6-hIL-2 (R38D/E61R)	79	CD25	1.29E-08	3.68E+05	4.73E-03
1H3-hIgG1-L6-hIL-2 (R38D/E61R/K43E)	80	CD25	7.47E-09	4.52E+05	3.38E-03

[a] SEQ ID NO: 345對應於野生型hIL-2。

[b] SEQ ID NO: 57僅為減弱之IL-2序列。

實例3：用基於細胞之效力pSTAT5固定濃度篩選法進行之高親和力及中等親和力hIL-2受體的減弱測試

【0184】 在固定濃度pSTAT5篩選法中，使用方案D中所描述之NK-92 (表現高親和力hIL-2受體)及TF1+IL-2Rβ (表現中等親和力hIL-2受體)細胞株來測試實例2中所描述之抗體減弱之hIL-2融合蛋白的減弱。表4至表8列出抗體減弱之hIL-2融合蛋白相對於游離細胞介素之野生型rhIL-2之幾何平均螢光強度(gMFI)的倍數變化，此量測IL-2活性之降低。對於固定濃度篩選法，由rhIL-2之gMFI除以變異體之gMFI，來計算倍數變化。對於具有完全滴定曲線之實驗，由rhIL-2之EC_{50}值除以變異體之EC_{50}，來計算相對於rhIL-2之倍數變化。將倍數變化捨入至最接近之整數。當與由rhIL-2產生之gMFI相比時，NK-92及TF1+IL-2Rβ細胞株兩者中降低之gMFI即指示高親和力及中等親和力受體兩者中之IL-2活性減弱。在基於細胞之效力pSTAT5固定濃度篩選法中未測試實例2中所描述之第1組變異體。

【0185】 亦評定所測試之各變異體的IL-2促效活性且表徵為完全或部分IL-2促效劑，或不具有IL-2活性(非活性)。以rhIL-2陽性對照所展現最大gMFI程度達成的1H3-hIgG1-L6-hIL-2融合蛋白劑量-滴定曲線視為具有完全促效劑活性之抗體減弱之hIL-2融合蛋白。採用rhIL-2最大gMFI作

為100%，以相對完全活性之百分比來計算部分促效劑活性。在1200 nM之最高濃度下，小於rhIL-2最大gMFI之10%之抗體減弱之hIL-2融合蛋白質則視為不具有促效劑活性(無活性)。一些EC_{50}值及減弱程度可能無法使用GraphPad Prism 7軟體精確計算，因為活性未達到最大值且因此，此等值為估計值。

【0186】 pSTAT5固定濃度結果證實，雖然一些單一殘基取代減弱高親和力細胞株(NK-92)上之IL-2活性，但必需由調節與α鏈及β鏈兩者或α鏈及γ鏈兩者之結合性的取代之組合才可實質上減弱高親和力IL-2受體上之IL-2活性(相對於重組hIL-2，減弱超過20倍)。

表4. 在固定濃度pSTAT5篩選中來自第2組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化

變異體	hIL-2變異體之SEQ ID NO	相對於hIL-2之倍數變化(NK-92)	相對於hIL-2之倍數變化(TF1+IL-2Rβ)
1H3-hIgG1-L6-hIL-2 (R38D)	47	7	1
1H3-hIgG1-L6-hIL-2 (R38E)	48	12	1
1H3-hIgG1-L6-hIL-2 (R38Q)	49	1	1
1H3-hIgG1-L6-hIL-2 (F42R)	50	7	1
1H3-hIgG1-L6-hIL-2 (F42A)	51	1	1
1H3-hIgG1-L6-hIL-2 (F42H)	53	1	1
1H3-hIgG1-L6-hIL-2 (K43E)	55	1	1
1H3-hIgG1-L6-hIL-2 (K43Q)	56	1	1
1H3-hIgG1-L6-hIL-2 (Y45A)	57	1	1
1H3-hIgG1-L6-hIL-2 (Y45K)	58	1	1
1H3-hIgG1-L6-hIL-2 (Y45S)	59	1	1
1H3-hIgG1-L6-hIL-2 (Y45R)	60	10	1
1H3-hIgG1-L6-hIL-2 (E68Y)	68	1	1
1H3-hIgG1-L6-hIL-2 (E68A)	69	1	1
1H3-hIgG1-L6-hIL-2 (E68L)	72	2	1
1H3-hIgG1-L6-hIL-2 (L72Y)	73	1	1
1H3-hIgG1-L6-hIL-2 (L72A)	75	1	1
1H3-hIgG1-L6-hIL-2 (L72F)	78	1	1
1H3-hIgG1-L6-hIL-2 (R38D/E61R)	79	NT-1	1
1H3-hIgG1-L6-hIL-2 (R38D/E61R/K43E)	80	NT-1	1
1H3-hIgG1-L6-hIL-2 (T3A/F42A/Y45A/L72G/C125A)	81	10	1

NT-1 =已首先在pSTAT5完全滴定中測試，無固定濃度分析法之資料。

表5. 在固定濃度pSTAT5篩選中來自第3組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化

變異體	hIL-2變異體之SEQ ID NO	相對於hIL-2之倍數變化 (NK-92)	相對於hIL-2之倍數變化 (TF1+IL-2Rβ)
1H3-hIgG1-L6-hIL-2 (E15A)	82	1	1
1H3-hIgG1-L6-hIL-2 (E15R)	83	1	1
1H3-hIgG1-L6-hIL-2 (E15K)	84	1	1
1H3-hIgG1-L6-hIL-2 (H16A)	85	1	1
1H3-hIgG1-L6-hIL-2 (H16Y)	86	1	1
1H3-hIgG1-L6-hIL-2 (H16E)	87	1	NT-1
1H3-hIgG1-L6-hIL-2 (L19A)	88	1	NT-1
1H3-hIgG1-L6-hIL-2 (D20I)	89	12	NT-1
1H3-hIgG1-L6-hIL-2 (D20S)	90	4	NT-1
1H3-hIgG1-L6-hIL-2 (D20H)	91	10	NT-1
1H3-hIgG1-L6-hIL-2 (D20W)	93	16	NT-1
1H3-hIgG1-L6-hIL-2 (D20Y)	94	17	NT-1
1H3-hIgG1-L6-hIL-2 (D20R)	95	19	NT-1
1H3-hIgG1-L6-hIL-2 (D20F)	96	17	NT-1
1H3-hIgG1-L6-hIL-2 (R81A)	97	1	1
1H3-hIgG1-L6-hIL-2 (D84A)	98	1	NT-1
1H3-hIgG1-L6-hIL-2 (D84R)	99	3	NT-1
1H3-hIgG1-L6-hIL-2 (D84K)	100	2	NT-1
1H3-hIgG1-L6-hIL-2 (S87A)	101	1	1
1H3-hIgG1-L6-hIL-2 (N88Y)	102	22	NT-1
1H3-hIgG1-L6-hIL-2 (N88D)	103	2	NT-1
1H3-hIgG1-L6-hIL-2 (N88R)	104	3	NT-1
1H3-hIgG1-L6-hIL-2 (N88E)	105	10	NT-1
1H3-hIgG1-L6-hIL-2 (N88F)	106	19	NT-1
1H3-hIgG1-L6-hIL-2 (N88I)	107	9	NT-1
1H3-hIgG1-L6-hIL-2 (I92A)	108	1	1
1H3-hIgG1-L6-hIL-2 (I92Y)	109	1	NT-1
1H3-hIgG1-L6-hIL-2 (I92S)	110	1	NT-1
1H3-hIgG1-L6-hIL-2 (I92F)	111	1	1
1H3-hIgG1-L6-hIL-2 (I92R)	112	1	NT-1
1H3-hIgG1-L6-hIL-2 (I92D)	113	3	NT-1
1H3-hIgG1-L6-hIL-2 (I92E)	114	1	1
1H3-hIgG1-L6-hIL-2 (E95A)	115	1	1
1H3-hIgG1-L6-hIL-2 (E95R)	116	1	NT-1
1H3-hIgG1-L6-hIL-2 (E95K)	117	1	1
1H3-hIgG1-L6-hIL-2 (D20T)	92	3	2
1H3-hIgG1-L6-hIL-2 (D20A)	31	7	2

1H3-hIgG1-L6-hIL-2 (D20Y/H16E)	118	6	4
1H3-hIgG1-L6-hIL-2 (D20Y/H16A)	119	10	3
1H3-hIgG1-L6-hIL-2 (D20Y/H16Y)	120	10	4
1H3-hIgG1-L6-hIL-2 (D20Y/I92A)	121	11	4
1H3-hIgG1-L6-hIL-2 (D20Y/I92S)	122	11	4
1H3-hIgG1-L6-hIL-2 (D20Y/I92R)	123	12	5
1H3-hIgG1-L6-hIL-2 (D20Y/E95R)	124	12	5
1H3-hIgG1-L6-hIL-2 (D20Y/E95A)	125	11	5

NT-1 =已首先在pSTAT5完全滴定中測試，無固定濃度分析法之資料。

表6. 在固定濃度pSTAT5篩選中來自第4組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化

變異體	**hIL-2變異體之SEQ ID NO**	**相對於hIL-2之倍數變化 (NK-92)**	**相對於hIL-2之倍數變化 (TF1+IL-2Rβ)**
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A)	82	17	1
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20I)	89	21	15
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S)	90	2	14
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20H)	91	22	15
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W)	93	23	15
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y)	94	23	16
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20R)	95	23	16
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20F)	96	23	18
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K)	100	23	17
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A)	101	17	2
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88Y)	102	23	18
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D)	103	23	17
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R)	104	24	17
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88E)	105	25	18
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88F)	106	25	18
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88I)	107	25	20
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (I92A)	108	15	3
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95A)	115	14	1
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K)	117	25	8

表7. 在固定濃度pSTAT5篩選中來自第5組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化

變異體	hIL-2變異體之SEQ ID NO	相對於hIL-2之倍數變化(NK-92)	相對於hIL-2之倍數變化(TF1+IL-2Rβ)
1H3-hIgG1-L6-hIL-2 (F42D/D20A)	127	11	3
1H3-hIgG1-L6-hIL-2 (F42R/D20A)	128	10	2
1H3-hIgG1-L6-hIL-2 (F42K/D20A)	129	10	4
1H3-hIgG1-L6-hIL-2 (F42A/D20A)	130	11	3
1H3-hIgG1-L6-hIL-2 (F42H/D20A)	131	12	2
1H3-hIgG1-L6-hIL-2 (Y45R/D20A)	132	11	1
1H3-hIgG1-L6-hIL-2 (Y45K/D20A)	133	11	2
1H3-hIgG1-L6-hIL-2 (R38N/D20A)	134	14	3
1H3-hIgG1-L6-hIL-2 (R38G/D20A)	135	13	2
1H3-hIgG1-L6-hIL-2 (R38H/D20A)	136	12	3
1H3-hIgG1-L6-hIL-2 (R38I/D20A)	137	11	3
1H3-hIgG1-L6-hIL-2 (R38L/D20A)	138	11	4
1H3-hIgG1-L6-hIL-2 (R38M/D20A)	139	11	3
1H3-hIgG1-L6-hIL-2 (R38F/D20A)	140	12	3
1H3-hIgG1-L6-hIL-2 (R38P/D20A)	141	13	3
1H3-hIgG1-L6-hIL-2 (R38S/D20A)	142	15	2
1H3-hIgG1-L6-hIL-2 (R38T/D20A)	143	13	3
1H3-hIgG1-L6-hIL-2 (R38W/D20A)	144	14	2
1H3-hIgG1-L6-hIL-2 (R38Y/D20A)	145	14	3
1H3-hIgG1-L6-hIL-2 (R38V/D20A)	146	12	3
1H3-hIgG1-L6-hIL-2 (R38A/D20A)	147	13	3
1H3-hIgG1-L6-hIL-2 (R38Q/D20A)	148	14	3
1H3-hIgG1-L6-hIL-2 (R38E/D20A)	149	15	3
1H3-hIgG1-L6-hIL-2 (R38D/D20A)	150	15	3
1H3-hIgG1-L6-hIL-2 (K43E/D20A)	151	13	2
1H3-hIgG1-L6-hIL-2 (E61A/D20A)	152	14	2
1H3-hIgG1-L6-hIL-2 (E62A/D20A)	153	14	2
1H3-hIgG1-L6-hIL-2 (E62Y/D20A)	154	14	3
1H3-hIgG1-L6-hIL-2 (L72D/D20A)	155	14	2
1H3-hIgG1-L6-hIL-2 (L72H/D20A)	156	14	3
1H3-hIgG1-L6-hIL-2 (L72R/D20A)	157	10	3
1H3-hIgG1-L6-hIL-2 (F42D/I92D)	158	12	5
1H3-hIgG1-L6-hIL-2 (F42R/I92D)	159	12	3
1H3-hIgG1-L6-hIL-2 (F42H/I92D)	160	12	2
1H3-hIgG1-L6-hIL-2 (F42A/I92D)	161	12	3
1H3-hIgG1-L6-hIL-2 (K43E/I92D)	162	13	4
1H3-hIgG1-L6-hIL-2 (Y45R/I92D)	163	13	1
1H3-hIgG1-L6-hIL-2 (Y45K/I92D)	164	13	1
1H3-hIgG1-L6-hIL-2 (E62A/I92D)	165	13	3
1H3-hIgG1-L6-hIL-2 (E62Y/I92D)	166	14	5
1H3-hIgG1-L6-hIL-2 (L72D/I92D)	167	14	5
1H3-hIgG1-L6-hIL-2 (L72H/I92D)	168	14	5

1H3-hIgG1-L6-hIL-2 (L72R/I92D)	169	14	5
1H3-hIgG1-L6-hIL-2 (R38D/I92D)	170	15	2
1H3-hIgG1-L6-hIL-2 (R38E/I92D)	171	15	2
1H3-hIgG1-L6-hIL-2 (R38Q/I92D)	172	14	2
1H3-hIgG1-L6-hIL-2 (R38A/I92D)	173	13	4
1H3-hIgG1-L6-hIL-2 (R38E/N88R)	174	16	1
1H3-hIgG1-L6-hIL-2 (R38E/D84R)	175	14	2
1H3-hIgG1-L6-hIL-2 (R38E/D84K)	176	14	2
1H3-hIgG1-L6-hIL-2 (F42A/Y45R/D20A)	177	11	2
1H3-hIgG1-L6-hIL-2 (F42H/Y45R/D20A)	178	12	2
1H3-hIgG1-L6-hIL-2 (R38D/E61R/D20A)	179	12	3
1H3-hIgG1-L6-hIL-2 (R38E/E61R/D20A)	180	11	3
1H3-hIgG1-L6-hIL-2 (R38Q/E61R/D20A)	181	12	3
1H3-hIgG1-L6-hIL-2 (R38A/E61R/D20A)	182	13	3
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38A)	183	6	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38D)	184	21	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38E)	185	21	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38Q)	186	19	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42R)	187	21	4
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42A)	188	21	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42D)	189	22	12
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42H)	190	22	4
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42K)	191	21	4
1H3-hIgG1-L6-hIL-2 (D20A/E95A/K43A)	192	5	7
1H3-hIgG1-L6-hIL-2 (D20A/E95A/K43E)	193	13	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/K43Q)	194	5	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45A)	195	4	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45K)	196	22	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45S)	197	5	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45R)	198	25	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E61A)	199	10	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62A)	200	23	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62R)	201	25	17
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62K)	202	25	15
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62Y)	203	25	10
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68Y)	204	8	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68A)	205	5	8
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68L)	206	7	9
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72Y)	207	1	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72R)	208	12	9
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72A)	209	2	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72D)	210	21	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72H)	211	14	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72F)	212	2	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42K/Y45R)	214	21	5
1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A)	215	16	3
1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E)	216	18	2
1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	217	18	3

1H3-hIgG1-L6-hIL-2 (Δ1-3APT/D20A/R38E)	218	13	1
1H3-hIgG1-L6-hIL-2 (Δ1-3APT/D20A/R38E/C125A)	219	15	4
1H3-hIgG1-L6-hIL-2 (R38E/Q22A)	220	12	0
1H3-hIgG1-L6-hIL-2 (R38E/T123A)	221	12	0
1H3-hIgG1-L6-hIL-2 (R38E/I129A)	222	13	1
1H3-hIgG1-L6-hIL-2 (R38E/S130A)	223	12	0
1H3-hIgG1-L6-hIL-2 (R38E/Q126A)	224	13	1
1H3-hIgG1-L6-hIL-2 (R38E/Q126D)	225	15	4
1H3-hIgG1-L6-hIL-2 (R38E/Q126V)	226	14	1
1H3-hIgG1-L6-hIL-2 (R38E/Q22A/S130A)	227	13	1

表8. 在固定濃度pSTAT5篩選中來自第6組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化

變異體	**hIL-2變異體之SEQ ID NO**	**相對於hIL-2之倍數變化(NK-92)**	**相對於hIL-2之倍數變化(TF1+IL-2Rβ)**
1H3-hIgG1-L6-hIL-2 (D20A/E61R)	230	25	4
1H3-hIgG1-L6-hIL-2 (D20A/E61N)	231	15	1
1H3-hIgG1-L6-hIL-2 (D20A/E61D)	232	11	0
1H3-hIgG1-L6-hIL-2 (D20A/E61Q)	233	16	2
1H3-hIgG1-L6-hIL-2 (D20A/E61G)	234	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61H)	235	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61I)	236	16	1
1H3-hIgG1-L6-hIL-2 (D20A/E61L)	237	16	1
1H3-hIgG1-L6-hIL-2 (D20A/E61K)	238	17	2
1H3-hIgG1-L6-hIL-2 (D20A/E61M)	239	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61F)	240	14	0
1H3-hIgG1-L6-hIL-2 (D20A/E61P)	241	15	1
1H3-hIgG1-L6-hIL-2 (D20A/E61S)	242	16	1
1H3-hIgG1-L6-hIL-2 (D20A/E61T)	243	16	2
1H3-hIgG1-L6-hIL-2 (D20A/E61W)	244	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61Y)	245	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61V)	246	17	3
1H3-hIgG1-L6-hIL-2 (D20A/F42N)	247	15	2
1H3-hIgG1-L6-hIL-2 (D20A/F42Q)	248	15	2
1H3-hIgG1-L6-hIL-2 (D20A/F42E)	249	16	1
1H3-hIgG1-L6-hIL-2 (D20A/F42G)	250	17	2
1H3-hIgG1-L6-hIL-2 (D20A/F42I)	251	17	2
1H3-hIgG1-L6-hIL-2 (D20A/F42L)	252	14	2
1H3-hIgG1-L6-hIL-2 (D20A/F42M)	253	15	2
1H3-hIgG1-L6-hIL-2 (D20A/F42P)	254	17	2
1H3-hIgG1-L6-hIL-2 (D20A/F42S)	255	15	2
1H3-hIgG1-L6-hIL-2 (D20A/F42T)	256	16	2
1H3-hIgG1-L6-hIL-2 (D20A/F42W)	257	16	2
1H3-hIgG1-L6-hIL-2 (D20A/F42Y)	258	17	2
1H3-hIgG1-L6-hIL-2 (D20A/F42V)	259	18	2

1H3-hIgG1-L6-hIL-2 (D20A/Y45A)	260	15	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45N)	261	14	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45D)	262	18	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45Q)	263	17	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45E)	264	18	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45G)	265	18	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45H)	266	16	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45I)	267	13	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45L)	268	13	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45M)	269	16	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45F)	270	13	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45P)	271	25	4
1H3-hIgG1-L6-hIL-2 (D20A/Y45S)	272	14	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45T)	273	24	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45W)	274	19	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45V)	275	21	3
1H3-hIgG1-L6-hIL-2 (I92D/F42N)	276	29	5
1H3-hIgG1-L6-hIL-2 (I92D/F42Q)	277	29	4
1H3-hIgG1-L6-hIL-2 (I92D/F42E)	278	30	5
1H3-hIgG1-L6-hIL-2 (I92D/F42G)	279	32	5
1H3-hIgG1-L6-hIL-2 (I92D/F42I)	280	31	4
1H3-hIgG1-L6-hIL-2 (I92D/F42L)	281	31	5
1H3-hIgG1-L6-hIL-2 (I92D/F42K)	282	26	4
1H3-hIgG1-L6-hIL-2 (I92D/F42M)	283	28	5
1H3-hIgG1-L6-hIL-2 (I92D/F42P)	284	29	4
1H3-hIgG1-L6-hIL-2 (I92D/F42S)	285	30	5
1H3-hIgG1-L6-hIL-2 (I92D/F42T)	286	28	3
1H3-hIgG1-L6-hIL-2 (I92D/F42W)	287	18	4
1H3-hIgG1-L6-hIL-2 (I92D/F42Y)	288	22	3
1H3-hIgG1-L6-hIL-2 (I92D/F42V)	289	30	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45A)	290	11	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45N)	291	4	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45D)	292	29	5
1H3-hIgG1-L6-hIL-2 (I92D/Y45Q)	293	25	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45E)	294	27	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45G)	295	20	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45H)	296	7	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45I)	297	20	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45L)	298	5	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45M)	299	14	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45F)	300	10	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45P)	301	28	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45S)	302	11	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45T)	303	28	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45W)	304	27	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45V)	305	28	5
1H3-hIgG1-L6-hIL-2 (R38E/D20H)	306	17	5
1H3-hIgG1-L6-hIL-2 (R38E/D20S)	307	17	3
1H3-hIgG1-L6-hIL-2 (F42A/N88R)	308	18	3
1H3-hIgG1-L6-hIL-2 (F42A/N88D)	309	18	3

1H3-hIgG1-L6-hIL-2 (R38E/D84A)	310	18	1
1H3-hIgG1-L6-hIL-2 (R38E/D84N)	311	18	1
1H3-hIgG1-L6-hIL-2 (R38E/D84Q)	312	18	1
1H3-hIgG1-L6-hIL-2 (R38E/D84E)	313	16	1
1H3-hIgG1-L6-hIL-2 (R38E/D84G)	314	18	1
1H3-hIgG1-L6-hIL-2 (R38E/D84H)	315	19	2
1H3-hIgG1-L6-hIL-2 (R38E/D84I)	316	20	1
1H3-hIgG1-L6-hIL-2 (R38E/D84L)	317	19	1
1H3-hIgG1-L6-hIL-2 (R38E/D84M)	318	20	2
1H3-hIgG1-L6-hIL-2 (R38E/D84F)	319	20	2
1H3-hIgG1-L6-hIL-2 (R38E/D84P)	320	20	1
1H3-hIgG1-L6-hIL-2 (R38E/D84S)	321	21	1
1H3-hIgG1-L6-hIL-2 (R38E/D84T)	322	20	1
1H3-hIgG1-L6-hIL-2 (R38E/D84W)	323	21	1
1H3-hIgG1-L6-hIL-2 (R38E/D84Y)	324	21	1
1H3-hIgG1-L6-hIL-2 (R38E/D84V)	325	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92A)	326	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92R)	327	22	2
1H3-hIgG1-L6-hIL-2 (R38E/I92N)	328	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92Q)	329	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92E)	330	22	2
1H3-hIgG1-L6-hIL-2 (R38E/I92G)	331	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92H)	332	21	1
1H3-hIgG1-L6-hIL-2 (R38E/I92L)	333	17	1
1H3-hIgG1-L6-hIL-2 (R38E/I92K)	334	24	3
1H3-hIgG1-L6-hIL-2 (R38E/I92M)	335	20	1
1H3-hIgG1-L6-hIL-2 (R38E/I92F)	336	16	1
1H3-hIgG1-L6-hIL-2 (R38E/I92P)	337	24	5
1H3-hIgG1-L6-hIL-2 (R38E/I92S)	338	22	2
1H3-hIgG1-L6-hIL-2 (R38E/I92T)	339	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92W)	340	23	1
1H3-hIgG1-L6-hIL-2 (R38E/I92Y)	341	21	1
1H3-hIgG1-L6-hIL-2 (R38E/I92V)	342	21	1
1H3-hIgG1-L6-hIL-2 (R38E/H16E)	343	25	3
1H3-hIgG1-L6-hIL-2 (R38K/D20A)	344	17	3

實例4：用基於細胞之效力pSTAT5劑量-滴定篩選進行之高親和力及中等親和力hIL-2受體中之各者的IL-2融合蛋白之減弱測試

【0187】 在pSTAT5滴定曲線中使用經方案D中所描述之NK-92及TF1+IL-2Rβ細胞株來測試實例2中所描述之所選擇抗體減弱之hIL-2融合蛋白(來自第2至6組之1H3-hIgG1-L6-hIL-2融合蛋白)的減弱。

【0188】 使用Alexa Fluor 647 pSTAT5-正信號之gMFI產生四參數邏輯曲線，且隨後使用GraphPad Prism 7軟體計算EC_{50}值。此等值與重組

hIL-2 (rhIL-2)對照相比作為減弱之量測。表9至表13概述使用Alexa Fluor 647信號之gMFI所計算的相對於rhIL-2之活性倍數變化。

【0189】 相對於rhIL-2之倍數變化的增加指示hIL-2活性之減弱程度。亦評定在pSTAT5滴定曲線中測試之各抗體減弱之hIL-2融合蛋白的促效活性且表徵為完全、部分或無活性(非活性)。將達到由rhIL-2展現之最大gMFI程度的抗體減弱之hIL-2融合蛋白質劑量-滴定曲線視為具有完全促效劑活性之變異體。以實例3中所描述計算部分促效劑活性。將非活性抗體減弱之hIL-2融合蛋白歸類為相比於rhIL-2具有小於10%之活性。相對於rhIL-2之一些倍數變化無法使用GraphPad Prism 7軟體精確計算(表示為未計算或「NC」)，因為未產生完全四參數邏輯曲線且因此，此等值為估計值(在表9至表13中標註為[a])。然而，此等變異體相對於rhIL-2在圖上具有大於10,000倍之減弱(資料未示出)。此在表9至表13上表示為「在圖上>10,000；NC」。

【0190】 完全滴定pSTAT5曲線證實如實例3中所呈現之類似發現，其中與僅結合α或β鏈之單取代相比，調節與α鏈及β鏈兩者之結合的取代實質上減弱高親和力IL-2受體上之IL-2活性。另外，完全滴定pSTAT5分析法能夠在具有引起非活性之取代的變異體相對於高度減弱之變異體之間進行區分。最後，劑量-滴定曲線之比較說明與固定濃度分析法相比，更精確之減弱程度。

表9. 來自第2組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2變異體之SEQ ID NO**	**相對於rhIL-2之倍數變化 (NK-92)**	**促效活性(NK-92)**	**相對於rhIL-2之倍數變化(TF1+IL-2Rβ)**	**促效活性(TF1+IL-2Rβ)**
1H3-hIgG1-L6-hIL-2 (R38A)	46	2	完全	0	完全
1H3-hIgG1-L6-hIL-2 (R38D)	47	55	完全	1	完全
1H3-hIgG1-L6-hIL-2 (R38E)	48	99-136	完全	0	完全
1H3-hIgG1-L6-hIL-2 (F42R)	50	65	完全	0	完全
1H3-hIgG1-L6-hIL-2 (F42D)	52	193	完全	0	完全
1H3-hIgG1-L6-hIL-2 (K43A)	54	3 [a]	完全	0	完全
1H3-hIgG1-L6-hIL-2 (Y45R)	57	81 [a]	完全	0	完全
1H3-hIgG1-L6-hIL-2 (E61A)	61	3 [a]	完全	0	完全
1H3-hIgG1-L6-hIL-2 (E61R)	62	22 [a]	完全	0	完全
1H3-hIgG1-L6-hIL-2 (E61K)	63	14 [a]	完全	0	完全
1H3-hIgG1-L6-hIL-2 (E62A)	64	6 [a]	完全	0	完全
1H3-hIgG1-L6-hIL-2 (E62R)	65	>10,000	部分，80%	38	完全
1H3-hIgG1-L6-hIL-2 (E62K)	66	2048	完全	10	完全
1H3-hIgG1-L6-hIL-2 (E62Y)	67	18	完全	0	完全
1H3-hIgG1-L6-hIL-2 (E68K)	70	2 [a]	完全	0	完全
1H3-hIgG1-L6-hIL-2 (E68R)	71	3 [a]	完全	0	完全
1H3-hIgG1-L6-hIL-2 (L72R)	74	2 [a]	完全	1	完全
1H3-hIgG1-L6-hIL-2 (L72D)	76	4 [a]	完全	0	完全
1H3-hIgG1-L6-hIL-2 (L72H)	77	1 [a]	部分，80%	0	完全
1H3-hIgG1-L6-hIL-2 (R38D/E61R)	79	479	部分，80%	NT	NT
1H3-hIgG1-L6-hIL-2 (R38D/E61R/K43E)	80	598	完全	NT	NT
1H3-hIgG1-L6-hIL-2 (T3A/F42A/Y45A/L72G/C125A)	81	360 - 1426	完全	0	完全

NT =未測試

[a] = 倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

表10. 來自第3組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2 變異體之 SEQ ID NO**	**相對於 rhIL-2 之倍數變化 (NK-92)**	**促效活性 (NK-92)**	**相對於 rhIL-2 之倍數變化 (TF1+IL-2Rβ)**	**促效活性 (TF1+IL-2Rβ)**
1H3-hIgG1-L6-hIL-2 (H16E)	87	63	完全	63	完全
1H3-hIgG1-L6-hIL-2 (L19A)	88	0	完全	0	完全
1H3-hIgG1-L6-hIL-2 (D20I)	89	NT	NT	在圖上 >10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (D20S)	90	28	部分，80%	277 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (D20H)	91	>10,000 [a]	部分，90%	2767 [a]	部分，50%
1H3-hIgG1-L6-hIL-2 (D20W)	93	NT	NT	在圖上 >10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (D20Y)	94	>10,000 [a]	部分，50%至70%	84 - 143 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (D20R)	95	NT	NT	在圖上 >10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (D20F)	96	NT	NT	在圖上 >10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (D84A)	98	NT	NT	14	完全
1H3-hIgG1-L6-hIL-2 (D84R)	99	16	完全	244 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (D84K)	100	14	部分，90%	195 [a]	完全
1H3-hIgG1-L6-hIL-2 (N88Y)	102	NT	NT	在圖上 >10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (N88D)	103	21	部分，90%	130	完全
1H3-hIgG1-L6-hIL-2 (N88R)	104	5- 27	部分，80%至完全	289 - 556	部分，40%
1H3-hIgG1-L6-hIL-2 (N88E)	105	NT	NT	在圖上 >10,000，NC [a]	部分，40%
1H3-hIgG1-L6-hIL-2 (N88F)	106	NT	NT	在圖上 >10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (N88I)	107	NT	NT	在圖上 >10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (I92Y)	109	NT	NT	1	完全

1H3-hIgG1-L6-hIL-2 (I92S)	110	NT	NT	8	完全
1H3-hIgG1-L6-hIL-2 (I92R)	112	NT	NT	31	完全
1H3-hIgG1-L6-hIL-2 (I92D)	113	8 - 20	完全	68 - 365 [a]	部分，70%至90%
1H3-hIgG1-L6-hIL-2 (E95R)	116	NT	NT	5	完全
1H3-hIgG1-L6-hIL-2 (D20T)	92	8	完全	167 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A)	31	21	部分，80%	117 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (D20Y/H16E)	94	52 [a]	部分，80%	2159 [a]	部分，30%
1H3-hIgG1-L6-hIL-2 (D20Y/H16A)	119	>10,000 [a]	部分，40%	30 [a]	部分，20%
1H3-hIgG1-L6-hIL-2 (D20Y/H16Y)	120	>10,000 [a]	部分，40%	343 [a]	部分，20%
1H3-hIgG1-L6-hIL-2 (D20Y/I92A)	121	>10,000 [a]	部分，20%	4 [a]	部分，10%
1H3-hIgG1-L6-hIL-2 (D20Y/I92S)	122	>10,000 [a]	部分，10%	12 [a]	部分，10%

NT =未測試；NC =未藉由GraphPad Prism 7計算

[a] =倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

表11. 來自第4組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2變異體之SEQ ID NO**	**相對於rhIL-2之倍數變化(NK-92)**	**促效活性(NK-92)**	**相對於rhIL-2之倍數變化(TF1+IL-2Rβ)**	**促效活性(TF1+IL-2Rβ)**
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A)	82	184	完全	20	完全
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20I)	89	>10,000 [a]	部分，80%	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S)	90	2403	完全	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20H)	91	>10,000 [a]	部分，80%	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W)	93	>10,000 [a]	部分，60%	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y)	94	>10,000 [a]	部分，90%	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20R)	95	>10,000 [a]	部分，80%	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20F)	96	>10,000 [a]	部分，70%	在圖上>10,000，NC [a]	非活性

1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K)	100	>10,000	完全	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A)	101	305	完全	44	完全
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88Y)	102	>10,000 [a]	部分，50%	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D)	103	393	完全	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R)	104	274	完全	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88E)	105	>10,000 [a]	完全	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88F)	106	>10,000 [a]	部分，80%	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88I)	107	7780	完全	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (I92A)	108	26	完全	95	完全
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95A)	115	30	完全	16	完全
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K)	117	792	完全	434 [a]	部分，60%

NC =未藉由GraphPad Prism 7計算

[a] =倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

表12. 來自第5組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2變異體之SEQ ID NO**	**相對於rhIL-2之倍數變化(NK-92)**	**促效活性(NK-92)**	**相對於rhIL-2之倍數變化(TF1+IL-2Rβ)**	**促效活性(TF1+IL-2Rβ)**
1H3-hIgG1-L6-hIL-2 (F42K/D20A)	129	>10,000 [a]	部分，30%	219 [a]	部分，50%
1H3-hIgG1-L6-hIL-2 (F42A/D20A)	130	>10,000 [a]	部分，70%	96 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (R38N/D20A)	134	4497	部分，70%	121 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (R38G/D20A)	135	2811	部分，70%	139 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (R38H/D20A)	136	1752	部分，80%	107 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (R38I/D20A)	137	658	部分，70%	107 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (R38L/D20A)	138	532	部分，80%	125 [a]	部分，70%

1H3-hIgG1-L6-hIL-2 (R38M/D20A)	139	786	部分，90%	85 [a]	部分，90%
1H3-hIgG1-L6-hIL-2 (R38F/D20A)	140	1072	部分，80%	124 [a]	部分，90%
1H3-hIgG1-L6-hIL-2 (R38P/D20A)	141	337	部分，70%	337 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (R38S/D20A)	142	571	部分，70%	571 [a]	部分，90%
1H3-hIgG1-L6-hIL-2 (R38V/D20A)	146	765	部分，70%	765 [a]	部分，90%
1H3-hIgG1-L6-hIL-2 (R38A/D20A)	147	619	部分，80%	70 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (R38Q/D20A)	148	4700	部分，80%	91 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/R38E)	149	>10,000 [a]	部分，60%至完全	409 [a]	部分，50%
1H3-hIgG1-L6-hIL-2 (R38D/D20A)	150	>10,000 [a]	部分，70%	172 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (K43E/D20A)	151	584	部分，90%	231 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (F42R/I92D)	159	801 [a]	部分，40%	52 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (F42H/I92D)	160	194	完全	801 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (F42A/I92D)	161	338 [a]	部分，70%	194 [a]	完全
1H3-hIgG1-L6-hIL-2 (R38D/I92D)	170	>10,000 [a]	部分，80%	338 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (R38E/I92D)	171	>10,000 [a]	部分，70%	51 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (R38Q/I92D)	172	561	完全	48 [a]	部分，90%
1H3-hIgG1-L6-hIL-2 (R38E/D84R)	175	>10,000 [a]	部分，60%	50 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (R38E/D84K)	176	>10,000 [a]	部分，40%	45 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (R38D/E61R/D20A)	179	在圖上 >10,000，NC [a]	部分，40%	62 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (R38E/E61R/D20A)	180	>10,000 [a]	部分，90%	181 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (R38Q/E61R/D20A)	181	>10,000 [a]	部分，40%	115 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (R38A/E61R/D20A)	182	>10,000 [a]	部分，40%	130 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38A)	183	149 - 199	部分，70%至80%	157 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38D)	184	>10,000	部分，60%至70%	84 - 508 [a]	完全

1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38E)	185	>10,000 [a]	部分，70%至90%	188 - 427 [a]	部分，70%至完全
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38Q)	186	3725	部分，70%	124 - 413 [a]	部分，80%至完全
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42R)	187	>10,000 [a]	部分，70%	87 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42A)	188	3000 - 5718 [a]	部分，90%	45 - 244 [a]	部分，70%至完全
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42D)	189	>10,000 [a]	部分，10%	1451 [a]	部分，30%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42H)	190	3579	部分，80%	411 [a]	完全
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42K)	191	>10,000 [a]	部分，50%	82 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/K43E)	193	386 - 553	部分，80%至90%	46- 142 [a]	部分，50%至80%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45A)	195	62	部分，90%	300 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45K)	196	7951 [a]	部分，70%	205 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45R)	198	>10,000 [a]	部分，80%	293 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E61A)	199	367	部分，80%	195 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62A)	200	3265 [a]	部分，70%	230 [a]	部分，50%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62R)	201	>10,000 [a]	非活性，5%	在圖上>10,000，NC [a]	部分，10%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62K)	202	>10,000 [a]	非活性，10%	在圖上>10,000，NC [a]	部分，10%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62Y)	203	>10,000 [a]	部分，70%	265 [a]	部分，40%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68Y)	204	131	部分，80%	61 [a]	部分，50%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68A)	205	45	部分，60%	620 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68L)	206	187	部分，80%	172 [a]	部分，40%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72R)	208	1178	完全	499 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72D)	210	>10,000 [a]	部分，70%	456 - 504 [a]	部分，60%至70%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72H)	211	798	部分，70%	117 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42K/Y45R)	214	>10,000 [a]	部分，60%至70%	155 185 [a]	部分，70%

1H3-hIgG1-L6-hIL-2 (F42K/Y45R/D20A/S87A)	213	840 [a]	部分，70%	155 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A)	215	在圖上 >10,000，NC [a]	部分，50%	183 - 584 [a]	部分，50%至70%
hIgG1-L6-hIL-2 (T3A/D20A/R38E)	216	>10,000 [a]	部分，60%至90%	77 - 484 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	217	>10,000 [a]	部分，90%	218-512 [a]	部分，50%至60%
1H3-hIgG1-L6-hIL-2 (Δ1-3APT/D20A/R38E)	218	24 - 69	完全	6	完全
1H3-hIgG1-L6-hIL-2 (Δ1-3APT/D20A/R38E/C125A)	219	49 - 619	部分，30%至70%	165 - 619 [a]	部分，40%至50%
1H3-hIgG1-L6-hIL-2 (R38E/Q126D)	225	在圖上 >10,000，NC [a]	部分，60%	在圖上 >10,000，NC [a]	部分，40%
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/Q126D)	228	>10,000 [a]	部分，60%	226 [a]	部分，50%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Q126D)	229	在圖上 >10,000，NC [a]	非活性	在圖上 >10,000，NC [a]	非活性

NC =未藉由GraphPad Prism 7計算

[a] = 倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

表13. 來自第6組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2變異體之SEQ ID NO**	**相對於rhIL-2之倍數變化(NK-92)**	**促效活性(NK-92)**	**相對於rhIL-2之倍數變化(TF1+IL-2Rβ)**	**促效活性(TF1+IL-2Rβ)**
1H3-hIgG1-L6-hIL-2 (D20A/F42N)	247	>10,000 [a]	部分，60%	在圖上 >10,000，NC [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/F42Q)	248	>10,000 [a]	部分，50%	16 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/F42P)	254	>10,000 [a]	部分，60%	13 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/F42S)	255	>10,000 [a]	部分，60%	17 [a]	部分，40%
1H3-hIgG1-L6-hIL-2 (D20A/Y45E)	264	4717	部分，80%	32 [a]	部分，50%
1H3-hIgG1-L6-hIL-2 (I92D/F42Q)	277	>10,000 [a]	部分，50%	24 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (I92D/F42I)	280	>10,000 [a]	部分，30%	117 [a]	部分，20%
1H3-hIgG1-L6-hIL-2 (I92D/F42K)	282	>10,000 [a]	部分，50%	58 [a]	部分，90%

1H3-hIgG1-L6-hIL-2 (I92D/F42T)	286	>10,000 [a]	部分，60%	在圖上 >10,000，NC [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (R38E/D20S)	307	>10,000 [a]	部分，50%	25 [a]	部分，40%
1H3-hIgG1-L6-hIL-2 (F42A/N88R)	308	>10,000 [a]	部分，70%	34 [a]	部分，30%

NC =未藉由GraphPad Prism計算

[a] =倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

實例5：用基於細胞之增殖分析法進行之高親和力及中等親和力hIL-2受體之減弱測試

【0191】 在增殖分析法中，在經方案E中所描述之NK-92及TF1+IL-2Rβ細胞株兩者中，測試來自實例2中之第1至6組的抗體減弱之hIL-2融合蛋白 (2D12-mIgG1-D265A-L6-hIL-2 、 2D12-hIgG1-L6-hIL-2 及 1H3-hIgG1-L6-hIL-2融合蛋白)之IL-2活性的減弱。分析法之結果提供於表14至表19中。

【0192】 在此基於細胞之增殖分析法中測試來自實例4之在pSTAT5滴定曲線中具有實質性減弱的所選擇之1H3-hIgG1-L6-hIL-2融合蛋白。pSTAT5為IL-2活性之下游讀出，且分析法僅需要刺激10分鐘，此可為IL-2依賴性活性之小的快照。對於增殖分析法，將細胞與2D12-mIgG1-D265A-L6-hIL-2、2D12-hIgG1-L6-hIL-2、1H3-hIgG1-L6-hIL-2融合蛋白或重組hIL-2對照一起培育3至4天，從而在活體內提供IL-2依賴性活性之生理學相關性更高的讀出。使用此增殖分析法來分析在pSTAT5分析法中產生但未測試之其他2D12-mIgG1-D265A-L6-hIL-2及2D12-hIgG1-L6-hIL-2融合蛋白的IL-2依賴性活性。

【0193】 與基於細胞之pSTAT5劑量-滴定實驗類似，EC_{50}之計算值係由相對發光單位(RLU)而非gMFI確定，且一旦計算出EC_{50}，就按照與

實例4相同之方式進行結果分析。與實例4中所鑑別之結果類似，增殖曲線證實，與僅結合至α或β鏈之單取代相比，一些調節與α鏈及β鏈兩者之結合的取代實質上減弱高親和力受體上之IL-2活性。亦測試所選擇之此等1H3-hIgG1-L6-hIL-2融合蛋白在TF1+IL-2Rβ細胞株上之增殖，且證實此等相同取代中之一些實質上減弱中等親和力受體上之IL-2活性。

表14. 在基於細胞之增殖分析法中，來自第1組之2D12-mIgG1-D265A-L6-hIL-2或2D12-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2變異體之SEQ ID NO**	**相對於rhIL-2之倍數變化(NK-92)**	**促效活性(NK-92)**	**相對於rhIL-2之倍數變化(TF1+IL-2Rβ)**	**促效活性(TF1+IL-2Rβ)**
2D12-mIgG1-D265A-L6-hIL-2 (F42K)	1	2	完全	0	完全
2D12-mIgG1-D265A-L6-hIL-2 (Y45R)	60	3	完全	2	完全
2D12-hIgG1-L6-hIL-2 (V69A)	2	0	完全	0	完全
2D12-hIgG1-L6-hIL-2 (V69E)	3	13	部分，60%	83	完全
2D12-hIgG1-L6-hIL-2 (V69H)	6	41	部分，60%	544	完全
2D12-hIgG1-L6-hIL-2 (V69K)	8	在圖上>10,000，NC [a]	非活性	3033	部分，40%
2D12-hIgG1-L6-hIL-2 (V69L)	9	1	完全	1	完全
2D12-hIgG1-L6-hIL-2 (V69F)	4	0	完全	1	完全
2D12-hIgG1-L6-hIL-2 (V69G)	5	108	完全	396	完全
2D12-hIgG1-L6-hIL-2 (V69I)	7	1	完全	1	完全
2D12-hIgG1-L6-hIL-2 (V69M)	10	2	完全	3	完全
2D12-hIgG1-L6-hIL-2 (V69Q)	11	7	完全	16	完全
2D12-mIgG1-D265A-L6-hIL-2 (V69R)	581	2392	部分，70%	2973	部分，50%
2D12-hIgG1-L6-hIL-2 (V69S)	12	6	完全	13	完全
2D12-hIgG1-L6-hIL-2 (V69T)	13	3	完全	3	完全
2D12-hIgG1-L6-hIL-2 (V69W)	14	0	完全	1	完全
2D12-hIgG1-L6-hIL-2 (V69Y)	15	1	完全	1	完全
2D12-mIgG1-D265A-L6-hIL-2 (D20A)	31	1	完全	>10,000 [a]	完全
2D12-mIgG1-D265A-L6-hIL-2 (D20N)	32	0	完全	>10,000 [a]	完全

2D12-mIgG1-D265A-L6-hIL-2 (D20K)	33	4	完全	在圖上 >10,000，NC [a]	非活性
2D12-mIgG1-D265A-L6-hIL-2 (N88A)	34	0	完全	2289	完全
2D12-mIgG1-D265A-L6-hIL-2 (N88G)	35	0	完全	2978	完全
2D12-mIgG1-D265A-L6-hIL-2 (N88H)	36	1-3	完全	在圖上 >10,000，NC [a]	非活性
2D12-mIgG1-D265A-L6-hIL-2 (N88K)	37	564-9557	部分，40%	在圖上 >10,000，NC [a]	非活性
2D12-mIgG1-D265A-L6-hIL-2 (Q126L)	375	0-12	完全	118	完全
2D12-mIgG1-D265A-L6-hIL-2 (Q126E)	376	0-3	完全	40	完全
2D12-mIgG1-D265A-L6-hIL-2 (F42K/F44K)	16	44	完全	在圖上 >10,000，NC [a]	非活性
2D12-mIgG1-D265A-L6-hIL-2 (F42K/Y45R)	17	1-2	完全	0-3	完全
2D12-mIgG1-D265A-L6-hIL-2 (F42K/V69R)	18	1500	部分，80%	841	部分，80%
2D12-mIgG1-D265A-L6-hIL-2 (Y45R/V69R)	19	1	完全	3	完全
2D12-mIgG1-D265A-L6-hIL-2 (D20A/D84A)	38	1	完全	在圖上 >10,000，NC [a]	非活性
2D12-mIgG1-D265A-L6-hIL-2 (D20A/E15A)	39	0	完全	在圖上 >10,000，NC [a]	部分，40%
2D12-mIgG1-D265A-L6-hIL-2 (D20A/E95A)	40	0	完全	>10,000 [a]	完全
2D12-mIgG1-D265A-L6-hIL-2 (D20A/N88A)	41	6	部分，60%	在圖上 >10,000，NC [a]	非活性
2D12-mIgG1-D265A-L6-hIL-2 (D20A/S87A)	42	0	完全	>10,000 [a]	完全
2D12-mIgG1-D265A-L6-hIL-2 (D84A/N88A)	43	0	完全	在圖上 >10,000，NC [a]	非活性
2D12-mIgG1-D265A-L6-hIL-2 (E15A/N88A)	44	0	完全	4201	部分，80%
2D12-mIgG1-D265A-L6-hIL-2 (S87A/N88A)	45	0	完全	1521	完全
2D12-mIgG1-D265A-L6-hIL-2 (F42K/F44K/Y45R)	20	NT	NT	0	完全
2D12-mIgG1-D265A-L6-hIL-2 (F42A/Y45A/L72G)	574	0-1	完全	0-3	完全
2D12-mIgG1-D265A-L6-hIL-2 (R38A/F42K/Y45R)	21	1	完全	0	完全
2D12-mIgG1-D265A-L6-hIL-2 (R38E/F42K/Y45R)	22	1-3	完全	0	完全
2D12-mIgG1-D265A-L6-hIL-2 (K43E/F42K/Y45R)	23	0	完全	3	完全

2D12-mIgG1-D265A-L6-hIL-2 (K43T/F42K/Y45R)	24	0	完全	3	完全
2D12-mIgG1-D265A-L6-hIL-2 (F42K/Y45R/E62A)	25	1	完全	0-3	完全
2D12-mIgG1-D265A-L6-hIL-2 (P65R/F42K/Y45R)	26	1	完全	0-2	完全
2D12-mIgG1-D265A-L6-hIL-2 (P65S/F42K/Y45R)	27	1	完全	0-2	完全
2D12-mIgG1-D265A-L6-hIL-2 (V69A/F42K/Y45R)	28	1	完全	0-4	完全
2D12-mIgG1-D265A-L6-hIL-2 (V69D/F42K/Y45R)	29	1	完全	0-5	完全
2D12-mIgG1-D265A-L6-hIL-2 (V69R/F42K/Y45R)	30	1-4	完全	0-6	完全

NT =未測試

NC =未藉由GraphPad Prism 7計算

[a] = 倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

表15. 在基於細胞之增殖分析法中，來自第2組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2 變異體之 SEQ ID NO**	**相對於 rhIL-2 之倍數變化 (NK-92)**	**促效活性 (NK-92)**	**相對於 rhIL-2 之倍數變化 (TF1+IL-2Rβ)**	**促效活性 (TF1+IL-2Rβ)**
1H3-hIgG1-L6-hIL-2 (R38A)	46	0	完全	1	完全
1H3-hIgG1-L6-hIL-2 (R38D)	47	3	完全	0	完全
1H3-hIgG1-L6-hIL-2 (R38E)	48	7	完全	1 [a]	完全
1H3-hIgG1-L6-hIL-2 (F42R)	50	6	完全	0 [a]	完全
1H3-hIgG1-L6-hIL-2 (F42D)	52	10	完全	2	完全
1H3-hIgG1-L6-hIL-2 (K43A)	54	1 [a]	完全	2	完全
1H3-hIgG1-L6-hIL-2 (Y45R)	60	4	完全	0 [a]	完全
1H3-hIgG1-L6-hIL-2 (E61A)	61	0 [a]	完全	1	完全
1H3-hIgG1-L6-hIL-2 (E61R)	62	1	完全	1	完全
1H3-hIgG1-L6-hIL-2 (E61K)	63	1	完全	1	完全
1H3-hIgG1-L6-hIL-2 (E62A)	64	1	完全	1	完全
1H3-hIgG1-L6-hIL-2 (E62R)	65	在圖上 >10,000，NC [a]	非活性	209	部分，60%
1H3-hIgG1-L6-hIL-2 (E62K)	66	>10,000 [a]	部分，40%至70%	67 - 99	部分，60%
1H3-hIgG1-L6-hIL-2 (E62Y)	67	1	完全	1	完全
1H3-hIgG1-L6-hIL-2 (E68K)	70	0	完全	1	完全

1H3-hIgG1-L6-hIL-2 (E68R)	71	1	完全	1	完全
1H3-hIgG1-L6-hIL-2 (L72R)	74	3	完全	3	完全
1H3-hIgG1-L6-hIL-2 (L72D)	76	2	完全	0	完全
1H3-hIgG1-L6-hIL-2 (L72H)	77	1	完全	1	完全
1H3-hIgG1-L6-hIL-2 (R38D/E61R)	79	36	完全	2	完全
1H3-hIgG1-L6-hIL-2 (R38D/E61R/K43E)	80	27	完全	1	完全
1H3-hIgG1-L6-hIL-2 (T3A/F42A/Y45A/L72G/C125A)	81	142	完全	1 - 2	部分，40%至完全

NT =未測試

NC =未藉由GraphPad Prism 7計算

[a] = 倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

表16. 在基於細胞之增殖分析法中，來自第3組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2變異體之SEQ ID NO**	**相對於rhIL-2之倍數變化(NK-92)**	**促效活性(NK-92)**	**相對於rhIL-2之倍數變化(TF1+IL-2Rβ)**	**促效活性(TF1+IL-2Rβ)**
1H3-hIgG1-L6-hIL-2 (H16E)	87	0	完全	34	完全
1H3-hIgG1-L6-hIL-2 (L19A)	88	NT	NT	1	完全
1H3-hIgG1-L6-hIL-2 (D20I)	89	NT	NT	8 [a]	部分，50%
1H3-hIgG1-L6-hIL-2 (D20S)	90	1	完全	201 - 304	部分，80%至完全
1H3-hIgG1-L6-hIL-2 (D20H)	91	239	完全	986 - 6461 [a]	部分，50%至70%
1H3-hIgG1-L6-hIL-2 (D20W)	93	NT	NT	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (D20Y)	94	880 - 2097 [a]	完全	383	完全
1H3-hIgG1-L6-hIL-2 (D20R)	95	NT	NT	262 - 275	完全
1H3-hIgG1-L6-hIL-2 (D20F)	96	NT	NT	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (D84A)	98	NT	NT	21	完全
1H3-hIgG1-L6-hIL-2 (D84R)	99	9	完全	269 - 455	部分，80%至90%
1H3-hIgG1-L6-hIL-2 (D84K)	100	4	完全	354 - 385	部分，70%至完全

1H3-hIgG1-L6-hIL-2 (N88Y)	102	NT	NT	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (N88D)	103	0	完全	115 - 137	部分，70%至完全
1H3-hIgG1-L6-hIL-2 (N88R)	104	1 -5	部分，80%至完全	959	部分，80%
1H3-hIgG1-L6-hIL-2 (N88E)	105	NT	NT	1162	部分，50%
1H3-hIgG1-L6-hIL-2 (N88F)	106	NT	NT	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (N88I)	107	NT	NT	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (I92Y)	109	NT	NT	1	完全
1H3-hIgG1-L6-hIL-2 (I92S)	110	NT	NT	10	完全
1H3-hIgG1-L6-hIL-2 (I92R)	112	NT	NT	13	完全
1H3-hIgG1-L6-hIL-2 (I92D)	113	15 - 20	完全	609 - 1006	部分，90%至完全
1H3-hIgG1-L6-hIL-2 (E95R)	116	NT	NT	8	完全
1H3-hIgG1-L6-hIL-2 (D20T)	92	2	完全	124 - 149	完全
1H3-hIgG1-L6-hIL-2 (D20Y/H16E)	118	5	完全	8076 [a]	部分，80%

NT =未測試

NC =未藉由GraphPad Prism 7計算

[a] = 倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

表17. 在基於細胞之增殖分析法中，來自第4組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2變異體之SEQ ID NO**	**相對於rhIL-2之倍數變化(NK-92)**	**促效活性(NK-92)**	**相對於rhIL-2之倍數變化(TF1+IL-2Rβ)**	**促效活性(TF1+IL-2Rβ)**
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A)	82	14	部分，90%	13	部分，70%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S)	90	127	完全	8709 [a]	部分，50%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W)	93	在圖上>10,000，NC [a]	非活性	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y)	94	在圖上>10,000，NC [a]	部分，50%	在圖上>10,000，NC [a]	非活性

1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K)	100	783	部分，90%	2051 [a]	部分，30%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A)	101	19	部分，90%	20	部分，90%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D)	103	50	完全	3284 [a]	部分，90%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R)	104	42	完全	6864 [a]	部分，50%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K)	117	51	完全	164	部分，80%

NC =未藉由GraphPad Prism 7計算

[a] =倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

表18. 在基於細胞之增殖分析法中，來自第5組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2 變異體之 SEQ ID NO**	**相對於 rhIL-2 之倍數變化 (NK-92)**	**促效活性 (NK-92)**	**相對於 rhIL-2 之倍數變化 (TF1+IL-2Rβ)**	**促效活性 (TF1+IL-2Rβ)**
1H3-hIgG1-L6-hIL-2 (F42K/D20A)	129	在圖上 >10,000，NC [a]	部分，20%	3060 [a]	完全
1H3-hIgG1-L6-hIL-2 (F42A/D20A)	130	在圖上 >10,000，NC [a]	完全	2081 [a]	完全
1H3-hIgG1-L6-hIL-2 (R38P/D20A)	141	86	完全	761	完全
1H3-hIgG1-L6-hIL-2 (R38S/D20A)	142	140	完全	662	完全
1H3-hIgG1-L6-hIL-2 (R38V/D20A)	146	11	完全	843	完全
1H3-hIgG1-L6-hIL-2 (D20A/R38E)	149	1183 - 2016	部分，70%至完全	>10,000 [a]	部分，80%至完全
1H3-hIgG1-L6-hIL-2 (R38D/D20A)	150	2262 [a]	完全	680	完全
1H3-hIgG1-L6-hIL-2 (F42R/I92D)	159	在圖上 >10,000，NC [a]	部分，30%	1210	完全
1H3-hIgG1-L6-hIL-2 (F42H/I92D)	160	288 [a]	完全	242 [a]	完全
1H3-hIgG1-L6-hIL-2 (F42A/I92D)	161	在圖上 >10,000，NC [a]	部分，60%	2275	部分，80%
1H3-hIgG1-L6-hIL-2 (R38D/I92D)	170	746 [a]	部分，90%	172	完全
1H3-hIgG1-L6-hIL-2 (R38E/I92D)	171	1611 [a]	完全	116	完全

1H3-hIgG1-L6-hIL-2 (R38E/D84R)	175	在圖上 >10,000，NC [a]	完全	147	完全
1H3-hIgG1-L6-hIL-2 (R38E/D84K)	176	在圖上 >10,000，NC [a]	部分，70%	315	完全
1H3-hIgG1-L6-hIL-2 (R38D/E61R/D20A)	179	在圖上 >10,000，NC [a]	部分，50%	984	完全
1H3-hIgG1-L6-hIL-2 (R38E/E61R/D20A)	180	在圖上 >10,000，NC [a]	完全	417	完全
1H3-hIgG1-L6-hIL-2 (R38Q/E61R/D20A)	181	在圖上 >10,000，NC [a]	部分，80%	803	完全
1H3-hIgG1-L6-hIL-2 (R38A/E61R/D20A)	182	在圖上 >10,000，NC [a]	部分，60%	1031	完全
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38A)	183	42	部分，70%	537	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38D)	184	5315 [a]	部分，50%	492	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38E)	185	在圖上 >10,000，NC [a]	完全	439	部分，90%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38Q)	186	572	完全	859	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42R)	187	2096	部分，70%	356	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42A)	188	369	部分，70%	73	部分，90%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42D)	189	在圖上 >10,000，NC [a]	非活性	在圖上 >10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42H)	190	641	部分，90%	320	完全
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42K)	191	在圖上 >10,000，NC [a]	非活性	272	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/K43E)	193	80	部分，90%	1876 [a]	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45A)	195	25	完全	82	部分，90%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45K)	196	在圖上 >10,000，NC [a]	部分，20%	383	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45R)	198	在圖上 >10,000，NC [a]	非活性	57	部分，50%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E61A)	199	306 [a]	部分，80%	702	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62A)	200	在圖上 >10,000，NC [a]	部分，20%	661	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62R)	201	在圖上 >10,000，NC [a]	非活性	在圖上 >10,000，NC [a]	非活性

1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62K)	202	在圖上>10,000，NC [a]	非活性	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62Y)	203	721	部分，40%	982 [a]	部分，30%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68Y)	204	11	完全	469	完全
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68A)	205	6	部分，50%	535	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68L)	206	15	完全	972	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72R)	208	655 [a]	部分，50%	316	部分，40%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72D)	210	5415	非活性	125	部分，90%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72H)	211	583 [a]	部分，60%	135	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42K/Y45R)	214	在圖上>10,000，NC [a]	非活性	58 - 209	部分，40%至80%
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/D20A/S87A)	213	123	完全	0	完全
1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A)	215	>10,000 [a]	部分，30%至90%	2102 [a]	部分，80%
1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E)	216	2338 - 5870	部分，80%至完全	353 - 571	完全
1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	217	>10,000 [a]	完全	1086 [a]	部分，80%至完全
1H3-hIgG1-L6-hIL-2 (Δ1-3APT/D20A/R38E)	218	4 -16	完全	32	部分，90%
1H3-hIgG1-L6-hIL-2 (Δ1-3APT/D20A/R38E/C125A)	219	>10,000 [a]	非活性至部分，50%	993 [a]	部分，60%
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/Q126D)	228	>10,000 [a]	部分，50%	597	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Q126D)	229	106 [a]	非活性	在圖上>10,000，NC [a]	非活性

NC =未藉由GraphPad Prism 7計算

[a] =倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

表19. 在基於細胞之增殖分析法中，來自第6組之1H3-hIgG1-L6-hIL-2融合蛋白相對於rhIL-2之倍數變化及促效活性

變異體	**hIL-2 變異體之 SEQ ID NO**	**相對於 rhIL-2 之倍數變化 (NK-92)**	**促效活性(NK-92)**	**相對於 rhIL-2 之倍數變化 (TF1+IL-2Rβ)**	**促效活性 (TF1+IL-2Rβ)**
1H3-hIgG1-L6-hIL-2 (D20A/E61R)	230	3950 [a]	部分，10%	278	部分，50%
1H3-hIgG1-L6-hIL-2 (D20A/F42N)	247	>10,000 [a]	部分，50%	662	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/F42Q)	248	在圖上 >10,000，NC [a]	部分，30%	630	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/F42I)	251	1307 [a]	部分，20%	494	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/F42L)	252	68	完全	533	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/F42M)	253	53	完全	370	部分，50%
1H3-hIgG1-L6-hIL-2 (D20A/F42P)	254	9374 [a]	部分，80%	702	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/F42S)	255	1286	部分，70%	687	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/F42T)	256	1474 [a]	部分，10%	622	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/F42W)	257	414 [a]	部分，70%	400	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/F42Y)	258	322	部分，70%	545	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A, F42V)	259	5796 [a]	部分，30%	579	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/Y45A)	260	61	部分，80%	554	部分，80%
1H3-hIgG1-L6-hIL-2 (D20A/Y45N)	261	31	完全	390	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/Y45D)	262	363	部分，60%	729	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/Y45Q)	263	730 [a]	部分，70%	348	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/Y45E)	264	1414 [a]	部分，60%	486	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/Y45G)	265	613 [a]	部分，80%	392	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/Y45H)	266	420 [a]	部分，70%	427	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/Y45I)	267	39	部分，70%	137	部分，30%

1H3-hIgG1-L6-hIL-2 (D20A/Y45L)	268	11	完全	426	部分，70%
1H3-hIgG1-L6-hIL-2 (D20A/Y45M)	269	107	完全	449	部分，60%
1H3-hIgG1-L6-hIL-2 (D20A/Y45F)	270	25	部分，90%	272	部分，50%
1H3-hIgG1-L6-hIL-2 (D20A/Y45P)	271	577 [a]	完全	710	完全
1H3-hIgG1-L6-hIL-2 (I92D/F42Q)	277	7227 [a]	部分，30%	872	完全
1H3-hIgG1-L6-hIL-2 (I92D/F42I)	280	4587 [a]	部分，10%	3644 [a]	完全
1H3-hIgG1-L6-hIL-2 (I92D/F42K)	282	>10,000 [a]	部分，20%	848 [a]	完全
1H3-hIgG1-L6-hIL-2 (I92D/F42T)	286	>10,000 [a]	部分，40%	1068 [a]	完全
1H3-hIgG1-L6-hIL-2 (I92D/F42W)	287	405 [a]	完全	3954 [a]	完全
1H3-hIgG1-L6-hIL-2 (I92D/F42Y)	288	58	完全	106	完全
1H3-hIgG1-L6-hIL-2 (I92D/F42V)	289	1075 [a]	部分，60%	343	完全
1H3-hIgG1-L6-hIL-2 (I92D/Y45A)	290	15	完全	285	完全
1H3-hIgG1-L6-hIL-2 (I92D/Y45Q)	293	53	完全	80	完全
1H3-hIgG1-L6-hIL-2 (I92D/Y45G)	295	41	完全	91	完全
1H3-hIgG1-L6-hIL-2 (I92D/Y45M)	299	7	完全	146	完全
1H3-hIgG1-L6-hIL-2 (I92D/Y45F)	300	33	完全	1650 [a]	完全
1H3-hIgG1-L6-hIL-2 (I92D/Y45S)	302	20	完全	306	完全
1H3-hIgG1-L6-hIL-2 (R38E/D20H)	306	13	非活性	2945	部分，40%
1H3-hIgG1-L6-hIL-2 (R38E/D20S)	307	在圖上>10,000，NC [a]	部分，50%	626	完全
1H3-hIgG1-L6-hIL-2 (F42A/N88R)	308	8351 [a]	部分，70%	1456	完全
1H3-hIgG1-L6-hIL-2 (F42A/N88D)	309	1966 [a]	完全	86	完全
1H3-hIgG1-L6-hIL-2 (R38E/I92K)	334	>10,000 [a]	部分，70%	239	完全
1H3-hIgG1-L6-hIL-2 (R38E/I92P)	337	在圖上>10,000，NC [a]	非活性	在圖上>10,000，NC [a]	非活性
1H3-hIgG1-L6-hIL-2 (R38E/H16E)	343	658 [a]	完全	58	完全
1H3-hIgG1-L6-hIL-2 (R38K/D20A)	344	66	完全	369	部分，70%

NC = 未藉由GraphPad Prism 7計算

[a] = 倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

實例6：抗hPD-1抗體之產生

【0194】使用若干方法產生具有所需特性之各種不同抗hPD-1抗體。

【0195】在一種方法中，使用表現人類抗體基因(人類輕鏈(VLCL或VKCK)及人類VH)及雞重鏈恆定區的基因轉殖之雞(OmniChicken™)來產生抗hPD-1人類單株抗體(Ching等人, mAbs 2018)。用100 μg經Fc標記之人類PD-1蛋白(huPD-1-Fc) (SEQ ID NO: 380)每14天對基因轉殖之雞進行免疫接種持續14週。在另一方法中，用編碼人類PD-1 (SEQ ID NO: 347)之DNA對基因轉殖之雞進行六次基因免疫接種，隨後用100 μg huPD-1-Fc (SEQ ID NO: 380)進行最終增強免疫接種。藉由ELISA監測各動物對塗佈鏈黴抗生物素蛋白之盤上的經生物素標記之人類PD-1的血清免疫反應。

【0196】自各經免疫接種之動物分離脾細胞，使用凝膠囊封微環境(Gel Encapsulated Microenvironment ; GEM)分析法(經Mettler Izquierdo, S., Varela, S., Park, M., Collarini, E. J., Lu, D., Pramanick, S., Rucker, J., Lopalco, L., Etches, R., & Harriman, W. (2016). High-efficiency antibody discovery achieved with multiplexed microscopy. *Microscopy (Oxford, England)*, *65*(4), 341-352中所描述)測試陽性抗體殖株，且針對人類PD-1標記之珠粒進行篩選。將陽性殖株定序且選殖重鏈及輕鏈之可變區，組裝成單鏈可變片段，並與免疫球蛋白之鉸鏈及Fc區融合(ScFv-Fc)。此等獨特scFv-Fc融合蛋白短暫表現於Expi293細胞中，且

藉由ELISA在塗佈有huPD-1-Fc (SEQ ID NO: 380)或石蟹獼猴-PD-1-Fc (SEQ ID NO: 381)之盤上測試上清液之結合活性。總計，使用此方法鑑別102種獨特抗人類PD-1可變重鏈及可變輕鏈對。2H7-hIgG4 (SEQ ID NO: 382至391、424及425)及A2-hIgG4 (SEQ ID NO: 402至411、428及429)屬於在此方法中鑑別之抗體。

【0197】 其他方法產生鑑別表示為C51E6-hIgG4之抗hPD-1抗體，該抗體經生殖系最佳化以變成指定為C51E6-5-hIgG4 (SEQ ID NO: 392至401、426、427)之抗體，且經人類化及進一步序列最佳化以變成指定為Abz1mod-hIgG4 (SEQ ID NO: 449、450)之抗體。

【0198】 將抗PD-1可變區序列表示為人類IgG4 κ抗體，且使用經通用方法方案A中所描述之流式細胞分析技術評估與表現PD-1之細胞結合的能力。使用表現重組人類PD-1之Jurkat細胞株(Jurkat + hPD-1細胞株)，首先篩選所測試之抗體以用於與人類PD-1之結合。自280 nM之最高濃度連續稀釋抗體且隨後向細胞中添加別藻藍蛋白結合之抗人類IgG二級抗體以用於偵測。在92種命中物中，79種測試抗PD-1抗體具有<30 nM之EC_{50}結合(藉由流式細胞分析技術)。2H7-hIgG4 (SEQ ID NO: 382至391、424、425)、C51E6-5-hIgG4 (SEQ ID NO: 392至401、426及427)、A2-hIgG4 (SEQ ID NO: 402至411、428及429)、OMC.1.B6-hIgG4 (SEQ ID NO: 438及439)、OMC.1.D6-hIgG4 (SEQ ID NO: 442及443)、OMC.2.C6-hIgG4 (SEQ ID NO: 440及441)、1H9-hIgG4 (SEQ ID NO: 576及525)、1D5-hIgG4 (SEQ ID NO: 577及527)及2A3.H7-hIgG4 (SEQ ID NO: 424及523)屬於一組抗體，其使用表現人類PD-1 (SEQ ID NO: 346)之Jurkat細胞株鑑別為與hPD-1具有中等至高親和力結合之抗體。在

多個實驗中，藉由流式細胞分析技術，2H7-hIgG4、1H9-hIgG4、1D5-hIgG4及2A3.H7-hIgG4與以重組方式表現hPD-1之Jurkat細胞結合之EC_{50}計算值為0.1至0.3 nM。藉由流式細胞分析技術，C51E6-5-hIgG4與表現hPD-1之Jurkat細胞結合之EC_{50}計算值為2至4 nM，且A2-hIgG4、OMC.1.B6-hIgG4、OMC.1.D6-hIgG4及OMC.2.C6-hIgG4為3至16 nM。結合對hPD-1具有特異性，因為2H7-hIgG4、C51E6-5-hIgG4、A2-hIgG4、1H9-hIgG4、1D5-hIgG4、2A3.H7-hIgG4、OMC.1.B6-hIgG4、OMC.1.D6-hIgG4及OMC.2.C6-hIgG4抗體滴定未結合不表現hPD-1之親本Jurkat細胞株(資料未示出)。

實例7：抗hPD-1抗體結合在存在抗hPD-1 #1-mIgG2b-N297A及抗hPD-1 #2-mIgG2b-N297A抗體之情況下的表徵

【0199】經通用方法方案B中所描述，評估2H7-hIgG4、C51E6-5-hIgG4及A2-hIgG4在存在抗hPD-1 #1-mIgG2b-N297A及抗hPD-1 #2-mIgG2b-N297A抗體之情況下與hPD-1之結合競爭。

【0200】作為對照，在存在飽和濃度之10 μM抗hPD-1 #1-mIgG2b-N297A之情況下滴定OPDIVO® (納武單抗) (圖4A)。當與無抗hPD-1 #1-mIgG2b-N297A競爭物之OPDIVO®的劑量-滴定曲線相比時，劑量-滴定曲線在存在抗hPD-1 #1-mIgG2b-N297A競爭物之情況下大大降低(劑量-滴定曲線向圖右側移動100至1000倍)。如藉由圖4B至圖4D中小於10倍之移動所繪示，在2H7-hIgG4、C51E6-5-hIgG4或A2-hIgG4暴露之前，以飽和濃度(10 μM)添加抗hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A並不消除2H7-hIgG4、C51E6-5-hIgG4或A2-hIgG4與hPD-1之結合，表明2H7-hIgG4、C51E6-5-hIgG4及A2-hIgG4在存在抗

hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A之情況下未競爭結合至PD-1。

實例8：非拮抗劑hPD-1抗體之表徵

【0201】 使用經通用方法方案C中所描述之基於活體外細胞之人類PD-1/PD-L1阻斷生物分析法，測試抗hPD-1抗體2H7-hIgG4、C51E6-5-hIgG4及A2-hIgG4之PD-1拮抗劑活性。在200 nM之最終濃度下測試除A2-hIgG4之外的所有抗體。在500 nM之最終濃度下測試A2-hIgG4。

【0202】 抗hPD-1抗體2H7-hIgG4、C51E6-5-hIgG4、A2-hIgG4、OMC.1.B6-hIgG4、OMC.1.D6-hIgG4、OMC.2.C6-hIgG4、1H9-hIgG4、1D5-hIgG4及2A3.H7-hIgG4中之每一者均未展示hPD-1拮抗劑活性，因為所有均顯示平均3000個相對發光單位(RLU)之發光程度且顯現與陰性對照KLH-C3-hIgG4類似之RLU (資料未示出)。相比之下，抗hPD-1 #1為一種已知之hPD-1拮抗劑，其阻斷hPD-L1 (SEQ ID NO: 584)與hPD-1之接合，展現高於14,000 RLU之發光(資料未示出)。

實例9：抗hPD-1減弱之hIL-2融合蛋白結合表現人類PD-1之Jurkat細胞

【0203】 為了構築各種抗體及抗體減弱之hIL-2融合蛋白表現載體，產生編碼抗體、細胞介素、細胞介素受體及連接子之序列的對應聚核苷酸且將其選殖入表現載體中。抗體或抗體融合蛋白短暫表現於人類胎腎(Human Embryonic Kidney；HEK) 293細胞中，隨後藉由親和力層析使用蛋白A-瓊脂糖或蛋白G-瓊脂糖純化。使用超速離心過濾將經純化之蛋白質濃縮且將緩衝液更換成磷酸鹽緩衝鹽水或含有100 mM L-精胺酸及10 mM L-組胺酸之磷酸鹽緩衝鹽水，其後測定蛋白質濃度。

【0204】 在一些方法中，攜帶S228P鉸鏈穩定化突變之2H7-

hIgG4、C51E6-5-hIgG4及A2-hIgG4在免疫球蛋白重鏈之C端處直接融合(df)至hIL-2或使用L6連接子融合至hIL-2。此等抗PD-1減弱之hIL-2融合蛋白之說明概述於圖5中。經實例2中所描述，產生具有減弱hIL-2活性之hIL-2取代的各種構築體。使用經通用方法方案A中所描述之表現hPD-1之Jurkat細胞株，測試表20中所列出之抗hPD-1減弱之hIL-2融合蛋白與hPD-1之結合。進一步最佳化2H7-hIgG4 (SEQ ID NO: 384及385)之可變區，且將同型切換為具有效應功能無效取代L235A/G237A (LAGA，經WO1998/006248中所描述)之人類IgG1以變成H7-632-hIgG1-LAGA (SEQ ID NO: 414及415)。最佳化之H7-632-hIgG1-LAGA亦直接融合(df)至具有減弱之hIL-2活性的hIL-2變異體(hIL-2 T3A/D20A/R38E/C125A；SEQ ID NO: 217)以變成H7-767 (SEQ ID NO: 412至413、415至423、532)，且測試H7-632-hIgG1-LAGA及H7-767兩者與hPD-1之結合(表20)。使用GraphPad Prism 7軟體，自所滴定濃度中之幾何平均螢光強度(gMFI)計算EC_{50}值。

【0205】 抗hPD-1減弱之hIL-2融合蛋白之產生並不減少與hPD-1之結合，且抗hPD-1減弱之hIL-2融合蛋白仍能夠結合至表現人類PD-1之Jurkat細胞。與無減弱之hIL-2部分的各別抗hPD-1抗體相比，所測試之抗hPD-1減弱之hIL-2融合蛋白之EC_{50}計算值概述於表20中。

表20. 藉由流式細胞分析技術分析之抗hPD-1減弱之hIL-2融合蛋白與表現hPD-1之Jurkat細胞株的結合(EC_{50})

抗hPD-1抗體	EC_{50} (nM)	對應之抗hPD-1-hIL-2融合蛋白	EC_{50} (nM)
抗hPD-1 #1	0.3586	抗hPD-1 #1-hIgG4-L6-hIL-2 (D20A/R38E)	0.5318
C51E6-5-hIgG4	2.048	C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)	1.587
OMC.1.B6-hIgG4	7.422	OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E)	5.635
OMC.2.C6-hIgG4	11.52	OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E)	16.32
OMC.1.D6-hIgG4	15.96	OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E)	8.87
A2-hIgG4	5.968	A2-hIgG4-df-hIL-2 (D20A/R38E)	10.67
D12-hIgG4	9.674	D12-hIgG4-df-hIL-2 (D20A/R38E)	17.09
G12-hIgG4	5.36	G12-hIgG4-df-hIL-2 (D20A/R38E)	7.578
2H7-hIgG4	0.2769	2H7-hIgG4-df-hIL-2 (D20A/R38E)	0.1946
H7-632-hIgG1-LAGA	0.115	H7-767	0.218

【0206】 在抗hPD-1抗體上添加減弱之hIL-2部分並不消除與人類PD-1之結合，如藉由與無減弱之hIL-2部分的抗hPD-1抗體相比，抗hPD-1-hIL-2融合蛋白與Jurkat + hPD-1細胞之EC_{50}結合之增加小於2倍所證實。

實例10：抗hPD-1減弱之hIL-2融合蛋白在存在抗hPD-1 #1及抗hPD-1 #2之情況下結合hPD-1

【0207】 經通用方法方案B及實例7中所描述，測試抗hPD-1減弱之hIL-2融合蛋白在存在抗hPD-1 #1及抗hPD-1 #2之情況下與hPD-1受體之結合。亦進行相反實驗，其中檢驗抗hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A在存在飽和濃度之測試抗體減弱之hIL-2融合蛋白的情況下與hPD-1之結合。在此格式中，將表現hPD-1之Jurkat細胞以100,000個細胞/孔接種於FACS緩衝液中，在4℃下用抗人類FcγR阻斷試劑(Miltenyi)阻斷10分鐘並洗滌。將測試抗體減弱之hIL-2融合蛋白2H7-hIgG4-df-hIL-2 (D20A/R38E)、C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)、A2-hIgG4-df-hIL-2 (D20A/R38E)、H7-767及同型對照抗

DNA酶1H3-hIgG4-df-hIL-2 (D20A/R38E)在100 μL FACS緩衝液中稀釋至280 nM之最終濃度，且與表現hPD-1細胞之Jurkat細胞一起在冰上培育1小時。洗滌細胞且在冰上再懸浮於含有六倍連續滴定之抗hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A之FACS緩衝液中1小時，該滴定以50 nM之最大濃度開始。洗滌細胞且在冰上再懸浮於1:100稀釋度之藻紅素(Phycoerythrin)結合之抗小鼠IgG輕鏈κ單株抗體中45分鐘。再次洗滌細胞且再懸浮於具有1:1000稀釋度之Sytox Green (Thermo Fisher)之FACS緩衝液中。使用BD FACS Canto II (BD Biosciences)進行流式細胞分析技術分析且使用FlowJo軟體版本10計算gMFI。使用GraphPad Prism 7軟體，自所滴定濃度中之藻紅素信號之gMFI計算EC_{50}值。

【0208】 將減弱之hIL-2添加至抗hPD-1抗體2H7-hIgG4、C51E6-5-hIgG4及A2-hIgG4未減弱抗hPD-1蛋白在存在抗hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A之情況下結合至人類PD-1之能力，其與實例7中所描述之結果類似(圖16B至圖16D)。在此競爭分析法中亦測試H7-767，且圖13B繪示H7-767在存在抗hPD-1-#1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A之情況下繼續結合至hPD-1受體。相比之下，陽性對照抗hPD-1 #1在存在抗hPD-1 #1-mIgG2b-N297A或抗hPD-1 #2-mIgG2b-N297A之情況下的結合實質上降低(圖16A、圖13A)。

【0209】 圖6A及圖6B展示對於相反之競爭分析法，抗hPD-1 #1-mIgG2b-N297A (圖6A)及抗hPD-1 #2-mIgG2b-N297A (圖6B)仍能夠在存在飽和(280 nM)抗hPD-1減弱之hIL-2融合蛋白2H7-hIgG4-df-hIL-2 (D20A/R38E)、C51E6-5-hIgG4-df-hIL-2 (D20A/R38E)或A2-hIgG4-df-

hIL-2 (D20A/R38E)之情況下結合至Jurkat細胞上之hPD-1。在抗hPD-1融合蛋白暴露之前，飽和抗hPD-1減弱之hIL-2融合蛋白之此等結合曲線與抗hPD-1 #1-mIgG2b-N297A (無競爭)或抗hPD-1 #2-mIgG2b-N297A (無競爭)之結合曲線重疊。結合曲線亦與不結合至hPD-1之飽和陰性對照融合蛋白1H3-hIgG4-df-hIL-2 (D20A/R38E)重疊。

實例11：抗hPD-1減弱之hIL-2融合蛋白結合以重組方式表現之石蟹獼猴PD-1

【0210】 使用經短暫轉染而以重組方式表現石蟹獼猴PD-1的表現SV40大型T細胞抗原(HEK-293T)之人類胎腎293細胞株，在流式細胞分析技術中測試抗hPD-1減弱之hIL-2融合蛋白與石蟹獼猴PD-1之結合。對於各轉染反應，用2 μg之pCMV6-hygro-HA-cyno-PD-1 (1-185) (SEQ ID NO: 448)轉染2百萬個HEK-293T細胞，該pCMV6-hygro-HA-cyno-PD-1為一種哺乳動物載體，該載體包含經人類流感血球凝集素標記之石蟹獼猴PD-1胞外域及編碼潮黴素抗性之序列。藉由電穿孔進行轉染。將經轉染之細胞用人類FcγR阻斷試劑阻斷且用滴定量之抗hPD-1減弱之hIL-2融合蛋白染色。另外，將藻紅素結合之抗血球凝集素殖株15B12添加至細胞中以對經轉染之細胞進行染色，且將別藻藍蛋白結合之抗人類IgG Fc二級殖株HP6017 (BioLegend目錄號409306)添加至細胞中以對經結合之抗體進行染色。在BD Canto II上分析細胞且使用FlowJo軟體版本10以閘控存活、經傳染(血球凝集素陽性)之細胞且計算別藻藍蛋白信號之gMFI。使用GraphPad Prism 7軟體，自所滴定濃度中之gMFI計算EC_{50}值。

【0211】 抗hPD-1減弱之hIL-2融合蛋白以與表現人類PD-1之Jurkat T細胞上所發現之結合概況類似的方式結合至表現石蟹獼猴PD-1之HEK-

293T細胞(圖17)。2H7-hIgG4-df-hIL-2 (D20A/R38E)與表現石蟹獼猴PD-1之HEK-293T細胞結合之EC_{50}為5 nM，C51E6-5-hIgG4-df-hIL-2 (D20A/R38E)為6 nM且A2-hIgG4-df-hIL-2 (D20A/R38E)為11 nM。經格式化成抗hPD-1減弱之hIL-2融合蛋白比較物的抗hPD-1 #1及抗hPD-1 #2亦分別以9 nM及2 nM之EC_{50}值結合至石蟹獼猴PD-1，表明在抗hPD-1抗體上添加減弱之hIL-2部分並不消除與石蟹獼猴PD-1之結合。

實例12：抗hPD-1減弱之hIL-2融合蛋白結合活化之初代人類及石蟹獼猴PD-1

【0212】藉由流式細胞分析技術檢驗抗hPD-1抗體及抗hPD-1減弱之hIL-2融合蛋白在表現hPD-1之活化初級T細胞上的結合。為了測試2H7-hIgG4、C51E6-5-hIgG4或A2-hIgG4是否與天然hPD-1結合，將冷凍保存之人類周邊血液單核細胞(PBMC)解凍且用50 ng/mL佛波醇12-肉豆蔻酸酯13-乙酸酯(PMA)及1 μg/mL離子黴素活化來上調hPD-1受體。收集經活化之PBMC，在4℃下用1:50稀釋度之人類FcγR阻斷試劑(Miltenyi)阻斷10分鐘，且用滴定濃度之抗hPD-1抗體2H7-hIgG4、C51E6-5-hIgG4、A2-hIgG4、抗hPD-1 #1及同型對照染色。隨後，用1:20稀釋度之別藻藍蛋白結合之抗人類IgG Fc對細胞進行染色以偵測經結合之抗體。為了界定免疫亞群，使用包括抗人類CD3、抗CD4及抗CD8抗體之表面標記物的混合物。另外，檢驗樣品溶離份之hPD-1、hCD25、hCD122及hCD132之細胞表現。在BD Fortessa (BD Biosciences)上分析細胞，使用FlowJo軟體版本10以閘控T細胞亞群，隨後計算別藻藍蛋白信號之gMFI。使用GraphPad Prism 7軟體，自所滴定濃度中之gMFI計算EC_{50}值。為了測試抗hPD-1-hIL-2融合蛋白之結合，用PMA/離子黴素活化冷凍保存之CD3+

T細胞，且以上文所描述相同之方式進行流式細胞分析技術結合。

【0213】 亦使用流式細胞分析技術測試人類PD-1抗體減弱之hIL-2融合蛋白與活化石蟹獼猴T細胞之結合。用0.081 μM PMA與1.34 μM離子黴素之混合物活化石蟹獼猴PBMC。24小時後，使用與上文所描述之人類PD-1初代細胞結合相同的程序對細胞進行染色，不同之處在於使用石蟹獼猴交叉反應性標記物。使用FlowJo軟體版本10以閘控存活之$CD3^+CD4^+$或$CD3^+CD8^+$ T細胞且隨後計算別藻藍蛋白信號之gMFI。使用GraphPad Prism 7軟體，自抗hPD-1抗體或hPD-1抗體減弱之hIL-2融合蛋白的所滴定濃度中之gMFI計算EC_{50}值。

【0214】 在一些所測試之變異體中，減弱之hIL-2亦包括取代T3A及C125A，該等取代T3A及C125A分別移除O連接之醣基化部位且取代游離半胱胺酸殘基。

【0215】 在PMA及離子黴素活化之後，40%至50%之$CD4^+$ T細胞為$PD\text{-}1^+$，而30%至40%之$CD8^+$ T細胞為$PD\text{-}1^+$ (資料未示出)。藉由流式細胞分析技術，2H7-hIgG4與活化人類$CD3^+CD4^+$ T細胞結合之EC_{50}計算值為0.1至0.7 nM，C51E6-5-hIgG4為12 nM，A2-hIgG4為30 nM且2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A)為0.04 nM。2H7-hIgG4與活化人類$CD3^+CD8+$ T細胞結合之EC_{50}為0.1至0.8 nM，C51E6-5-hIgG4為16 nM，A2-hIgG4為22 nM且2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A)為0.03 nM。H7-767與活化人類$CD3^+CD4^+$ T細胞結合之EC_{50}為0.19 nM，且活化人類$CD3^+CD8^+$ T細胞為0.12 nM。2H7-hIgG4與活化石蟹獼猴$CD3^+CD4+$ T細胞結合之EC_{50}為0.09 nM，且2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A)為0.04 nM。2H7-hIgG4與活

化石蟹獼猴$CD3^+CD8+$ T細胞結合之EC_{50}為0.08 nM，且2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A)為0.03 nM。H7-767與活化石蟹獼猴$CD3^+CD4^+$ T細胞結合之EC_{50}為0.26 nM，且活化石蟹獼猴$CD3^+CD8^+$ T細胞為0.24 nM。此資料證實，當hPD-1抗體轉化為抗hPD-1減弱之hIL-2融合蛋白時，與活化hPD-1結合之EC_{50}計算值類似於hPD-1裸抗體與hPD-1結合之EC_{50}計算值。

【0216】藉由流式細胞分析技術，測試H7-767及H7-632-hIgG1-LAGA抗PD-1裸抗體在初代未活化之人類$CD4^+$及$CD8^+$ T細胞上之結合。解凍冷凍之人類$CD3^+$ T細胞且以上文所描述進行流式細胞分析技術。H7-767及H7-632-hIgG1-LAGA抗PD-1裸抗體兩者並不結合未活化之人類$CD4^+$及$CD8^+$ T細胞(資料未示出)。

實例13：藉由表面電漿子共振(SPR)進行之抗hPD-1抗體及抗hPD-1減弱之hIL-2融合蛋白與重組人類或石蟹獼猴PD-1之結合的定量

【0217】使用高通量SPR Carterra® LSA™進行表面電漿子共振結合分析以測定抗hPD-1抗體及抗hPD-1減弱之hIL-2融合蛋白之結合親和力。將蛋白質在含有0.01% Tween-20之10 mM乙酸鈉pH 4.5中稀釋至2或10 μg/mL，且使用磺基-N-羥基丁二醯亞胺/ 1-乙基-3-(3-二甲胺基)丙基碳化二亞胺(磺基-NHS/EDC)偶合化學方法偶合至HC30M (Carterra Bio)晶片且用乙醇胺阻斷。使用非再生性動力學偶合方法以測定商業來源之經重組His標記之人類PD-1及經His標記之石蟹獼猴PD-1 (Acro Biosystems)的結合動力學。

【0218】用具有κ輕鏈構架之經修飾之人類IgG1或經修飾之IgG4同型表現抗hPD-1抗體及抗hPD-1減弱之hIL-2融合蛋白。將額外取代L235E

或L235A/G237A (LAGA，經國際公開案第WO1998/006248號中所描述)(基於EU編號系統進行編號)引入至Fc區中以消除免疫球蛋白組分之效應功能。

【0219】 自滴定曲線及Carterra動力學軟體測定各種抗hPD-1抗體及抗hPD-1抗體減弱之hIL-2融合蛋白與重組人類或石蟹獼猴PD-1蛋白之結合的締合常數(k_a)、解離常數(k_d)及平衡常數(K_D)。亦計算所產生之最大可行SPR信號(R_{max})及剩餘標準差(residual standard deviation；Res SD)。來自動力學篩選之結果概述於表21中且證實，在抗hPD-1抗體上添加減弱之hIL-2部分不調節PD-1抗體與人類PD-1或石蟹獼猴PD-1抗原之結合。在獨立實驗中，H7-632-hIgG1-LAGA (SEQ ID NOs: 414及415)係藉由SPR量測且穩態平衡解離常數(K_D)為1.23×10^{-9} M，且H7-767之$K_D = 1.93\times10^{-9}$ M。

表21. 藉由高通量SPR Carterra® LSA™進行之抗hPD-1及抗hPD-1-hIL-2融合蛋白與重組人類PD-1及石蟹獼猴PD-1之結合動力學

		動力學概述									
		人類PD-1					石蟹獼猴PD-1				
	名稱	k_a (M-1 s-1)	k_d (s-1)	K_D (M)	Rmax	Res SD	k_a (M-1 s-1)	k_d (s-1)	K_D (M)	Rmax	Res SD
抗hPD-1抗體	2H7-hIgG4-LE	2.60E+05	8.20E-04	3.10E-09	146	8.5	1.40E+05	1.00E-03	7.10E-09	186	6.5
	2H7-hIgG4-LAGA	1.70E+05	9.10E-04	5.30E-09	258	13	9.10E+04	1.10E-03	1.20E-08	295	11
	Abz1mod-hIgG4	1.40E+05	6.00E-05	4.26E-10	123	8.1	1.70E+05	6.20E-04	3.70E-09	183	10
	A2-hIgG4	3.70E+04	1.30E-03	3.60E-08	341	7.8	6.80E+04	4.00E-02	5.89E-07	238	4.8
	OMC.1.B6-hIgG4	7.70E+04	4.00E-03	5.20E-08	241	6.8	8.80E+04	4.40E-03	5.10E-08	262	5.5
	OMC.2.C6-hIgG4	5.70E+04	6.60E-04	1.20E-08	229	8.7	5.50E+04	7.40E-04	1.30E-08	268	8.9
	OMC.1.D6-hIgG4	4.10E+04	1.70E-03	4.20E-08	263	5.1	5.80E+04	4.00E-02	6.94E-07	182	4
	OMC476pH7-hIgG4	6.00E+04	1.10E-03	1.80E-08	225	8.9	7.80E+04	1.70E-02	2.21E-07	254	2.8
	OMC476pB11-hIgG4	5.00E+04	1.50E-03	3.00E-08	221	7	8.00E+04	2.60E-02	3.21E-07	204	2.7
	OMC476pG10-hIgG4	9.30E+04	4.10E-03	4.40E-08	256	4.9	1.20E+05	6.00E-02	4.87E-07	188	4.9
	OMC476pH10-hIgG4	1.00E+05	6.50E-03	6.40E-08	63	1.8	1.20E+05	5.90E-02	4.80E-07	81	3.8
	OMC476pE4-hIgG4	7.90E+04	8.80E-04	1.10E-08	216	9.6	1.00E+05	3.50E-02	3.31E-07	204	6.3
	D12-hIgG4	5.70E+04	4.60E-04	8.10E-09	234	9.9	5.90E+04	1.60E-02	2.72E-07	297	2.4
	G12-hIgG4	5.30E+04	2.60E-03	5.00E-08	477	8.5	8.60E+04	6.50E-02	7.54E-07	327	7.8
	EH12.2H7-mIgG1*	1.10E+05	2.20E-03	1.90E-08	309	5.2	8.60E+04	7.30E-03	8.50E-08	307	4.2
	J105-mIgG1*	6.20E+04	5.30E-03	8.60E-08	186	2.8	5.00E+04	6.60E-02	1.30E-09	92	1.2
	MIH4-mIgG1*	1.30E+05	1.40E-03	1.00E-08	117	3.8	1.30E+05	1.20E-01	8.91E-07	61	1.8
	J110-hIgG1	1.00E+05	1.00E-03	1.00E-08	346	15	4.10E+04	5.00E-02	1.20E-09	228	8.2
	OPDIVO® (納武單抗)	1.70E+05	1.70E-03	1.00E-08	55	2.6	1.50E+05	9.50E-04	6.40E-09	75	3.2
	KEYTRUDA® (帕博利珠單抗)	2.90E+05	1.30E-03	4.50E-09	19	2.6	7.00E+05	4.00E-04	5.75E-07	53	3.7
抗hPD-1減弱	2H7-hIgG1-LAGA-hIL-2 (T3A/D20A/R38E/C125A)	1.50E+05	8.30E-04	5.40E-09	420	28	8.80E+04	9.70E-04	1.10E-08	502	21
	2H7-hIgG4-LE-hIL-2 (T3A/D20A/R38E/C125A)	1.90E+05	8.10E-04	4.30E-09	374	17	9.00E+04	1.00E-03	1.10E-08	449	15
	2H7-hIgG4-LAGA-hIL-2 (T3A/D20A/R38E/C125A)	1.70E+05	8.20E-04	4.80E-09	359	22	9.60E+04	9.80E-04	1.00E-08	429	17
	2H7-hIgG1-LAGA-hIL-2 (T3A/R38E/I92K/C125A)	1.80E+05	7.80E-04	4.30E-09	417	25	9.10E+04	9.70E-04	1.10E-08	505	19
	hIgG4-LE-hIL-2 (T3A/R38E/I92K/C125A)	1.90E+05	8.80E-04	4.70E-09	380	19	9.50E+04	1.10E-03	1.20E-08	429	17

	2H7-hIgG4-LAGA-hIL-2 (T3A/R38E/I92K/C125A)	2.20E+05	8.20E-04	3.70E-09	355	17	1.00E+05	1.10E-03	1.10E-08	418	16
	2H7-hIgG1-LAGA-hIL-2 (T3A/R38E/D84K/C125A)	1.30E+05	8.10E-04	6.20E-09	458	29	7.60E+04	1.00E-03	1.30E-08	532	23
	2H7-hIgG4-LE-hIL-2 (T3A/R38E/D84K/C125A)	2.00E+05	9.40E-04	4.70E-09	232	13	1.30E+05	1.10E-03	8.20E-09	262	10
	2H7 hIgG4LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	1.70E+05	7.30E-04	4.40E-09	400	20	8.10E+04	1.00E-03	1.30E-08	482	20

*商業來源，序列無法獲得

實例14：藉由表面電漿子共振(SPR)測定抗hPD-1抗體及抗hPD-1減弱之hIL-2融合蛋白是否與抗hPD-1 #1及抗hPD-1 #2競爭結合至PD-1

【0220】 使用夾層法分析抗hPD-1及抗hPD-1減弱之hIL-2融合蛋白與彼此之競爭。使用實例13中所描述之胺偶合化學方法將抗體及對應之抗體-IL-2細胞介素融合蛋白固定至HC30M晶片。在實例13中所描述之動力學分析之後，將80 nM 人類PD-1 (Acro Biosystems，目錄號PD-1-H5221-100ug)注射至全陣列中。將競爭抗hPD-1及抗hPD-1減弱之hIL-2融合蛋白(分析物)稀釋至30 μg/mL且隨後注射至陣列中，且使用SPR評估結合參數。對所有抗hPD-1及抗hPD-1-hIL-2融合蛋白之評估均重複進行兩次。所測試之一些變異體具有經修飾之人類IgG1或IgG4 κ輕鏈構架以消除免疫球蛋白之效應功能，該構架具有額外L235E或L235A/G237A (LAGA)取代。

【0221】 抗hPD-1或抗hPD-1減弱之hIL-2融合蛋白對之篩選允許鑑別兩個分組，如表22中所示。來自第1組之抗體及融合蛋白能夠在存在來自第2組之所有抗體及融合蛋白的情況下結合hPD-1，但與同一組之所有成員競爭。來自第2組之抗體及融合蛋白能夠在存在來自第1組之所有抗體及融合蛋白的情況下結合hPD-1，但與同一組之所有成員競爭。表22之第1組中所列出之抗hPD-1中之每一者均不與KEYTRUDA®及OPDIVO®競爭。

表22. 來自藉由SPR進行之抗hPD-1及抗hPD-1減弱之hIL-2融合蛋白分組篩選的第1組及第2組

第1組	第2組
Abz1mod-hIgG4	KEYTRUDA®
OMC.1.B6-hIgG4	OPDIVO®
OMC.1.D6-hIgG4	抗hPD-1殖株EH12.2H7-mIgG1*
OMC.2.C6-hIgG4	抗hPD-1殖株J105-mIgG1*
OMC476pE4-hIgG4	
OMC476pH7-hIgG4	
OMC476pB11-hIgG4	
OMC476pH10-hIgG4	
OMC476pG10-hIgG4	
A2-hIgG4	
D12-hIgG4	
G12-hIgG4	
2H7-hIgG4-LE	
2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	
2H7-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	
2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	
2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	
2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	
2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	
2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	
2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	
2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	
抗PD-1殖株MIH4 mIgG1	
抗PD-1殖株J110 hIgG1	

*商業來源，序列無法獲得

實例15：在存在抗hPD-1 #1及抗hPD-1 #2之情況下抗hPD-1減弱之hIL-2融合蛋白對hPD-1之拮抗作用

【0222】 測試抗hPD-1減弱之hIL-2融合蛋白對hPD-1之拮抗作用。根據通用方法方案C進行抗hPD-1減弱之hIL-2融合蛋白之表徵。圖7繪示此等結果。當與PD-1拮抗劑KEYTRUDA®或OPDIVO®相比時，如藉由低程度之可偵測發光所證實，2H7-hIgG4-df-hIL-2 (D20A/R38E)、C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E) 及 A2-hIgG4-df-hIL-2 (D20A/R38E)對人類PD-1無拮抗性。經通用方案C中所描述，亦測試H7-632-hIgG1-LAGA及H7-767之拮抗劑活性。圖15繪示H7-632-hIgG1-

LAGA及H7-767不阻斷hPD-L1 (SEQ ID NO: 584)與hPD-1受體之相互作用。

【0223】 對使用通用方案C中所描述之基於細胞之共培養分析法進行之競爭分析法進行少量修改。將抗hPD-1減弱之hIL-2融合蛋白之樣品稀釋至400 nM之固定濃度且將20 μL添加至20 μL經滴定之抗hPD-1 #1或抗hPD-1 #2中。將40 μL混合物添加至CHO細胞中。將四十(40) μL之Jurkat PD-1效應細胞覆蓋於CHO細胞與抗hPD-1減弱之hIL-2融合蛋白之混合物上。在此競爭分析法中，測試飽和100 nM抗hPD-1減弱之hIL-2融合蛋白以及經滴定之抗hPD-1 #1或抗hPD-1 #2之最終濃度。以通用方案C中所描述進行分析法之其餘部分。圖18A及圖18B證實，100 nM抗hPD-1減弱之hIL-2融合蛋白之添加不與經滴定之抗hPD-1 #1與hPD-L1 (SEQ ID NO: 584)之結合的阻斷競爭。抗hPD-1 #1之劑量-滴定曲線相對於無競爭抗體之曲線保持不變，表明即使在高濃度下，抗hPD-1減弱之hIL-2融合蛋白之存在仍不與抗hPD-1 #1功能競爭。在存在100 nM 2H7-hIgG4-df-hIL-2 (D20A/R38E)及100 nM C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)之情況下，在較高濃度之抗hPD-1 #2下，抗hPD-1 #2展現35%之發光(RLU)減少(圖18B)，但由於標準差之程度，尚不清楚此減少是否顯著。

【0224】 在相反實驗中，將抗hPD-1 #1或抗hPD-1 #2稀釋至400 nM之濃度且將20 μL與20 μL經滴定之抗hPD-1減弱之hIL-2融合蛋白組合。將抗hPD-1減弱之hIL-2融合蛋白連續滴定且將40 μL混合物添加至CHO細胞中，隨後用40 μL之Jurkat PD-1效應細胞覆蓋。以通用方案C中所描述進行分析法之其餘部分。圖18C及圖18D證實，100 nM抗hPD-1 #1 (圖18C)或100 nM抗hPD-1 #2 (圖18D)之添加並不損害抗hPD-1減弱之hIL-2

融合蛋白成為拮抗劑之能力。觀測到的高於18,000個相對發光單位(RLU)之平坦曲線指示不存在拮抗劑活性競爭，且所測試之抗hPD-1減弱之hIL-2融合蛋白即使在存在抗hPD-1 #1或抗hPD-1 #2之情況下仍能夠展現拮抗劑功能。

實例16：用基於細胞之增殖分析法測試抗hPD-1減弱之hIL-2融合蛋白對高親和力及中等親和力hIL-2受體之減弱

【0225】 經通用方案E中所描述，使用細胞增殖分析法在NK-92及TF1+IL-2Rβ細胞株上評估抗hPD-1減弱之hIL-2融合蛋白的hIL-2活性之減弱程度。對照融合蛋白包括併入抗DNA酶I抗體(指定為1H3)與人類IgG4或人類IgG1主鏈之融合蛋白，該主鏈直接或用連接子(SEQ ID NO: 355)融合至hIL-2，以展現非靶向減弱之hIL-2融合蛋白之作用。此等構築體之hIL-2序列含有經實例2中所描述之減弱之hIL-2活性的取代。亦與實例3類似地評估完全、部分或無促效IL-2活性(非活性)。一些所測試之變異體在具有κ輕鏈之經修飾之人類IgG1或IgG4同型上表現，其中在Fc區中具有額外L235E或L235A/G237A (LAGA)取代以消除免疫球蛋白效應功能。在一些抗體-細胞介素融合蛋白中，hIL-2細胞介素係融合至輕鏈之C端(LC融合)。

【0226】 由相對發光單位(RLU)測定各抗體-細胞介素融合蛋白之EC_{50}計算值，且當與重組人類IL-2 (rhIL-2)相比時計算倍數變化EC_{50}。相對於rhIL-2之倍數變化及促效活性概述於表23中。藉由抗體減弱之hIL-2融合蛋白之最大發光與rhIL-2之最大發光相比所測定，將促效活性量測為完全、部分或非活性的。將達到相對於rhIL-2之最大冷光的抗體減弱之hIL-2融合蛋白質劑量-滴定曲線視為具有完全活性之變異體。使用100%

之rhIL-2最大發光，將部分活性計算為完全活性之百分比。將在1200 nM之最高濃度下抗體減弱之hIL-2融合蛋白的最大RLU小於rhIL-2最大RLU之10%視為不具有促效劑活性或非活性。對於一些變異體，EC_{50}值僅為估計值，因為未達到最大發光，如表23中之[a]所標註。

表23. 抗體減弱之hIL-2融合蛋白在NK-92（高親和力IL-2R)及TF1+IL-2Rβ（中等親和力IL-2R)細胞株上相對於rhIL-2之倍數變化及促效活性。

	變異體	**相對於rhIL-2之倍數變化(NK-92)**	**促效活性(NK-92)**	**相對於rhIL-2之倍數變化(TF1+IL-2Rβ)**	**促效活性(TF1+IL-2Rβ)**
非靶向抗體減弱之hIL-2融合蛋白	1H3-hIgG4-df-hIL-2 (WT)	0 [a]	完全	0 - 1	完全
	1H3-hIgG4-L6-hIL-2 (WT)	0 [a]	完全	0 - 1	完全
	1H3-hIgG4-df-hIL-2 (WT) LC融合物	0 [a]	完全	24	完全
	1H3-hIgG4-L6-hIL-2 (WT) LC融合物	0 [a]	完全	2	完全
	1H3-hIgG4-L6-hIL-2 (D20Y)	在圖上>10,000，NC [a]	非活性	在圖上>10,000，NC [a]	非活性
	1H3-hIgG4-df-hIL-2 (D20Y)	在圖上>10,000，NC [a]	部分，60%	在圖上>10,000，NC [a]	非活性
	1H3-hIgG1-df-hIL-2 (D20Y)	8539 [a]	部分，90%	在圖上>10,000，NC [a]	非活性
	1H3-hIgG4-L6-hIL-2 (D20A/R38P)	>10,000 [a]	部分，80%	4132 [a]	完全
	1H3-hIgG4-L6-hIL-2 (D20A/R38S)	在圖上>10,000，NC [a]	部分，90%	9225 [a]	完全
	1H3-hIgG4-L6-hIL-2 (D20A/R38D)	118 [a]	部分，90%	8591 [a]	部分，90%
	1H3-hIgG4-L6-hIL-2 (D20A/R38Q/E95A)	153	完全	5738 [a]	完全
	1H3-hIgG4-L6-hIL-2 (D20A/F42H/E95A)	>10,000 [a]	完全	1368 [a]	完全
	1H3-hIgG4-L6-hIL-2 (R38D/I92D)	190	完全	437	完全
	1H3-hIgG4-L6-hIL-2 (R38E/I92D)	377 [a]	完全	296	完全
	1H3-hIgG4-L6-hIL-2 (F42H/I92D)	794 [a]	完全	393	完全

	1H3-hIgG4-df-hIL-2 (D20A/R38E)	868 [a]	部分，90%至完全	>10,000 [a]	部分，70%至完全
	1H3-hIgG4-L6-hIL-2 (D20A/R38E)	177 [a]	部分，60%至80%	>10,000 [a]	部分，70%至完全
	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E)	在圖上>10,000，NC [a]	部分，40%	>10,000	部分，70%
	1H3-hIgG4-L6-hIL-2 (D20A/R38E/C125A)	>10,000 [a]	部分，20%	6436	部分，40%
	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E/C125A)	在圖上>10,000，NC [a]	部分，20%	>10,000	完全
	1H3-hIgG1-L6-hIL-2 (D20A/R38E)	NT	NT	250 - 372	完全
	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E)	392	部分，80%	186	部分，60%
	1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A)	2346 [a]	部分，80%	2157 [a]	部分，60%
	1H3-hIgG4-df-hIL-2 (D20A/R38E) LC融合物	在圖上>10,000，NC [a]	非活性	在圖上>10,000，NC [a]	非活性
	1H3-hIgG4-L6-hIL-2 (D20A/R38E) LC融合物	在圖上>10,000，NC [a]	非活性	2155 [a]	部分，30%
	1H3-hIgG1-L6-hIL2 (H16A)	0	完全	0 [a]	完全
	1H3-hIgG1-L6-hIL2 (F42A)	0	完全	0 [a]	完全
	1H3-hIgG1-L6-hIL2 (H16A/F42A)	1	完全	0 [a]	完全
抗hPD-1減弱之hIL-2融合蛋白	A2-hIgG4-df-hIL-2 (D20A/R38E)	811 [a]	部分，20%至90%	>10,000 [a]	部分，60%至80%
	D12-hIgG4-df-hIL-2 (D20A/R38E)	在圖上>10,000，NC [a]	部分，20%	>10,000 [a]	部分，40%
	G12-hIgG4-df-hIL-2 (D20A/R38E)	>10,000 [a]	部分，20%	>10,000 [a]	部分，50%
	OMC476pB11-hIgG4-df-hIL-2 (D20A/R38E)	在圖上>10,000，NC [a]	部分，70%	36	完全
	OMC476pE4-hIgG4-df-hIL-2 (D20A/R38E)	在圖上>10,000，NC [a]	部分，70%	1619	完全
	OMC476pG10-hIgG4-df-hIL-2 (D20A/R38E)	>10,000 [a]	部分，70%	NC [a]	非活性
	OMC476pH10-hIgG4-df-hIL-2 (D20A/R38E)	在圖上>10,000，NC [a]	部分，70%	3563 [a]	部分，80%
	A2-hIgG4-df-hIL-2 (D20A/F42A)	284	完全	4323 [a]	部分，80%
	A2-hIgG4-df-hIL-2 (D20A/F42S)	3542	完全	4052 [a]	部分，90%
	A2-hIgG4-df-hIL-2 (D20S/R38E)	NT	NT	7035 [a]	完全

	A2-hIgG4-df-hIL-2 (F42A/N88R)	6423	完全	3757 [a]	部分，90%
	A2-hIgG4-df-hIL-2 (F42I/I92D)	9543	完全	5611 [a]	部分，90%
	A2-hIgG4-df-hIL-2 (F42Q/I92D)	8572	完全	3363 [a]	完全
	A2-hIgG4-df-hIL-2 (F42T/I92D)	2175	完全	5649 [a]	完全
	A2-hIgG4-df-hIL-2 (F42W/I92D)	1239	完全	4409 [a]	部分，50%
	A2-hIgG4-df-hIL-2 (R38E/D84K)	160 - 1503	完全	1158 - 1716	部分，90%
	A2-hIgG4-df-hIL-2 (R38E/I92K)	252 - 977	完全	864 - 1655	部分，80%至完全
	C51E6-5-hIgG4-df-hIL-2 (D20A/R38E)	4317	部分，70%	>10,000 [a]	部分，60%
	C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)	NT	NT	>10,000 [a]	部分，80%
	C51E6-5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	4326	部分，80%	>10,000 [a]	部分，70%
	C51E6-5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	4336	部分，60%	在圖上>10,000，NC [a]	部分，60%
	OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E)	NT	NT	8460 [a]	部分，70%
	OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E)	NT	NT	>10,000 [a]	部分，70%
	OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E)	NT	NT	>10,000 [a]	部分，70%
	2A3.H7-hIgG4-df-hIL-2 (D20A/R38E)	NT	NT	6603 [a]	部分，60%
	1H9-hIgG4-df-hIL-2 (D20A/R38E)	NT	NT	9769 [a]	部分，90%
	1D5-hIgG4-df-hIL-2 (D20A/R38E)	NT	NT	7420 [a]	部分，80%
	1D5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	NT	NT	NC [a]	非活性
	1D5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	NT	NT	NC [a]	部分，20%
	2H7-hIgG1-df-hIL-2 (T3A/D20A/R38E/C125A)	4839 [a]	完全	2057 [a]	完全
	2H7-hIgG1-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	7727 [a]	完全	6729 [a]	部分，80%
	2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	>10,000 [a]	完全	3428 [a]	部分，50%至60%
	2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A)	707 - 7206 [a]	完全	>10,000 [a]	部分，60%至完全
	2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	>10,000	完全	>10,000 [a]	部分，50%至60%
	2H7-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	>10,000	完全	7480 [a]	部分，40%至50%
	H7-767	>10,000 [a]	部分，完全	>10,000 [a]	完全
	2H7-hIgG1-df-hIL-2 (T3A/R38E/D84K/C125A)	1500	部分，90%	140 [a]	完全
	2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	1268	部分，90%	517 [a]	完全

	2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	2157 - 4035	部分，90%至完全	774 - 1650 [a]	完全
	2H7-hIgG4-df-hIL-2 (T3A/R38E/D84K/C125A)	1602	部分，90%	>10,000 [a]	完全
	2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	1675 - 5096	部分，90%	1281 - 2842 [a]	完全
	2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	1596 - 5689	部分，90%至完全	1203 - 3515 [a]	部分，60%至80%
	2H7-hIgG1-df-hIL-2 (T3A/R38E/I92K/C125A)	370	完全	160	完全
	2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	319	完全	656	完全
	2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	406 - 1280	完全	514 - 1569 [a]	完全
	2H7-hIgG4-df-hIL-2 (T3A/R38E/I92K/C125A)	520	完全	789 - 926	部分，80%至完全
	2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	610 - 1675	完全	474 - 2080 [a]	完全
	2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	827 - 2888	完全	737 - 2845 [a]	部分，70%至完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/D20S/R38E/C125A)	6689	完全	9711 [a]	部分，70%
	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/D84F/C125A)	6199	完全	3915	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92R/C125A)	75	完全	89	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92E/C125A)	118	完全	53	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92S/C125A)	9	完全	30	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92D/C125A)	2717	完全	3396 [a]	部分，80%
	2H7-hIgG1-LAGA-df-hIL2 (T3A/H16E/R38E/C125A)	126	完全	122	完全

NT =未測試

NC =未藉由GraphPad Prism 7計算

[a] = 倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

實例17：抗hPD-1減弱之hIL-2融合蛋白在表現中等親和力hIL-2受體及hPD-1之細胞株上之IL-2活性的拯救

【0227】 使用表現hPD-1之靶向細胞株評估抗hPD-1減弱之hIL-2融合蛋白之hIL-2活性的拯救。簡言之，通用方法方案D中所描述之TF1+IL-

2Rβ細胞株係經由慢病毒轉導進行修飾以表現hPD-1受體(SEQ ID NO: 580)。使用Brilliant Blue 515結合之hPD-1抗體(BD Biosciences目錄號565936)之流式細胞分析技術來偵測表現hPD-1之TF1+IL-2Rβ細胞。針對低hPD-1表現(在Brilliant Blue 515螢光團上強度小於10^3個)對細胞進行分類。將池再分類兩次以收集與活化初代細胞上之hPD-1表現量近似的細胞。擴增且以等分試樣冷凍此細胞株(TF1+IL-2Rβ+hPD-1)以用於基於細胞之增殖分析法。以通用方法方案E中所描述進行增殖分析法，其中培育期為3天。所測試之一些變異體具有經修飾之人類IgG1或IgG4 κ輕鏈構架以消除免疫球蛋白之效應功能，該構架具有額外L235E或L235A/G237A (LAGA)取代。

【0228】 表24概述對所靶向之TF1+IL-2Rβ+hPD-1細胞株之增殖分析法之結果。藉由抗體減弱之hIL-2融合蛋白之最大發光與rhIL-2之最大發光相比所測定，將促效活性量測為完全、部分或非活性的。將達到相對於rhIL-2之最大發光的抗體減弱之hIL-2融合蛋白質劑量-滴定曲線視為具有完全活性之變異體。使用100%之rhIL-2最大發光，將部分活性計算為完全活性之百分比。將在1200 nM之最高濃度下抗體減弱之hIL-2融合蛋白的最大RLU小於rhIL-2最大RLU之10%視為不具有促效劑活性或非活性。對於一些變異體，EC_{50}值僅為估計值，因為未達成完全曲線。具有減弱之hIL-2的抗hPD-1-hIL-2融合蛋白之許多實例在所靶向之細胞株上展示拯救之hIL-2活性，其中非靶向抗體對照物(用1H3表示)未證實hIL-2活性之拯救。藉由相對於rhIL-2之倍數變化減少至0或1之值來說明完全拯救。

表24. 抗體-hIL-2融合蛋白在TF1+IL-2Rβ+hPD-1細胞株(具有中等親和力IL-2R的表現人類PD-1之細胞株)上相對於rhIL-2之倍數變化及促效活

性。

	變異體	相對於 rhIL-2之倍數減少 (TF1+IL-2Rβ+hPD-1)	促效活性(TF1+IL-2Rβ+hPD-1)
非靶向抗體減弱之hIL-2融合蛋白	1H3-hIgG4-df-hIL-2 (WT)	1	完全
	1H3-hIgG4-L6-hIL-2 (WT)	1	完全
	1H3-hIgG4-L6-hIL-2 (D20Y)	NC [a]	非活性
	1H3-hIgG4-df-hIL-2 (D20Y)	NC [a]	非活性
	1H3-hIgG4-L6-hIL-2 (D20A/R38P)	3074 [a]	部分，80%
	1H3-hIgG4-L6-hIL-2 (D20A/R38S)	4482 [a]	部分，80%
	1H3-hIgG4-L6-hIL-2 (D20A/R38D)	2964 [a]	部分，60%
	1H3-hIgG4-L6-hIL-2 (D20A/R38Q/E95A)	3538 [a]	部分，80%
	1H3-hIgG4-L6-hIL-2 (D20A/F42H/E95A)	657 [a]	部分，70%
	1H3-hIgG4-L6-hIL-2 (R38D/I92D)	1428 [a]	完全
	1H3-hIgG4-L6-hIL-2 (R38E/I92D)	1887 [a]	完全
	1H3-hIgG4-L6-hIL-2 (F42H/I92D)	2024 [a]	完全
	1H3-hIgG4-df-hIL-2 (D20A/R38E)	307 - 3628 [a]	部分，70%至完全
	1H3-hIgG4-L6-hIL-2 (D20A/R38E)	4883 - 5226	部分，70%至完全
	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E)	9167 [a]	部分，80%
	1H3-hIgG4-L6-hIL-2 (D20A/R38E/C125A)	4714	部分，60%
	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E/C125A)	4626	部分，60%
	1H3-hIgG1-L6-hIL-2 (D20A/R38E)	297	完全
	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E)	513	部分，80%
	1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A)	3342	部分，80%
	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	1081	部分，90%
	1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	6459	完全
	1H3-hIgG1-L6-hIL-2 (H16A)	4 [a]	完全
	1H3-hIgG1-L6-hIL-2 (F42A)	0 [a]	完全
	1H3-hIgG1-L6-hIL-2 (H16A/F42A)	2 [a]	完全
	1H3-hIgG1-L6-hIL-2 (D20T)	75 [a]	完全
	1H3-hIgG1-L6-hIL-2 (T3A/F42A/Y45A/L72G/C125A)	2 [a]	完全
抗hPD-1減弱之hIL-2融合蛋白	A2-hIgG4-df-hIL-2 (D20A/R38E)	0-1 [a]	完全
	D12-hIgG4-df-hIL-2 (D20A/R38E)	1 [a]	完全
	G12-hIgG4-df-hIL-2 (D20A/R38E)	1 [a]	完全
	OMC476pB11-hIgG4-df-hIL-2 (D20A/R38E)	0 [a]	完全
	OMC476pE4-hIgG4-df-hIL-2 (D20A/R38E)	2 [a]	完全
	OMC476pG10-hIgG4-df-hIL-2 (D20A/R38E)	0 [a]	完全
	OMC476pH10-hIgG4-df-hIL-2 (D20A/R38E)	1 [a]	完全
	A2-hIgG4-df-hIL-2 (D20A/F42A)	2 [a]	完全
	A2-hIgG4-df-hIL-2 (D20A/F42S)	1 [a]	完全
	A2-hIgG4-df-hIL-2 (D20S/R38E)	0 [a]	完全

	A2-hIgG4-df-hIL-2 (F42A/N88R)	0 [a]	完全
	A2-hIgG4-df-hIL-2 (F42I/I92D)	9 [a]	完全
	A2-hIgG4-df-hIL-2 (F42Q/I92D)	5 [a]	完全
	A2-hIgG4-df-hIL-2 (F42T/I92D)	1 [a]	完全
	A2-hIgG4-df-hIL-2 (F42W/I92D)	4 [a]	完全
	A2-hIgG4-df-hIL-2 (R38E/D84K)	0 - 1 [a]	完全
	A2-hIgG4-df-hIL-2 (R38E/I92K)	0 - 1 [a]	完全
	C51E6-5-hIgG4-df-hIL-2 (D20A/R38E)	0 - 1 [a]	部分，70%至完全
	C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)	1 [a]	部分，90%
	C51E6-5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	1 [a]	完全
	C51E6-5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	0 [a]	完全
	OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E)	0 [a]	部分，60%
	OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E)	0 [a]	部分，90%
	OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E)	0 [a]	部分，60%
	2A3.H7-hIgG4-df-hIL-2 (D20A/R38E)	0 [a]	完全
	1H9-hIgG4-df-hIL-2 (D20A/R38E)	0 [a]	完全
	1D5-hIgG4-df-hIL-2 (D20A/R38E)	1 [a]	完全
	2H7-hIgG1-df-hIL-2 (T3A/D20A/R38E/C125A)	1 [a]	完全
	2H7-hIgG1-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	0 [a]	完全
	2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	1 [a]	完全
	2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A)	1 [a]	完全
	2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	1 - 4 [a]	完全
	2H7-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	1 [a]	完全
	H7-767	0 - 1 [a]	完全
	2H7-hIgG1-df-hIL-2 (T3A/R38E/D84K/C125A)	2 [a]	完全
	2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	1 [a]	完全
	2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	1 [a]	完全
	2H7-hIgG4-df-hIL-2 (T3A/R38E/D84K/C125A)	1 [a]	完全
	2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	0 - 2 [a]	完全
	2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	1 - 3 [a]	完全
	2H7-hIgG1-df-hIL-2 (T3A/R38E/I92K/C125A)	1 [a]	完全
	2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	1 [a]	完全
	2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	1 - 2 [a]	完全
	2H7-hIgG4-df-hIL-2 (T3A/R38E/I92K/C125A)	1 [a]	完全
	2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	1 [a]	完全
	2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	1 [a]	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/D20S/R38E/C125A)	在圖上未減弱；NC [a]	完全

	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/D84F/C125A)	0 [a]	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92R/C125A)	0 [a]	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92E/C125A)	2 [a]	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92S/C125A)	在圖上未減弱；NC [a]	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92D/C125A)	0 [a]	完全
	2H7-hIgG1-LAGA-df-hIL2 (T3A/H16E/R38E/C125A)	>10,000 [a]	完全

NC = 未藉由GraphPad Prism 7計算

[a] = 倍數變化僅為估計值，因為未達成完全四參數邏輯曲線

實例18：阻斷或不阻斷活體內鼠類結腸腺癌(MC38)模型中之小鼠PD-L1的抗hPD-1減弱之hIL-2融合蛋白替代物的評估

【0229】 由於還沒有公認模型來探究腫瘤學治療劑在靈長類動物中之活體內功效，因此在同基因型鼠類腫瘤模型中產生且測試抗mPD-1減弱之hIL-2融合蛋白替代物。此MC38結腸腺癌模型常規地用於測試免疫腫瘤學治療劑之功效。為了探究抗PD-1減弱之hIL-2融合蛋白之活體內功效，將指定為RMP1-14 (已知阻斷小鼠PD-L1結合)及RMP1-30 (描述為小鼠PD-L1非阻斷劑)之抗小鼠PD-1抗體替代物在小鼠IgG2b-N297A重鏈之C端處融合至減弱之hIL-2，且在MC38結腸腺癌模型中測試。hIL-2部分包括取代F42K、Y45R及V69R，其在IL-2依賴性小鼠T淋巴母細胞細胞株(CTLL-2)上測試且證實小鼠IL-2活性減弱。人類IL-2可刺激小鼠T細胞在類似濃度下增殖，然而減弱人類IL-2依賴性細胞株上之活性的相同取代並不減弱CTLL-2細胞株上之活性(資料未示出)。因此，在hIL-2中使用F42K/Y45R/V69R取代作為替代物，因為其在小鼠細胞株上展現減弱之IL-2活性。包含抗小鼠PD-1抗體RMP1-14及RMP1-30 (經Matsumoto K等人, J Immunol. 2004年2月15日;172(4):2530-41中所描述)之重鏈及輕鏈可變區序列的序列亦在鼠類IgG2b-N297A背景上格式化，以產生抗mPD-1 RMP1-14 mIgG2b-N297A (SEQ ID NO: 564及566)及抗mPD-1 RMP1-30

mIgG2b-N297A (SEQ ID NO: 567及568)。具有N297A取代之小鼠IgG2b同型為消除Fc免疫效應功能之Fc同型的鼠類等效物。使用標準技術來產生、表現及蛋白A純化抗體替代物及抗體減弱之hIL-2融合蛋白。

【0230】在此鼠類腫瘤模型中，對十週齡雌性C57BL/6NCrl (Charles River)小鼠之右側腹注射5×10^5個MC38結腸直腸癌細胞。當腫瘤達到80至120 mm^3時，將小鼠分類成群組(10隻小鼠/組)且在研究第1天開始治療。連同媒劑對照(磷酸鹽緩衝鹽水)一起，以5 mg/kg每週兩次腹膜內給藥抗mPD-1 RMP1-14 mIgG2b-N297A、抗mPD-1 RMP1-30 mIgG2b-N297A、抗mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) (SEQ ID NO: 565及566)及抗mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) (SEQ ID NO: 568及569)持續4週。在研究之持續時間內，使用公式$(w^2 \times L)/2$用測徑規每週兩次量測腫瘤尺寸，其中w =寬度且L =長度。研究終點為1000 mm^3之腫瘤體積或50天之存活期，以先到者為準。

【0231】圖8證實，雖然相對於用媒劑對照治療，單獨投與抗mPD-1 RMP1-14-mIgG2b-N297A或抗mPD-1 RMP1-30-mIgG2b-N297A抗體不會顯著促進功效，但投與抗mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)或抗mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)抗PD-1減弱之hIL-2融合蛋白分別與90%及100%之完全腫瘤消退相關。此等資料證實，由抗mPD-1-hIL-2 (F42K/Y45R/V69R)融合蛋白介導之抗腫瘤功效不需要PD-1檢查點阻斷且功效視hIL-2活性而定。資料進一步證實，表現PD-1之T細胞的抗體介導之靶向足以在MC38腫瘤模型中促進強抗腫瘤功效。

實例19：抗hPD-1減弱之hIL-2融合蛋白替代物在活體內鼠類結腸腺癌模型中擴增效應記憶CD8+ T細胞

【0232】 為了理解抗hPD-1減弱之hIL-2融合蛋白替代物之活體內作用機制，進行與實例18類似之活體內實驗，隨後在三次劑量之後對腫瘤、血液、脾臟及淋巴結中之所得T細胞群體進行免疫表現型分型。對十週齡雌性C57BL/6NCrl (Charles River)小鼠之右側腹皮下植入5×10^5個鼠類MC38結腸腺癌腫瘤細胞，且監測腫瘤生長。將腫瘤在150至260 mm^3之間的動物劃分成四組以用於研究，其中每組10隻小鼠。在植入後的21天之後，在第1天、第4天及第8天，用作為媒劑對照之0.2毫升/劑量之磷酸鹽緩衝鹽水(PBS)、5 mg/kg抗KLH-C3-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)、5 mg/kg抗mPD-1 RMP1-30 mIgG2b-N297A或5 mg/kg抗mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)對動物進行腹膜內給藥。在第9天，自所有小鼠收穫腫瘤、脾臟及腹股溝淋巴結且處理成單細胞懸浮液以用於後續流式細胞分析技術分析。

【0233】 圖9A用圖表示在第1天自第一次劑量之9天內的腫瘤體積增長(mm^3)，其中各點表示10隻小鼠之平均值。截至第8天，與其他治療組相比，抗mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)使腫瘤體積減小。圖9B概述各治療組之腫瘤中之各種$CD8^+$ T細胞亞群的貢獻，其中中央記憶T細胞經表現型分型為$CD45^+CD3^+CD4^-CD8^+CD44^+CD127^+CD69^-CD103^-$，效應記憶T細胞為$CD45^+CD3^+CD4^-CD8^+CD44^+CD127^+CD69^-CD103^-CD62L^-$，常駐記憶T細胞為$CD45^+CD3^+CD4^-CD8^+CD44^+CD127^+CD69^+CD103^+$，$CD44^-CD62L^-$ T細胞為$CD45^+CD3^+CD4^-CD8^+CD44^+CD62L^-$且初始T細胞為

$CD45^+CD3^+CD4^-CD8^+CD44^-CD62L^+$。與其他治療組相比，如圖9B之淺灰色圖塊之增加所指示，經抗mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)治療之小鼠中的$CD8^+$效應記憶T細胞亞群擴增。此亦在圖9C中以MC38剝離之腫瘤內的絕對計數(細胞/微升)繪示。此外，在腫瘤內，定義為表現$CD45^+CD3^+CD4^+CD8^-CD25^+FoxP3^+$標記物之調節T細胞之絕對計數(細胞/微升)減少。

【0234】 $CD8^+$效應記憶T細胞之擴增及調節T細胞之減少已與小鼠及人類兩者中之有效免疫療法相關。

實例20：抗hPD-1減弱之hIL-2融合蛋白在NCG-PBMC模型中在活體內具有活性

【0235】 將人類免疫細胞移植至缺乏功能性T細胞、B細胞及NK細胞之NOD-*Prkdc*^{em26Cd52}*IL-2rg*^{em26Cd22}/NjuCrl (NCG)中已成為評估經假設以刺激人類T細胞之治療劑之功效的寶貴工具。在此模型中，若治療劑活化人類T細胞，則將使得T細胞擴增並加速移植物抗宿主病(GvHD)。

【0236】 在4週之時段內，評估用於人類周邊單核細胞(hPBMC)移植之三種獨立供體的移植動力學以及T細胞上之人類PD-1及人類IL-2受體之表現。在所測試之三個供體中，選擇誘導最多T細胞且具有GvHD之中間窗的供體。將1.5×10^7個hPBMC經靜脈內注射至NCG小鼠中且劃分成8組，8至16隻小鼠。在第7天、第10天及第14天，對小鼠腹膜內注射三次劑量之2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) (SEQ ID NO: 471、425) (2.5 mg/kg、5 mg/kg或10 mg/kg)、1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) (SEQ ID NO: 546、374) (5 mg/kg或10 mg/kg)、1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A) (SEQ ID NO: 563,

374) (10 mg/kg)或2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) (SEQ ID NO: 474、425) (5 mg/kg)。作為野生型hIL-2 (1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A))及減弱之hIL-2部分(1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A))兩者之抗DNA酶融合蛋白係用作非靶向抗體對照。儘管1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A)融合蛋白在hIL-2部分中不具有降低hIL-2活性之變化，但其確實包含T3A及C125A取代以分別移除在人類IL-2上的經預測之O連接之醣基化部位(參見例如，國際公開第WO2012/107417號)及未成對之半胱胺酸殘基(參見例如，國際公開第WO2018/184964號)。此等取代在臨床中尚未展現hIL-2效力降低。在第21天，收穫血液、脾臟及肺，其中血液及脾臟經處理以用於流式細胞分析技術免疫表現型分型，同時對肺進行稱重。

【0237】 在21天之後，對動物之血液及脾臟進行流式細胞分析技術免疫表現型分型。表25概述用於界定人類T細胞群體之標記物以用於後續分析。

表25. 定義NCG-PBMC小鼠中之人類T細胞亞群之表現型標記物

細胞群體	表現型標記物
泛T細胞	CD3+
CD8+初始	CD3+CD4-CD8+CD45RO-CCR7+
CD8+效應	CD3+CD4-CD8+CD45RO-CCR7-
CD8+效應記憶	CD3+CD4-CD8+CD45RO+CCR7-
CD8+中央記憶	CD3+CD4-CD8+CD45RO+CCR7+
CD4+初始	CD3+CD4+CD8-CD45RO-CCR7+
CD4+效應	CD3+CD4+CD8-CD45RO-CCR7-
CD4+效應記憶	CD3+CD4+CD8-CD45RO+CCR7-
CD4+中央記憶	CD3+CD4+CD8-CD45RO+CCR7+
調節T細胞	CD3+CD4+CD8-CD25+Foxp3+
NK細胞	CD3-CD56+

【0238】 如圖10中所繪示，量測體重21天且針對各個別動物相對於第1天標準化，作為移植物抗宿主病(GvHD)之評估。在經10 mg/kg之

2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)治療之小鼠中觀測到GvHD加速。在經2.5 mg/kg、5 mg/kg之2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 及 5 mg/kg 之 2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)治療之小鼠中亦觀測到體重小幅降低。儘管體重減輕見於1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A)中，但其並不持續。

【0239】流式細胞分析技術分析與所觀測之移植物抗宿主病(GvHD)加速相關。使用表25中所提供之用於界定人類T細胞亞群之表現型標記物，對周邊血液之流式細胞分析技術分析證實，在用2.5 mg/kg及5 mg/kg之2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)治療之小鼠及用10 mg/kg之1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A)治療之小鼠中，$CD3^+$、$CD4^+$及$CD8^+$ T細胞亞群僅輕微擴增(如藉由$CD3^+$ T細胞相對於媒劑對照之倍數變化在10倍至50倍之間所定量)。此外，在用10 mg/kg之2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)治療之小鼠的周邊血液中，$CD3^+$、$CD4^+$及$CD8^+$ T細胞亞群大大擴增($CD3^+$ T細胞相對於媒劑對照之倍數變化大於50倍)。表26概述擴增之人類T細胞亞群。

表26. NCG-PBMC小鼠中之人類$CD3^+$、$CD4^+$及$CD8^+$ T細胞亞群之擴增

	數目之倍數變化(血液)		
藥劑	**$CD3^+$ T細胞**	**$CD4^+$ T細胞**	**$CD8^+$ T細胞**
媒劑(PBS)	1	1	1
1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A) 10 mg/kg	22.76	27.73	16.13
1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 5 mg/kg	1.94	2.12	1.74
1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 10 mg/kg	0.56	0.56	0.57
2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 2.5 mg/kg	24.57	32.4	14.4
2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 5 mg/kg	53.03	70.74	22.86
2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 10 mg/kg	203.3	296.94	58.82
2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) 5 mg/kg	31.79	48.76	8.79

N/A =不適用

【0240】 除了評估治療組之間的$CD3^+$、$CD4^+$及$CD8^+$ T細胞之外，亦評估$CD4^+$及$CD8^+$ T細胞亞群之記憶及初始亞群。用於界定$CD4^+$及$CD8^+$ T細胞兩者之初始、效應、效應記憶及中央記憶所使用之表現型標記物概述於表25中。治療組之間的初始、效應或中央記憶T細胞無變化(資料未示出)。然而，用2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)以10 mg/kg治療之小鼠的周邊血液中之$CD4^+$及$CD8^+$效應記憶(EM) T細胞大大擴增，其中每毫升之平均細胞數目為$CD8^+$ T細胞大於5百萬且$CD4^+$ T細胞大於5千萬(圖11A及圖11B)。用圍繞第一及第三四分位數之方框來圖示盒鬚圖(box-and-whisker plot)，水平線作為中值，且線指定最小值及最大值點。對於用2.5 mg/kg及5 mg/kg之2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)以及用1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A)治療之動物，將$CD8^+$效應記憶(EM) T細胞之中度擴增定義為每百萬之平均細胞數目在每毫升1至5百萬之間。在用2.5 mg/kg及5 mg/kg之2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)治療之小鼠中，對於$CD4^+$ T細胞，$CD4^+$效應記憶(EM) T細胞之中度擴增在每毫升600至1300萬之間。

【0241】 除了刺激效應T細胞之外，據描述，IL-2刺激NK細胞及調節T細胞(Treg)，且由於Treg表現高程度之CD25且NK細胞表現CD122，因此亦評估此等免疫細胞類型。圖12繪示在10 mg/kg之最高劑量下用2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)治療之動物未擴增人類調節T細胞，且實情為在動物之周邊血液中具有最低百分比之調節T細胞(如表25中以表現型所定義)。人類調節T細胞存在劑量依賴性降低且

與平均有1.6%之人類$CD3^+$ T細胞為Treg的媒劑對照相比，10 mg/kg之2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)平均有0.16%之人類$CD3^+$ T細胞為Treg。與媒劑對照(資料未展示)相比，在所有治療組中周邊血液中之人類NK細胞(表25中定義之表現型)之百分比無變化。

實例21：抗hPD-1減弱之hIL-2融合蛋白之非臨床安全概況

【0242】 先前已使用石蟹獼猴來評估未經修飾之IL-2之毒性。在石蟹獼猴中在低至50 μg/kg/天之外源性重組IL-2劑量下觀測到致死性。由於藉由流式細胞分析技術確認H7-767與初代活化PBMC上之石蟹獼猴hPD-1的結合(實例12)，因此對變異體H7-767 (H7-02-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) (SEQ ID NO: 582及583) 及H7-767兩者進行初步安全性評估之單劑量研究。以1 mg/kg (4隻動物)或10 mg/kg (4隻動物)，藉由15分鐘靜脈內輸注將H7-02-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)遞送至8隻猴。在輸注後至多360小時之時間點處進行取樣。未觀測到不良反應、總體毒性、體重減輕或致死性(資料未示出)。與第一次研究類似，以5 mg/kg及50 mg/kg之較高劑量進行使用H7-767之後續單劑量研究，其中在輸注後至多360小時之時間點處進行取樣。此外，未觀測到不良反應、總體毒性、體重減輕或致死性(資料未示出)。

實例22：經修飾之hIL-2蛋白質之IL-2活性之減弱

【0243】 在經上文實例5中所描述之NK-92及TF1+IL-2Rβ細胞株兩者中，在增殖分析法中測試包含在胺基酸位置20處之取代(D20)及在胺基酸位置38處之取代(R38)的經修飾之hIL-2蛋白質之IL-2活性的減弱。基於經修飾之hIL-2蛋白質之最大促效劑活性及相對於未經修飾之重組hIL-2對

中等及高親和力受體兩者之效力的減弱程度(表27)，將經修飾之hIL-2蛋白質分組成7個小組(1至7)。用於對經修飾之hIL-2蛋白質進行分組之準則為：

• 第1組：對中等親和力受體具有最高減弱(亦即>10,000倍)及至少約80%活性且對高親和力受體具有高減弱及至少約70%活性之變異體。

• 第2組：對中等親和力受體具有至少約70%活性及>1,000倍減弱且對高親和力受體具有約20%活性至約30%活性之變異體。

• 第3組：對中等親和力受體具有約50%活性至約70%活性及>1,000倍減弱且對高親和力受體具有約20%活性之變異體。

• 第4組：對中等親和力受體具有至少約70%活性但僅>500倍減弱且對高親和力受體具有約50%活性之變異體。

• 第5組：對兩種受體均具有至少約70%活性，但按降序對中等親和力受體具有>10倍至>300倍減弱，且亦按降序對高親和力受體具有70倍至1500倍減弱之變異體。

• 第6組：對中等親和力受體僅具有約30%活性及>2,500倍減弱且對高親和力受體無活性之變異體。

• 第7組：對中等親和力受體及高親和力受體兩者均無活性之變異體。

表27. 在基於細胞之增殖分析法中，包含在胺基酸位置20處之取代(D20)及在胺基酸位置38處之取代(D R38)的經修飾之hIL-2蛋白質相對於rhIL-2之倍數變化及促效活性

	變異體	**hIL-2 變異體之SEQ ID NO**	**相對於rhIL-2之倍數變化(NK-92)**	**促效活性(NK-92)**	**相對於rhIL-2之倍數變化(TF1+IL-2Rβ)**	**促效活性(TF1+IL-2Rβ)**
第1組	1H3-hIgG1-L6-hIL-2 (D20A/R38E)	149	1183 - 2016	至少約70%	>10,000 [a]	至少約80%
第2組	1H3-hIgG1-L6-hIL-2 (D20Q/R38E)	608	>10,000 [a]	約30%	6665	至少約70%
第2組	1H3-hIgG1-L6-hIL-2 (D20M/R38E)	614	>10,000 [a]	約30%	2607	至少約70%
第2組	1H3-hIgG1-L6-hIL-2 (D20I/R38E)	611	>10,000 [a]	約20%	1782	至少約70%
第3組	1H3-hIgG1-L6-hIL-2 (D20V/R38E)	620	在圖上>10,000，NC [a]	約20%	1849	約50%
第4組	1H3-hIgG1-L6-hIL-2 (D20S/R38E)	307	在圖上>10,000，NC [a]	約50%	626	至少約70%
第5組	1H3-hIgG1-L6-hIL-2 (D20N/R38E)	607	1521	至少約70%	378	至少約70%
第5組	1H3-hIgG1-L6-hIL-2 (D20G/R38E)	610	1288	至少約70%	212	至少約70%
第5組	1H3-hIgG1-L6-hIL-2 (D20T/R38E)	617	524	至少約70%	75	至少約70%
第5組	1H3-hIgG1-L6-hIL-2 (D20E/R38E)	609	77	至少約70%	12	至少約70%
第6組	1H3-hIgG1-L6-hIL-2 (D20H/R38E)	306	無活性	無活性	2945	約30%
第7組	1H3-hIgG1-L6-hIL-2 (D20L/R38E)	612	>10,000 [a]	無活性	>10,000 [a]	無活性

第7組	1H3-hIgG1-L6-hIL-2 (D20K/R38E)	613	無活性	無活性	544	無活性
第7組	1H3-hIgG1-L6-hIL-2 (D20F/R38E)	615	>10,000 [a]	無活性	>10,000 [a]	無活性
第7組	1H3-hIgG1-L6-hIL-2 (D20P/R38E)	616	>10,000 [a]	無活性	>10,000 [a]	無活性
第7組	1H3-hIgG1-L6-hIL-2 (D20W/R38E)	618	>10,000 [a]	無活性	>10,000 [a]	無活性
第7組	1H3-hIgG1-L6-hIL-2 (D20Y/R38E)	619	>10,000 [a]	無活性	1	無活性
第7組	1H3-hIgG1-L6-hIL-2 (D20R/R38E)	606	>10,000 [a]	無活性	>10,000 [a]	無活性

實例23：鼠類MC38結腸直腸腫瘤模型中之融合蛋白替代物之活性

【0244】 對十週齡雌性C57BL/6NCrl小鼠之右側腹注射5×10^5個同基因型MC38結腸直腸癌細胞。當腫瘤達到80至120 mm^3時，將小鼠分類成群組(10隻小鼠/組)且在研究第1天開始治療。在第1天開始，以5 mg/kg每週兩次腹膜內給藥除hIL-2以外的所有藥劑持續4週。自第1天至第5天，以36,000國際單位一天一次腹膜內給藥hIL-2。在研究持續時間內，用測徑規每週兩次量測腫瘤尺寸。研究終點為1000 mm^3之腫瘤體積或50天之存活期或70天之無惡化存活期，以先到者為準。

【0245】 包括抗體分子及抗體-hIL-2融合蛋白之所有測試藥劑係使用在位置297處具有單個N297A胺基酸取代之小鼠IgG2b Fc區來產生，該取代防止Fc區醣基化且顯著降低任何Fc區介導之免疫效應功能，由此防止活體內細胞消耗。抗mPD-1 RMP1-14為小鼠PD-1受體之單株抗體拮抗劑(Matsumoto, J Immunol 172: 2530-2541, 2004)。抗mPD-1 RMP1-14-hIL-2 F42K/Y45R/V69R為一種雙功能融合蛋白，係由小鼠PD-1受體之單株RMP1-14抗體拮抗劑組成，該抗體拮抗劑經由可撓性六胺基酸甘胺酸/

絲胺酸連接子在其C端處融合至效力降低之IL-2變異體hIL-2 F42K/Y45R/V69R (SEQ ID NO: 621)。此分子的設計使效力降低之hIL-2變異體在小鼠活體內直接靶向表現PD-1之T細胞。抗KLH-hIL-2 F42K、Y45R、V69R為一種由以下組成之對照融合蛋白：識別非哺乳動物抗原(鎖孔帽貝血氰蛋白，KLH)之同型對照單株抗體，其經由可撓性六胺基酸甘胺酸/絲胺酸連接子在其C端處融合至效力降低之IL-2變異體hIL-2 F42K、Y45R、V69R。

【0246】 結果呈現於圖19中。MC38結腸直腸腫瘤模型對抗體介導之PD-1受體抑制具有特異性反應。儘管在經媒劑處理之小鼠中生長之腫瘤快速達到研究終點，但用抗mPD-1 RMP1-14治療之50%之小鼠經歷完全腫瘤消退。反之，經抗mPD-1 RMP1-14-hIL-2 F42K、Y45R、V69R融合蛋白治療之100%之小鼠經歷持久、長期腫瘤消退。用抗mPD-1 RMP1-14-hIL-2 F42K、Y45R、V69R融合蛋白之個別組分的各種組合，包括抗mPD-1 RMP1-14與hIL-2游離細胞介素之組合(以等效於人類中之治療劑量的劑量及方案投與)或抗mPD-1 RMP1-14與非靶向抗KLH-hIL-2 F42K、Y45R、V69R融合蛋白之組合，進行治療之小鼠並未重現抗mPD-1 RMP1-14-hIL-2 F42K、Y45R、V69R中所見之功效。此等資料證實，相對於抗PD-1受體拮抗劑，將效力降低之hIL-2靶向表現PD-1之細胞顯著改善抗腫瘤功效，且融合蛋白之活性並非歸因於分子之個別組分的累加效應。

實例24：MC38結腸直腸腫瘤模型中由抗mPD-1 RMP1-14-hIL-2 F42K、Y45R、V69R替代物誘導之保護性抗腫瘤免疫性的評估

【0247】 使小鼠在無任何額外藥物療法之情況下經歷繼發性腫瘤攻

擊，該等小鼠在實例23中所描述之原發性腫瘤研究中已經歷完全腫瘤消退且已存活至第50天。為了腫瘤再攻擊，在小鼠之原發性腫瘤之位置對側的左側腹植入5×10^5個MC38腫瘤細胞。作為對照，亦向10隻年齡相符之未經腫瘤處理之小鼠植入MC38腫瘤細胞。

【0248】 圖20展示，此前已在先前原發性腫瘤研究中經歷完全腫瘤消退且在用抗mPD-1 RMP1-14-hIL-2 F42K、Y45R、V69R治療後存活至第50天的所有小鼠完全受保護而免於繼發性腫瘤發展。相比之下，所有植入有MC38腫瘤細胞之未經腫瘤處理之小鼠均繼續發展快速達到100 mm^3腫瘤體積之研究終點的腫瘤。在不存在持續藥物療法之情況下，保護性抗腫瘤免疫性之發展表明，抗mPD-1 RMP1-14-hIL-2 F42K、Y45R、V69R誘導抗腫瘤記憶T細胞反應。

【0249】 熟習此項技術者應瞭解，可對本文中所揭示之較佳實施例進行許多變化及修改，且此類變化及修改可在不背離本發明之精神的情況下進行。因此，意欲隨附申請專利範圍涵蓋屬於本發明之真實精神及範疇內的所有此類等效變化。

【0250】 此文件中所引用或所描述之各專利、專利申請案及公開案的揭示內容在此以全文引用之方式併入本文中。

表28. 例示性抗體

抗體名稱	重鏈	輕鏈
抗hPD-1 #1-mIgG2b-N297A	抗 hPD-1 #1-mIgG2b-N297A HC (SEQ ID NO: 348)	抗hPD-1 #1-mκ LC (SEQ ID NO: 349)
抗hPD-1 #2-mIgG2b-N297A	抗 hPD-1 #2-mIgG2b-N297A HC (SEQ ID NO: 350)	抗hPD-1 #2-mκ LC (SEQ ID NO: 351)
hIL-2 N端輕鏈df	1H3-hIgG1 HC (SEQ ID NO: 379)	hIL-2-df-1H3-hκ LC (SEQ ID NO: 356)
hIL-2 N端輕鏈L6融合物	1H3-hIgG1 HC (SEQ ID NO: 379)	hIL-2-L6-1H3-hκ LC (SEQ ID NO: 357)
hIL-2 N端重鏈df	hIL-2-df-1H3-hIgG1 HC (SEQ ID NO: 358)	1H3-hκ LC (SEQ ID NO: 374)

hIL-2 N端重鏈L6融合物	hIL-2-L6-1H3-hIgG1 HC (SEQ ID NO: 359)	1H3-hκ LC (SEQ ID NO: 374)
hIL-2 C端重鏈df	1H3-hIgG1-df-hIL-2 HC (SEQ ID NO: 360)	1H3-hκ LC (SEQ ID NO: 374)
hIL-2 C端重鏈L6融合物	1H3-hIgG1-L6-hIL-2 HC (SEQ ID NO: 361)	1H3-hκ LC (SEQ ID NO: 374)
hIL-2 C端輕鏈df	1H3-hIgG1 HC (SEQ ID NO: 379)	1H3-hκ-df-hIL-2 (WT) LC (SEQ ID NO: 362)
hIL-2 C端輕鏈L6融合物	1H3-hIgG1 HC (SEQ ID NO: 379)	1H3-hκ-L6-hIL-2 (WT) LC (SEQ ID NO: 363)
hCD25-L20-hIL-2 N端重鏈df	hCD25-L20-hIL-2-df-1H3-hIgG1 HC (SEQ ID NO: 365)	1H3-hκ LC (SEQ ID NO: 374)
hCD25-L20-hIL-2 N端重鏈L6融合物	hCD25-L20-hIL-2-L6-1H3-hIgG1 HC (SEQ ID NO: 366)	1H3-hκ LC (SEQ ID NO: 374)
hCD25-L20-hIL-2 N端輕鏈df	1H3-hIgG1 HC (SEQ ID NO: 379)	hCD25-L20-hIL-2-df-1H3-hκ LC (SEQ ID NO: 367)
hCD25-L20-hIL-2 N端輕鏈L6融合物	1H3-hIgG1 HC (SEQ ID NO: 379)	hCD25-L20-hIL-2-L6-1H3-hκ LC (SEQ ID NO: 368)
hCD25-L20-hIL-2 C端重鏈df	1H3-hIgG1-df-hCD25-L20-hIL-2 HC (SEQ ID NO: 369)	1H3-hκ LC (SEQ ID NO: 374)
hCD25-L20-hIL-2 C端重鏈L6融合物	1H3-hIgG1-L6-hCD25-L20-hIL-2 HC (SEQ ID NO: 370)	1H3-hκ LC (SEQ ID NO: 374)
hCD25-L20-hIL-2 C端輕鏈df	1H3-hIgG1 HC (SEQ ID NO: 379)	1H3-hκ-df-hCD25-L20-hIL-2 LC (SEQ ID NO: 371)
hCD25-L20-hIL-2 C端輕鏈L6融合物	1H3-hIgG1 HC (SEQ ID NO: 379)	1H3-hκ-L6-hCD25-L20-hIL-2 LC (SEQ ID NO: 372)
2D12-mIgG1-D265A-L6-hIL-2	2D12-mIgG1-D265A-L6-hIL-2 HC (SEQ ID NO: 375)	2D12-mκ LC (SEQ ID NO: 376)
2H7-hIgG4	2H7-hIgG4 HC (SEQ ID NO: 424)	2H7-hκ LC (SEQ ID NO: 425)
C51E6-5-hIgG4	C51E6-5-hIgG4 HC (SEQ ID NO: 426)	C51E6-5-hκ LC (SEQ ID NO: 427)
A2-hIgG4	A2-hIgG4 HC (SEQ ID NO: 428)	A2-hλ LC (SEQ ID NO: 429)
H7-632-hIgG1-LAGA	H7-632 HC (SEQ ID NO: 414)	H7-632 LC (SEQ ID NO: 415)
2H7-hIgG4-df-hIL-2 (D20A/R38E)	2H7-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 430)	2H7-hκ LC (SEQ ID NO: 425)
C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)	C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 432)	C51E6-5-hκ LC (SEQ ID NO: 427)
A2-hIgG4-df-hIL-2 (D20A/R38E)	A2-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 433)	A2-hλ LC (SEQ ID NO: 429)
1H3-hIgG4-df-hIL-2 (D20A/R38E)	1H3-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 434)	1H3-hκ LC (SEQ ID NO: 374)

2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 435)	2H7-hκ LC (SEQ ID NO: 425)
OMC.1.B6-hIgG4	OMC.1.B6-hIgG4 HC (SEQ ID NO: 438)	OMC.1.B6-hλ LC (SEQ ID NO: 439)
OMC.2.C6-hIgG4	OMC.2.C6-hIgG4 HC (SEQ ID NO: 440)	OMC.2.C6-hλ LC (SEQ ID NO: 441)
OMC.1.D6-hIgG4	OMC.1.D6-hIgG4 HC (SEQ ID NO: 442)	OMC.1.D6-hλ LC (SEQ ID NO: 443)
D12-hIgG4	D12-hIgG4 HC (SEQ ID NO: 444)	D12-hλ LC (SEQ ID NO: 445)
G12-hIgG4	G12-hIgG4 HC (SEQ ID NO: 446)	G12-hλ LC (SEQ ID NO: 447)
Abz1mod-hIgG4	Abz1mod-hIgG4 HC (SEQ ID NO: 449)	Abz1mod-hκ LC (SEQ ID NO: 450)
抗hPD-1 #1-hIgG4-L6-hIL-2 (D20A/R38E)	抗 hPD-1 #1-hIgG4-L6-hIL-2 (D20A/R38E) (SEQ ID NO: 451)	抗hPD-1 #1- hκ (SEQ ID NO: 452)
OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E)	OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 453)	OMC.1.B6-hλ LC (SEQ ID NO: 439)
OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E)	OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 454)	OMC.2.C6-hλ LC (SEQ ID NO: 441)
OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E)	OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 455)	OMC.1.D6-hλ LC (SEQ ID NO: 443)
D12-hIgG4-df-hIL-2 (D20A/R38E)	D12-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 456)	D12-hλ LC (SEQ ID NO: 445)
G12-hIgG4-df-hIL-2 (D20A/R38E)	G12-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 457)	G12-hλ LC (SEQ ID NO: 447)
2H7-hIgG4-LE	2H7-hIgG4-LE HC (SEQ ID NO: 458)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG4-LAGA	2H7-hIgG4-LAGA HC (SEQ ID NO: 459)	2H7-hκ LC (SEQ ID NO: 425)
OMC476pH7-hIgG4	OMC476pH7-hIgG4 HC (SEQ ID NO: 461)	OMC476pB11.H7 LC (SEQ ID NO: 462)
OMC476pB11-hIgG4	OMC476pB11-hIgG4 HC (SEQ ID NO: 463)	OMC476pB11.H7 LC (SEQ ID NO: 462)
OMC476pG10-hIgG4	OMC476pG10-hIgG4 HC (SEQ ID NO: 464)	OMC476pG10.H10 LC (SEQ ID NO: 466)
OMC476pH10-hIgG4	OMC476pH10-hIgG4 HC (SEQ ID NO: 465)	OMC476pG10.H10 LC (SEQ ID NO: 466)
OMC476pE4-hIgG4	OMC476pE4-hIgG4 HC (SEQ ID NO: 467)	OMC476pE4 LC (SEQ ID NO: 468)
J110-hIgG1	J110-hIgG1 HC (SEQ ID NO: 469)	J110-hκ LC (SEQ ID NO: 470)

2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 471)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 472)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 473)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 474)	2H7-hκ LC (SEQ ID NO: 425)
hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 475)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 476)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 477)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 478)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 479)	2H7-hκ LC (SEQ ID NO: 425)
1H3-hIgG4-df-hIL-2 (WT)	1H3-hIgG4-df-hIL-2 (WT) HC (SEQ ID NO: 480)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (WT)	1H3-hIgG4-L6-hIL-2 (WT) HC (SEQ ID NO: 481)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-df-hIL-2 (WT) LC融合物	1H3-hIgG4 HC (SEQ ID NO: 482)	1H3-hκ-df-hIL-2 (WT) LC (SEQ ID NO: 362)
1H3-hIgG4-L6-hIL-2 (WT) LC融合物	1H3-hIgG4 HC (SEQ ID NO: 482)	1H3-hκ-L6-hIL-2 (WT) LC (SEQ ID NO: 363)
1H3-hIgG4-L6-hIL-2 (D20Y)	1H3-hIgG4-L6-hIL-2 (D20Y) HC (SEQ ID NO: 485)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-df-hIL-2 (D20Y)	1H3-hIgG4-df-hIL-2 (D20Y) HC (SEQ ID NO: 486)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-df-hIL-2 (D20Y)	1H3-hIgG1-df-hIL-2 (D20Y) HC (SEQ ID NO: 487)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (D20A/R38P)	1H3-hIgG4-L6-hIL-2 (D20A/R38P) HC (SEQ ID NO: 488)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (D20A/R38S)	1H3-hIgG4-L6-hIL-2 (D20A/R38S) HC (SEQ ID NO: 489)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (D20A/R38D)	1H3-hIgG4-L6-hIL-2 (D20A/R38D) HC (SEQ ID NO: 490)	1H3-hκ LC (SEQ ID NO: 374)

1H3-hIgG4-L6-hIL-2 (D20A/R38Q/E95A)	1H3-hIgG4-L6-hIL-2 (D20A/R38Q/E95A) HC (SEQ ID NO: 491)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (D20A/F42H/E95A)	1H3-hIgG4-L6-hIL-2 (D20A/F42H/E95A) HC (SEQ ID NO: 492)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (R38D/I92D)	1H3-hIgG4-L6-hIL-2 (R38D/I92D) HC (SEQ ID NO: 493)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (R38E/I92D)	1H3-hIgG4-L6-hIL-2 (R38E/I92D) HC (SEQ ID NO: 494)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (F42H/I92D)	1H3-hIgG4-L6-hIL-2 (F42H/I92D) HC (SEQ ID NO: 495)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (D20A/R38E)	1H3-hIgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 496)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E)	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E) HC (SEQ ID NO: 497)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (D20A/R38E/C125A)	1H3-hIgG4-L6-hIL-2 (D20A/R38E/C125A) HC (SEQ ID NO: 498)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E/C125A)	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 499)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hIL-2 (D20A/R38E)	1H3-hIgG1-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 500)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E)	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E) HC (SEQ ID NO: 501)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A)	1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A) HC (SEQ ID NO: 502)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG4-df-hIL-2 (D20A/R38E) LC fusion	1H3-hIgG4 HC (SEQ ID NO: 482)	1H3-hκ-df-hIL-2 (D20A/R38E) LC (SEQ ID NO: 503)
1H3-hIgG4-L6-hIL-2 (D20A/R38E) LC fusion	1H3-hIgG4 HC (SEQ ID NO: 482)	1H3-hκ-L6-hIL-2 (D20A/R38E) LC (SEQ ID NO: 504)
OMC476pB11-hIgG4-df-hIL-2 (D20A/R38E)	OMC476pB11-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 505)	OMC476pB11.H7 LC (SEQ ID NO: 462)
OMC476pE4-hIgG4-df-hIL-2 (D20A/R38E)	OMC476pE4-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 506)	OMC476pE4 LC (SEQ ID NO: 468)
OMC476pG10-hIgG4-df-hIL-2 (D20A/R38E)	OMC476pG10-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 507)	OMC476pG10.H10 LC (SEQ ID NO: 466)

OMC476pH10-hIgG4-df-hIL-2 (D20A/R38E)	OMC476pH10-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 508)	OMC476pG10.H10 LC (SEQ ID NO: 466)
A2-hIgG4-df-hIL-2 (D20A/F42A)	A2-hIgG4-df-hIL-2 (D20A/F42A) HC (SEQ ID NO: 509)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4-df-hIL-2 (D20A/F42S)	A2-hIgG4-df-hIL-2 (D20A/F42S) HC (SEQ ID NO: 510)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4-df-hIL-2 (D20S/R38E)	A2-hIgG4-df-hIL-2 (D20S/R38E) HC (SEQ ID NO: 511)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4-df-hIL-2 (F42A/N88R)	A2-hIgG4-df-hIL-2 (F42A/N88R) HC (SEQ ID NO: 512)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4-df-hIL-2 (F42I/I92D)	A2-hIgG4-df-hIL-2 (F42I/I92D) HC (SEQ ID NO: 513)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4-df-hIL-2 (F42Q/I92D)	A2-hIgG4-df-hIL-2 (F42Q/I92D) HC (SEQ ID NO: 514)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4-df-hIL-2 (F42T/I92D)	A2-hIgG4-df-hIL-2 (F42T/I92D) HC (SEQ ID NO: 515)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4-df-hIL-2 (F42W/I92D)	A2-hIgG4-df-hIL-2 (F42W/I92D) HC (SEQ ID NO: 516)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4-df-hIL-2 (R38E/D84K)	A2-hIgG4-df-hIL-2 (R38E/D84K) HC (SEQ ID NO: 517)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4-df-hIL-2 (R38E/I92K)	A2-hIgG4-df-hIL-2 (R38E/I92K) HC (SEQ ID NO: 518)	A2-hλ LC (SEQ ID NO: 429)
C51E6-5-hIgG4-df-hIL-2 (D20A/R38E)	C51E6-5-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 519)	C51E6-5-hκ LC (SEQ ID NO: 427)
C51E6-5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	C51E6-5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 520)	C51E6-5-hκ LC (SEQ ID NO: 427)
C51E6-5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	C51E6-5-hIgG4-LAGA-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 521)	C51E6-5-hκ LC (SEQ ID NO: 427)
2A3.H7-hIgG4-df-hIL-2 (D20A/R38E)	2H7-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 430)	2A3-hκ LC (SEQ ID NO: 523)
1H9-hIgG4-df-hIL-2 (D20A/R38E)	1H9-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 524)	1H9-hκ LC (SEQ ID NO: 525)
1D5-hIgG4-df-hIL-2 (D20A/R38E)	1D5-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 526)	1D5-hκ LC (SEQ ID NO: 527)

1D5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	1D5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 528)	1D5-hκ LC (SEQ ID NO: 527)
1D5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	1D5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 529)	1D5-hκ LC (SEQ ID NO: 527)
2H7-hIgG1-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hIgG1-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 530)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hIgG1-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 531)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 533)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG4-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hIgG4-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 534)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hIgG1-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 535)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 536)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG4-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hIgG4-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 537)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LAGA-df-hIL2 (T3A/D20S/R38E/C125A)	2H7-hIgG1-LAGA-df-hIL2 (T3A/D20S/R38E/C125A) HC (SEQ ID NO: 538)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/D84F/C125A)	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/D84F/C125A) HC (SEQ ID NO: 539)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92R/C125A)	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92R/C125A) HC (SEQ ID NO: 540)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92E/C125A)	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92E/C125A) HC (SEQ ID NO: 541)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92S/C125A)	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92S/C125A) HC (SEQ ID NO: 542)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92D/C125A)	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92D/C125A) HC (SEQ ID NO: 543)	2H7-hκ LC (SEQ ID NO: 425)
2H7-hIgG1-LAGA-df-hIL2 (T3A/H16E/R38E/C125A)	2H7-hIgG1-LAGA-df-hIL2 (T3A/H16E/R38E/C125A) HC (SEQ ID NO: 544)	2H7-hκ LC (SEQ ID NO: 425)
1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 545)	1H3-hκ LC (SEQ ID NO: 374)

1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 546)	1H3-hκ LC (SEQ ID NO: 374)
C51E6-5-hIgG4/k-LE	C51E6-5-hIgG4/k-LE HC (SEQ ID NO: 547)	C51E6-5-hκ LC (SEQ ID NO: 427)
C51E6-5-hIgG4/k-LAGA	C51E6-5-hIgG4/k-LAGA HC (SEQ ID NO: 548)	C51E6-5-hκ LC (SEQ ID NO: 427)
C51E6-5-hIgG4/k-LEPG	C51E6-5-hIgG4/k-LEPG HC (SEQ ID NO: 549)	C51E6-5-hκ LC (SEQ ID NO: 427)
C51E6-5-hIgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A)	C51E6-5-hIgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 550)	C51E6-5-hκ LC (SEQ ID NO: 427)
C51E6-5-hIgG4/k-LEPG-hIL-2 (T3A/D20A/R38E/C125A)	C51E6-5-hIgG4/k-LEPG-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 551)	C51E6-5-hκ LC (SEQ ID NO: 427)
A2-hIgG4/k-LE	A2-hIgG4/k-LE HC (SEQ ID NO: 552)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4/k-LAGA	A2-hIgG4/k-LAGA HC (SEQ ID NO: 553)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4/k-LEPG	A2-hIgG4/k-LEPG HC (SEQ ID NO: 554)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A)	A2-hIgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 555)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4/k-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	A2-hIgG4/k-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 556)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4/k-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	A2-hIgG4/k-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 557)	A2-hλ LC (SEQ ID NO: 429)
A2-hIgG4/k-LEPG-df-hIL-2 (T3A/D20A/R38E/C125A)	A2-hIgG4/k-LEPG-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 558)	A2-hλ LC (SEQ ID NO: 429)
抗CD20-hIgG1/k	抗CD20-hIgG1/k HC (SEQ ID NO: 560)	抗CD20-hκ LC (SEQ ID NO: 562)
抗CD20-hIgG1/k-LAGA	抗 CD20-hIgG1/k-LAGA HC (SEQ ID NO: 561)	抗CD20-hκ LC (SEQ ID NO: 562)
1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A)	1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A) HC (SEQ ID NO: 563)	1H3-hκ LC (SEQ ID NO: 374)
抗mPD-1 RMP1-14 mIgG2b-N297A	抗 mPD-1 RMP1-14 mIgG2b-N297A HC (SEQ ID NO: 564)	抗mPD-1 RMP1-14 mκ LC (SEQ ID NO: 566)
抗mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)	抗 mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) HC (SEQ ID NO: 565)	抗mPD-1 RMP1-14 mκ LC (SEQ ID NO: 566)
抗mPD-1 RMP1-30 mIgG2b-N297A	抗 mPD-1 RMP1-30 mIgG2b-N297A HC (SEQ ID NO: 567)	抗mPD-1 RMP1-30 mκ LC (SEQ ID NO: 568)

抗mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)	抗 mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) HC (SEQ ID NO: 569)	抗 mPD-1 RMP1-30 mκ LC (SEQ ID NO: 568)
抗 KLH-C3-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)	抗 KLH-C3-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) HC (SEQ ID NO: 570)	KLH-C3-mκ LC (SEQ ID NO: 571)
2D12-hIgG1-L6-hIL-2	2D12-hIgG1-L6-hIL-2 HC (SEQ ID NO: 572)	2D12-hκ LC (SEQ ID NO: 573)
1H9-hIgG4	1H9-hIgG4 HC (SEQ ID NO: 576)	1H9-hκ LC (SEQ ID NO: 525)
1D5-hIgG4	1D5-hIgG4 HC (SEQ ID NO: 577)	1D5-hκ LC (SEQ ID NO: 527)
2A3.H7-hIgG4	2H7-hIgG4 HC (SEQ ID NO: 424)	2A3-hκ LC (SEQ ID NO: 523)
H7-02-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	H7-02-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 582)	H7-02-hκ LC (SEQ ID NO: 583)
KLH-C3-hIgG4	KLH-C3-hIgG4 HC (SEQ ID NO: 585)	KLH-C3-hκ LC (SEQ ID NO: 586)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A) HC (SEQ ID NO: 587)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20I)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20I) HC (SEQ ID NO: 588)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S) HC (SEQ ID NO: 589)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20H)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20H) HC (SEQ ID NO: 590)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W) HC (SEQ ID NO: 591)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y) HC (SEQ ID NO: 592)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20R)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20R) HC (SEQ ID NO: 593)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20F)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20F) HC (SEQ ID NO: 594)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K) HC (SEQ ID NO: 595)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A) HC (SEQ ID NO: 596)	1H3-hκ LC (SEQ ID NO: 374)

1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88Y)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88Y) HC (SEQ ID NO: 597)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D) HC (SEQ ID NO: 598)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R) HC (SEQ ID NO: 599)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88E)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88E) HC (SEQ ID NO: 600)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88F)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88F) HC (SEQ ID NO: 601)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88I)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88I) HC (SEQ ID NO: 602)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (I92A)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (I92A) HC (SEQ ID NO: 603)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95A)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95A) HC (SEQ ID NO: 604)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K)	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K) HC (SEQ ID NO: 605)	1H3-hκ LC (SEQ ID NO: 374)
H7-02-hIgG4	H7-02-hIgG4 HC (SEQ ID NO: 373)	H7-02 hκ LC (SEQ ID NO: 607)
H7-632-hIgG1-LAGA-df-hIL-2 (T3A/C125A)	H7-632-hIgG1-LAGA-df-hIL-2 (T3A/C125A) HC (SEQ ID NO: 431)	H7-632 LC (SEQ ID NO: 415)
1H3-hIgG1-LAGA-L6-hIL-2 (T3A/D20A/R38E/C125A)	1H3-hIgG1-LAGA-L6-hIL-2 (T3A/D20A/R38E/C125A) (SEQ ID NO: 522)	1H3-hκ LC (SEQ ID NO: 374)
1H3-hIgG1	1H3-hIgG1 HC (SEQ ID NO: 379)	1H3-hκ LC (SEQ ID NO: 374)
H7-767	H7-767 HC (SEQ ID NO: 532)	H7-632 LC (SEQ ID NO: 415)
抗hPD-1 #1	抗hPD-1 #1 HC (SEQ ID NO: 559)	抗hPD-1#1-hκ (SEQ ID NO: 452)
抗hPD-1 #2	抗hPD-1 #2 HC (SEQ ID NO: 578)	抗hPD-1 #2 LC (SEQ ID NO: 579)
2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 475)	2H7-hκ LC (SEQ ID NO: 425)

表29. 序列

SEQ ID NO:	名稱	序列
1	hIL-2 F42K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**K**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
2	hIL-2 V69A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**A** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
3	hIL-2 V69E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**E** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
4	hIL-2 V69F	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**F** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
5	hIL-2 V69G	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**G** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
6	hIL-2 V69H	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**H** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
7	hIL-2 V69I	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**I** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
8	hIL-2 V69K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**K** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
9	hIL-2 V69L	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**L** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
10	hIL-2 V69M	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**M** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
11	hIL-2 V69Q	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**Q** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
12	hIL-2 V69S	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**S** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
13	hIL-2 V69T	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**T** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
14	hIL-2 V69W	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**W** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
15	hIL-2 V69Y	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**Y** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
16	hIL-2 F42K/F44K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**K**K**K**YMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

17	hIL-2 F44K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFK**KR**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
18	hIL-2 F42K/V69R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKKFYMPKKATELKHLQCLEEELKPLEER LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
19	hIL-2 Y45R/V69R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFRMPKKATELKHLQCLEEELKPLEER LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
20	hIL-2 F42K/F44K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKKKRMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
21	hIL-2 R38A/F42K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTAMLTKKFRMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
22	hIL-2 R38E/F42K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTEMLTKKFRMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
23	hIL-2 K43E/F42K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKEFRMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
24	hIL-2 K43T/F42K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKTFRMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
25	hIL-2 F42K/Y45R/E62A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKKFRMPKKATELKHLQCLEEALKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
26	hIL-2 P65R/F42K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKKFRMPKKATELKHLQCLEEELKRLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
27	hIL-2 P65S/F42K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKKFRMPKKATELKHLQCLEEELKSLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
28	hIL-2 V69A/F42K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKKFRMPKKATELKHLQCLEEELKPLEEA LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
29	hIL-2 V69D/F42K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKKFRMPKKATELKHLQCLEEELKPLEED LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
30	hIL-2 V69R/F42K/Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKKFRMPKKATELKHLQCLEEELKPLEER LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
31	hIL-2 D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
32	hIL-2 D20N	APTSSSTKKTQLQLEHLLL**N**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
33	hIL-2 D20K	APTSSSTKKTQLQLEHLLL**K**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
34	hIL-2 N88A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**A**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

35	hIL-2 N88G	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**G**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
36	hIL-2 N88H	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**H**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
37	hIL-2 N88K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**K**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
38	hIL-2 D20A/D84A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**A**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
39	hIL-2 D20A/E15A	APTSSSTKKTQLQL**A**HLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
40	hIL-2 D20A/E95A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
41	hIL-2 D20A/N88A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**A**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
42	hIL-2 D20A/S87A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLI**A**NINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
43	hIL-2 D84A/N88A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**A**LIS**A**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
44	hIL-2 E15A/N88A	APTSSSTKKTQLQL**A**HLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**A**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
45	hIL-2 S87A/N88A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLI**AA**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
46	hIL-2 R38A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**A**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
47	hIL-2 R38D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**D**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
48	hIL-2 R38E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
49	hIL-2 R38Q	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**Q**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
50	hIL-2 F42R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**R**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
51	hIL-2 F42A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**A**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
52	hIL-2 F42D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**D**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

53	hIL-2 F42H	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**H**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
54	hIL-2 K43A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTF**A**FYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
55	hIL-2 K43E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTF**E**FYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
56	hIL-2 K43Q	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTF**Q**FYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
57	hIL-2 Y45A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**A**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
58	hIL-2 Y45K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**K**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
59	hIL-2 Y45S	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**S**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
60	hIL-2 Y45R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**R**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
61	hIL-2 E61A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**A**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
62	hIL-2 E61R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**R**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
63	hIL-2 E61K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**K**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
64	hIL-2 E62A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**A**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
65	hIL-2 E62R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**R**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
66	hIL-2 E62K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**K**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
67	hIL-2 E62Y	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**Y**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
68	hIL-2 E68Y	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLE**Y**V LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
69	hIL-2 E68A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLE**A**V LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
70	hIL-2 E68K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLE**K**V LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

71	hIL-2 E68R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLE**R**V LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
72	hIL-2 E68L	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLE**L**V LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
73	hIL-2 L72Y	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**Y**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
74	hIL-2 L72R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**R**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
75	hIL-2 L72A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**A**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
76	hIL-2 L72D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**D**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
77	hIL-2 L72H	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**H**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
78	hIL-2 L72F	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**F**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
79	hIL-2 R38D/E61R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**D**MLTFKFYMPKKATELKHLQCLE**R**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
80	hIL-2 R38D/E61R/K43E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**D**MLTF**E**FYMPKKATELKHLQCLE**R**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
81	hIL-2 T3A/F42A/Y45A/L72G/C125A	AP**A**SSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**A**KF**A**MPKKATELKHLQCLEEELKPLEEV LN**G**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITF**A**QSIISTLT
82	hIL-2 E15A	APTSSSTKKTQLQL**A**HLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
83	hIL-2 E15R	APTSSSTKKTQLQL**R**HLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
84	hIL-2 E15K	APTSSSTKKTQLQL**K**HLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
85	hIL-2 H16A	APTSSSTKKTQLQLE**A**LLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
86	hIL-2 H16Y	APTSSSTKKTQLQLE**Y**LLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
87	hIL-2 H16E	APTSSSTKKTQLQLE**E**LLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

88	hIL-2 L19A	APTSSSTKKTQLQLEHLL**A**DLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
89	hIL-2 D20I	APTSSSTKKTQLQLEHLLL**I**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
90	hIL-2 D20S	APTSSSTKKTQLQLEHLLL**S**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
91	hIL-2 D20H	APTSSSTKKTQLQLEHLLL**H**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
92	hIL-2 D20T	APTSSSTKKTQLQLEHLLL**T**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
93	hIL-2 D20W	APTSSSTKKTQLQLEHLLL**W**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
94	hIL-2 D20Y	APTSSSTKKTQLQLEHLLL**Y**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
95	hIL-2 D20R	APTSSSTKKTQLQLEHLLL**R**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
96	hIL-2 D20F	APTSSSTKKTQLQLEHLLL**F**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
97	hIL-2 R81A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHL**A**PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
98	hIL-2 D84A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**A**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
99	hIL-2 D84R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**R**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
100	hIL-2 D84K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**K**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
101	hIL-2 S87A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLI**A**NINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
102	hIL-2 N88Y	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**Y**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
103	hIL-2 N88D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**D**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
104	hIL-2 N88R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**R**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
105	hIL-2 N88E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**E**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

106	hIL-2 N88F	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**F**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
107	hIL-2 N88I	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**I**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
108	hIL-2 I92A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**A**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
109	hIL-2 I92Y	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**Y**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
110	hIL-2 I92S	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**S**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
111	hIL-2 I92F	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**F**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
112	hIL-2 I92R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**R**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
113	hIL-2 I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
114	hIL-2 I92E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**E**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
115	hIL-2 E95A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
116	hIL-2 E95R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**R**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
117	hIL-2 E95K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**K**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
118	hIL-2 D20Y/H16E	APTSSSTKKTQLQLE**E**LLL**Y**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
119	hIL-2 D20Y/H16A	APTSSSTKKTQLQLE**A**LLL**Y**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
120	hIL-2 D20Y/H16Y	APTSSSTKKTQLQLE**Y**LLL**Y**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
121	hIL-2 D20Y/I92A	APTSSSTKKTQLQLEHLLL**Y**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**A**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
122	hIL-2 D20Y/I92S	APTSSSTKKTQLQLEHLLL**Y**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**S**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
123	hIL-2 D20Y/I92R	APTSSSTKKTQLQLEHLLL**Y**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**R**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

124	hIL-2 D20Y/E95R	APTSSSTKKTQLQLEHLLL**Y**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**R**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
125	hIL-2 D20Y/E95A	APTSSSTKKTQLQLEHLLL**Y**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
126	hCD25(1-164)	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRAL HRGPAESVCKMTHGKTRWTQPQLICT
127	hIL-2 F42D/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**D**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
128	hIL-2 F42R/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**R**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
129	hIL-2 F42K/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**K**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
130	hIL-2 F42A/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**A**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
131	hIL-2 F42H/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**H**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
132	hIL-2 Y45R/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**R**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
133	hIL-2 Y45K/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**K**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
134	hIL-2 R38N/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**N**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
135	hIL-2 R38G/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**G**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
136	hIL-2 R38H/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**H**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
137	hIL-2 R38I/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**I**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
138	hIL-2 R38L/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**L**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
139	hIL-2 R38M/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**M**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
140	hIL-2 R38F/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**F**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

141	hIL-2 R38P/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**P**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
142	hIL-2 R38S/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**S**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
143	hIL-2 R38T/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**T**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
144	hIL-2 R38W/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**W**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
145	hIL-2 R38Y/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**Y**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
146	hIL-2 R38V/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**V**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
147	hIL-2 R38A/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**A**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
148	hIL-2 R38Q/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**Q**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
149	hIL-2 D20A/R38E	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
150	hIL-2 R38D/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**D**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
151	hIL-2 K43E/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTF**E**FYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
152	hIL-2 E61A/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**A**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
153	hIL-2 E62A/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**A**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
154	hIL-2 E62Y/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**Y**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
155	hIL-2 L72D/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**D**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
156	hIL-2 L72H/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**H**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
157	hIL-2 L72R/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**R**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
158	hIL-2 F42D/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**D**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

159	hIL-2 F42R/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**R**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
160	hIL-2 F42H/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**H**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
161	hIL-2 F42A/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**A**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
162	hIL-2 K43E/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTF**E**FYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
163	hIL-2 Y45R/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**R**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
164	hIL-2 Y45K/I92	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**K**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
165	hIL-2 E62A/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**A**LKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
166	hIL-2 E62Y/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**Y**LKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
167	hIL-2 L72D/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**D**AQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
168	hIL-2 L72H/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**H**AQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
169	hIL-2 L72R/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**R**AQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
170	hIL-2 R38D/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**D**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
171	hIL-2 R38E/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
172	hIL-2 R38Q/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**Q**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
173	hIL-2 R38A/I92D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**A**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
174	hIL-2 R38E/N88R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**R**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
175	hIL-2 R38E/D84R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**R**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
176	hIL-2 R38E/D84K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**K**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

177	hIL-2 F42A/Y45R/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**A**KF**R**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
178	hIL-2 F42H/Y45R/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**H**KF**R**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
179	hIL-2 R38D/E61R/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**D**MLTFKFYMPKKATELKHLQCLE**R**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
180	hIL-2 R38E/E61R/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLE**R**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
181	hIL-2 R38Q/E61R/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**Q**MLTFKFYMPKKATELKHLQCLE**R**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
182	hIL-2 R38A/E61R/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**A**MLTFKFYMPKKATELKHLQCLE**R**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
183	hIL-2 R38A/D20A/E95A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**A**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
184	hIL-2 D20A/E95A/R38D	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**D**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
185	hIL-2 D20A/ E95A/ R38E	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
186	hIL-2 D20A/E95A/R38Q	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**Q**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
187	hIL-2 D20A/E95A/F42R	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**R**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
188	hIL-2 D20A/E95A/F42A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**A**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
189	hIL-2 D20A/E95A /F42D	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**D**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
190	hIL-2 D20A/E95A /F42H	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**H**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
191	hIL-2 D20A/E95A/F42K	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**K**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
192	hIL-2 D20A/E95A /K43A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTF**A**FYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
193	hIL-2 D20A/E95A /K43E	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTF**E**FYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
194	hIL-2 D20A/E95A /K43Q	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTF**Q**FYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

195	hIL-2 D20A/E95A /Y45A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**A**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
196	hIL-2 D20A/E95A /Y45K	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**K**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
197	hIL-2 D20A/E95A /Y45S	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**S**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
198	hIL-2 D20A/E95A /Y45R	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**R**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
199	hIL-2 D20A/E95A /E61A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**A**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
200	hIL-2 D20A/E95A /E62A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**A**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
201	hIL-2 D20A/E95A/E62R	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**R**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
202	hIL-2 D20A/E95A /E62K	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**K**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
203	hIL-2 D20A/E95A /E62Y	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE**Y**LKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
204	hIL-2 D20A/E95A /E68Y	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLE**Y**V LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
205	hIL-2 D20A/E95A/E68A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLE**A**V LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
206	hIL-2 D20A/E95A /E68L	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLE**L**V LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
207	hIL-2 D20A/E95A /L72Y	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**Y**AQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
208	hIL-2 D20A/E95A /L72R	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**R**AQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
209	hIL-2 D20A/E95A /L72A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**A**AQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
210	hIL-2 D20A/E95A/L72D	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**D**AQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
211	hIL-2 D20A/E95A /L72H	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**H**AQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
212	hIL-2 D20A/E95A /L72F	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LN**F**AQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

213	hIL-2 F42K/Y45R/D20A/S87A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**K**KF**R**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLI**A**NINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
214	hIL-2 F42K/Y45R/D20A/E95A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**K**KF**R**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
215	hIL-2 D20A/R38E/C125A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITF**A**QSIISTLT
216	hIL-2 T3A/D20A/R38E	AP**A**SSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
217	hIL-2 T3A/D20A/R38E/C125A (IL-2-AAEA)	AP**A**SSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITF**A**QSIISTLT
218	hIL-2 Δ1-3APT/D20A/R38E	SSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEVLNL AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
219	hIL-2 Δ1-3APT/D20A/R38E/C125A	SSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEVLNL AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITF**A**QSIISTLT
220	hIL-2 R38E/Q22A	APTSSSTKKTQLQLEHLLLDL**A**MILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
221	hIL-2 R38E/T123A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI**A**FCQSIISTLT
222	hIL-2 R38E/I129A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI**A**STLT
223	hIL-2 R38E/S130A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSII**A**TLT
224	hIL-2 R38E/Q126A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFC**A**SIISTLT
225	hIL-2 R38E/Q126D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFC**D**SIISTLT
226	hIL-2 R38E/Q126V	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFC**V**SIISTLT
227	hIL-2 R38E/Q22A/S130A	APTSSSTKKTQLQLEHLLLDL**A**MILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSII**A**TLT
228	hIL-2 F42K/Y45R/Q126D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**K**KF**R**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFC**D**SIISTLT
229	hIL-2 D20A/E95A/Q126D	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVL**A**LKGSETTFMCEYADETATIVEFLNRWITFC**D**SIISTLT

230	hIL-2 D20A/E61R	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**R**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
231	hIL-2 D20A/E61N	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**N**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
232	hIL-2 D20A/E61D	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**D**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
233	hIL-2 D20A/E61Q	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**Q**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
234	hIL-2 D20A/E61G	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**G**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
235	hIL-2 D20A/E61H	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**H**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
236	hIL-2 D20A/E61I	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**I**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
237	hIL-2 D20A/E61L	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**L**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
238	hIL-2 D20A/E61K	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**K**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
239	hIL-2 D20A/E61M	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**M**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
240	hIL-2 D20A/E61F	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**F**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
241	hIL-2 D20A/E61P	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**P**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
242	hIL-2 D20A/E61S	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**S**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
243	hIL-2 D20A/E61T	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**T**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
244	hIL-2 D20A/E61W	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**W**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
245	hIL-2 D20A/E61Y	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**Y**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
246	hIL-2 D20A/E61V	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLE**V**ELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
247	hIL-2 D20A/F42N	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**N**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

248	hIL-2 D20A/F42Q	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**Q**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
249	hIL-2 D20A/F42E	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**E**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
250	hIL-2 D20A/F42G	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**G**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
251	hIL-2 D20A/F42I	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**I**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
252	hIL-2 D20A/F42L	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**L**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
253	hIL-2 D20A/F42M	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**M**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
254	hIL-2 D20A/F42P	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**P**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
255	hIL-2 D20A/F42S	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**S**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
256	hIL-2 D20A/F42T	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**T**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
257	hIL-2 D20A/F42W	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**W**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
258	hIL-2 D20A/F42Y	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**Y**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
259	hIL-2 D20A/F42V	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLT**V**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
260	hIL-2 D20A/Y45A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**A**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
261	hIL-2 D20A/Y45N	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**N**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
262	hIL-2 D20A/Y45D	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**D**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
263	hIL-2 D20A/Y45Q	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**Q**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
264	hIL-2 D20A/Y45E	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**E**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
265	hIL-2 D20A/Y45G	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**G**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

266	hIL-2 D20A/Y45H	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**H**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
267	hIL-2 D20A/Y45I	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**I**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
268	hIL-2 D20A/Y45L	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**L**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
269	hIL-2 D20A/Y45M	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**M**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
270	hIL-2 D20A/Y45F	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**F**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
271	hIL-2 D20A/Y45P	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**P**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
272	hIL-2 D20A/Y45S	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**S**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
273	hIL-2 D20A/Y45T	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**T**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
274	hIL-2 D20A/Y45W	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**W**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
275	hIL-2 D20A/Y45V	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLTRMLTFKF**V**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
276	hIL-2 I92D/F42N	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**N**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
277	hIL-2 I92D/F42Q	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**Q**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
278	hIL-2 I92D/F42E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**E**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
279	hIL-2 I92D/F42G	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**G**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
280	hIL-2 I92D/F42I	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**I**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
281	hIL-2 I92D/F42L	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**L**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
282	hIL-2 I92D/F42K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**K**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
283	hIL-2 I92D/F42M	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**M**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

284	hIL-2 I92D/F42P	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**P**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
285	hIL-2 I92D/F42S	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**S**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
286	hIL-2 I92D/F42T	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**T**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
287	hIL-2 I92D/F42W	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**W**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
288	hIL-2 I92D/F42Y	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**Y**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
289	hIL-2 I92D/F42V	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**V**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
290	hIL-2 I92D/Y45A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**A**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
291	hIL-2 I92D/Y45N	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**N**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
292	hIL-2 I92D/Y45D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**D**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
293	hIL-2 I92D/Y45Q	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**Q**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
294	hIL-2 I92D/Y45E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**E**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
295	hIL-2 I92D/Y45G	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**G**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
296	hIL-2 I92D/Y45H	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**H**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
297	hIL-2 I92D/Y45I	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**I**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
298	hIL-2 I92D/Y45L	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**L**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
299	hIL-2 I92D/Y45M	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**M**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
300	hIL-2 I92D/Y45F	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**F**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
301	hIL-2 I92D/Y45P	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**P**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

302	hIL-2 I92D/Y45S	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**S**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
303	hIL-2 I92D/Y45T	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**T**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
304	hIL-2 I92D/Y45W	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**W**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
305	hIL-2 I92D/Y45V	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKF**V**MPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**D**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
306	hIL-2 R38E/D20H	APTSSSTKKTQLQLEHLLL**H**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
307	hIL-2 R38E/D20S	APTSSSTKKTQLQLEHLLL**S**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
308	hIL-2 F42A/N88R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**A**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**R**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
309	hIL-2 F42A/N88D	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**A**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLIS**D**INVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
310	hIL-2 R38E/D84A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**A**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
311	hIL-2 R38E/D84N	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**N**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
312	hIL-2 R38E/D84Q	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**Q**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
313	hIL-2 R38E/D84E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**E**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
314	hIL-2 R38E/D84G	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**G**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
315	hIL-2 R38E/D84H	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**H**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
316	hIL-2 R38E/D84I	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**I**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
317	hIL-2 R38E/D84L	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**L**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
318	hIL-2 R38E/D84M	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**M**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
319	hIL-2 R38E/D84F	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**F**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

320	hIL-2 R38E/D84P	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**P**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
321	hIL-2 R38E/D84S	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**S**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
322	hIL-2 R38E/D84T	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**T**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
323	hIL-2 R38E/D84W	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**W**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
324	hIL-2 R38E/D84Y	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**Y**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
325	hIL-2 R38E/D84V	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPR**V**LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
326	hIL-2 R38E/I92A	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**A**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
327	hIL-2 R38E/I92R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**R**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
328	hIL-2 R38E/I92N	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**N**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
329	hIL-2 R38E/I92Q	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**Q**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
330	hIL-2 R38E/I92E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**E**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
331	hIL-2 R38E/I92G	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**G**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
332	hIL-2 R38E/I92H	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**H**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
333	hIL-2 R38E/I92L	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**L**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
334	hIL-2 R38E/I92K	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**K**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
335	hIL-2 R38E/I92M	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**M**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
336	hIL-2 R38E/I92F	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**F**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
337	hIL-2 R38E/I92P	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**P**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

338	hIL-2 R38E/I92S	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**S**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
339	hIL-2 R38E/I92T	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**T**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
340	hIL-2 R38E/I92W	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**W**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
341	hIL-2 R38E/I92Y	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**Y**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
342	hIL-2 R38E/I92V	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINV**V**VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
343	hIL-2 R38E/H16E	APTSSSTKKTQLQLE**E**LLLDLQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
344	hIL-2 R38K/D20A	APTSSSTKKTQLQLEHLLL**A**LQMILNGINNYKNPKLT**K**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
345	WT hIL-2	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
346	人類PD-1	PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQP GQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSP SPRPAGQFQTLVVGVVGGLLGSLVLLVWVLAVICSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELD FQWREKTPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
347	人類PD-1	CCAGGATGGTTCTTAGACTCCCCAGACAGGCCCTGGAACCCCCCCACCTTCTCCCCAGCCCTGCTCGTG GTGACCGAAGGGGACAACGCCACCTTCACCTGCAGCTTCTCCAACACATCGGAGAGCTTCGTGCTAAAC TGGTACCGCATGAGCCCCAGCAACCAGACGGACAAGCTGGCCGCCTTCCCCGAGGACCGCAGCCAGCCC GGCCAGGACTGCCGCTTCCGTGTCACACAACTGCCCAACGGGCGTGACTTCCACATGAGCGTGGTCAGG GCCCGGCGCAATGACAGCGGCACCTACCTCTGTGGGGCCATCTCCCTGGCCCCCAAGGCGCAGATCAAA GAGAGCCTGCGGGCAGAGCTCAGGGTGACAGAGAGAAGGGCAGAAGTGCCCACAGCCCACCCCAGCCCC TCACCCAGGCCAGCCGGCCAGTTCCAAACCCTGGTGGTTGGTGTCGTGGGCGGCCTGCTGGGCAGCCTG GTGCTGCTAGTCTGGGTCCTGGCCGTCATCTGCTCCCGGGCCGCACGAGGGACAATAGGAGCCAGGCGC ACCGGCCAGCCCCTGAAGGAGGACCCCTCAGCCGTGCCTGTGTTCTCTGTGGACTATGGGGAGCTGGAT TTCCAGTGGCGAGAGAAGACCCCGGAGCCCCCCGTGCCCTGTGTCCCTGAGCAGACGGAGTATGCCACC ATTGTCTTTCCTAGCGGAATGGGCACCTCATCCCCCGCCCGCAGGGGCTCAGCTGACGGCCCTCGGAGT GCCCAGCCACTGAGGCCTGAGGATGGACACTGCTCTTGGCCCCTC

348	抗 hPD-1 #1-mIgG2b-N297A HC	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFT ISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTTPPSVYPLAPGCGDTTGSSVTL GCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHPASSTTVD KKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQ ISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKEFKCKVNNKDLPSPIERTISKIKGLV RAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYFIYSKLNM KTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGK
349	抗hPD-1 #1-mκ LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGT DFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNN FYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVK SFNRNEC
350	抗 hPD-1 #2-mIgG2b-N297A HC	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVT LTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAKTTPPSVYPLAPGCGDT TGSSVTLGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHP ASSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVS EDDPDVQISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKEFKCKVNNKDLPSPIERTI SKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYF IYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGK
351	抗hPD-1 #2-mκ LC	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPARFSGS GSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIKRADAAPTVSIFPPSSEQLTSGGASVVC FLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTS PIVKSFNRNEC
352	IL-2Rγ	LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFNVEYMNCTWNSSSEPQPTNLTLHYWY KNSDNDKVQKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDPREPRRQATQMLKLQNLVIPWAPENL TLHKLSESQLELNWNNRFLNHCLEHLVQYRTDWDHSWTEQSVDYRHKFSLPSVDGQKRYTFRVRSRFNP LCGSAQHWSEWSHPIHWGSNTSKENPFLFALEAVVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLED LVTEYHGNFSAWSGVSKGLAESLQPDYSERLCLVSEIPPKGGALGEGPGASPCNQHSPYWAPPCYTLKP ET
353	人類CD122 (IL-2Rβ)	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDRRRWNQTCELLPVSQASWACNLILGAPDS QKLTTVDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNISWEISQASHYFERH LEFEARTLSPGHTWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKP AALGKDTIPWLGHLLVGLSGAFGFIILVYLLINCRNTGPWLKKVLKCNTPDPSKFFSQLSSEHGGDVQK WLSSPFPSSSFSPGGLAPEISPLEVLERDKVTQLLLQQDKVPEPASLSSNHSLTSCFTNQGYFFFHLPD ALEIEACQVYFTYDPYSEEDPDEGVAGAPTGSSPQPLQPLSGEDDAYCTFPSRDDLLLFSPSLLGGPSP PSTAPGGSGAGEERMPPSLQERVPRDWDPQPLGPPTPGVPDLVDFQPPPELVLREAGEEVPDAGPREGV SFPWSRPPGQGEFRALNARLPLNTDAYLSLQELQGQDPTHLV

354	IL-2Rα	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRAL HRGPAESVCKMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAA TMETSIFTTEYQVAVAGCVFLLISVLLLSGLTWQRRQRKSRRTI
355	L6連接子胺基酸	SGGGGS
356	hIL-2-df-1H3-hκ LC hIL-2為斜體	*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV* *LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*DTVLT QSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTDFTLTI DPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C
357	hIL-2-L6-1H3-hκ LC 連接子為下劃虛線 hIL-2為斜體	*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV* *LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*SGGGG SDTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGT DFTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
358	hIL-2-df-1H3-hIgG1 HC hIL-2為斜體	*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV* *LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*EVQLV ESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFTISRDN AKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK
359	hIL-2-L6-1H3-hIgG1 HC 連接子為下劃虛線 hIL-2為斜體	*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV* *LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*SGGGG SEVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRF TISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

360	1H3-hIgG1-df-hIL-2 HC hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKL* *TRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMC* *EYADETATIVEFLNRWITFCQSIISTLT*
361	1H3-hIgG1-L6-hIL-2 HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*SGGGGS*_APTSSSTKKTQLQLEHLLLDLQMILNGINN_ *YKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGS* *ETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
362	1H3-hκ-df-hIL-2 (WT) LC hIL-2為斜體	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEEL* *KPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL* *T*
363	1H3-hκ-L6-hIL-2 (WT) LC 連接子為下劃虛線 hIL-2為斜體	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC*SGGGGS*_*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQ* *CLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ* *SIISTLT*
364	L20連接子	SGGGGSGGGGSGGGGSGGGS

365	hCD25-L20-hIL-2-df-1H3-hIgG1 HC 連接子為下劃虛線 hIL-2為斜體	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRAL HRGPAESVCKMTHGKTRWTQPQLICTSGGGGSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQM *ILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVI* *VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*EVQLVESGGGLVQPGRSLKLSCAVSGFT FSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFTISRDNAKITLYLQMDSLRSEDTATYYCA RHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
366	hCD25-L20-hIL-2-L6-1H3-hIgG1 HC 連接子為下劃虛線 hIL-2為斜體	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRAL HRGPAESVCKMTHGKTRWTQPQLICTSGGGGSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQM *ILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVI* *VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*SGGGGSEVQLVESGGGLVQPGRSLKLSC AVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFTISRDNAKITLYLQMDSLRSEDT ATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK
367	hCD25-L20-hIL-2-df-1H3-hκ LC 連接子為下劃虛線 hIL-2為斜體	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRAL HRGPAESVCKMTHGKTRWTQPQLICTSGGGGSGGGGSGGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQM *ILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVI* *VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*DTVLTQSPALAVSPGERVTISCRASESV RTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTDFTLTIDPVEADDTATYFCQQSWNDPFTF GSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

368	hCD25-L20-hIL-2-L6-1H3-hκ LC 連接子為下劃虛線 hIL-2為斜體	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRAL HRGPAESVCKMTHGKTRWTQPQLICTSGGGGSGGGGSGGGGSGGGGS*APTSSSTKKTQLQLEHLLLDLQM* *ILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVI* *VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*SGGGGSDTVLTQSPALAVSPGERVTISC RASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTDFTLTIDPVEADDTATYFCQQSW NDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
369	1H3-hIgG1-df-hCD25-L20-hIL-2 HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRR IKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCR EPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGGGSGGGG SGGGGSGGGS*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCL* *EEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI* *ISTLT*
370	1H3-hIgG1-L6-hCD25-L20-hIL-2 HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGS*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL* *KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI* *TFCQSIISTLT*

371	1H3-hκ-df-hCD25-L20-hIL-2 LC 連接子為下劃虛線 hIL-2為斜體	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTS SATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQMVYYQCV QGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGGGSGGGGSGGGGSGGGGS*APTSSSTKKTQLQLEHL* *LLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLI* *SNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
372	1H3-hκ-L6-hCD25-L20-hIL-2 LC 連接子為下劃虛線 hIL-2為斜體	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSWDN QCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQM VYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGGGSGGGGSGGGGSGGGGS*APTSSSTKKTQ* *LQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHL* *RPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
373	H7-02-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
374	1H3-hκ LC	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
375	2D12-mIgG1-D265A-L6-hIL-2 HC	EVQLQQSGPELVKPGASVKISCKTSGYTFTEYTMHWVKQSHGKSLEWIGGINPNNGGTTYNQKFKGKAT LTVDKSSSTAYMELRSLTSQDSAVYYCARDYYRYGHYYAMDYWGQGTSVTVSSAKTTPPSVYPLAPGSA AQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVA HPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVAISKDDPEVQFSW FVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAP QVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKS NWEAGNTFTCSVLHEGLHNHHTEKSLSHSPGKSGGGGS*APTSSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFCQSIISTLT*

376	2D12-mκ LC	QIVLTQSPAIMSASPGEKVTMTCSVSSSVRFMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTS YSLTISSMEAEDAATYYCQQWSSNPPTFGGGTKLKIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNF YPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKS FNRNEC
377	hIL-2 Q126L	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCLSIISTLT
378	hIL-2 Q126E	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCESIISTLT
379	1H3-hIgG1 HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
380	huPD-1-Fc	MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYR MSPSNQTDKLAAFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESL RAELRVTERRAEVPTAHPSPSPRPAGQFQIEGRMDPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
381	石蟹獼猴-PD-1-Fc	MQIPQAPWPVVWAVLQLGWRPGWFLESPDRPWNAPTFSPALLLVTEGDNATFTCSFSNASESFVLNWYR MSPSNQTDKLAAFPEDRSQPGQDCRFRVTRLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESL RAELRVTERRAEVPTAHPSPSPRPAGQFQIEGRMDPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
382	2H7 VH	GAGGTGCAGCTGCTGGAAAGCGGCGGCGGACTGGTGCAGCCTGGAGGCAGCCTGCGGCTGTCTTGTGCC GCTTCTGGCTTCACCTTCAAGGACTACTGCATGACCTGGGTCAGACAGGCCCCTGGCAAGGGCCTCGAG TGGGTGTCCGCCATCGTGTACAGCGGCGGGTCAACATACTACGCCGACAGCGTGAAGGGCAGATTCACA ATCAGCAGAGATAACAGCAAGAACACCCTGTACCTGCAGATGAACAACCTGAGAGCTGAAGATACCGCC GTGTACTACTGCGCCAAGTACACCAGAGCCAGCTACTTCTACGACGCCATGGACGTGTGGGGCCAGGGC ACCACCGTGACAGTGTCCTCAT

383	2H7 VL	GAGATCGTGCTGACCCAGTCTCCTGGCACCCTGAGCCTGAGCCCTGGCGAGAGAGCTACACTGTCATGC AGAGCCTCTCAGAGCATCGGCAAGAGCTTCCTGGCCTGGTACCAGCAAAAGCCTGGACAGGCCCCTAGA CTGCTGATCTACGACGCCAGCACCAGAGCCGCTGATATCCCCGCCAGATTCAGCGGATCTGGCAGCGGC ACTGATTTCACCCTCACCATCAGCAGCCTGGAACCCGAGGACTTCGCCGTGTACTACTGCCAGCAGTAC TACGACTGGCCCCCCCTGTCTTTTGGCGGAGGCACAAAGGTGGAAATCAAG
384	2H7 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSS
385	2H7 VL	EIVLTQSPGTLSLSPGERATLSCRASQSIGKSFLAWYQQKPGQAPRLLIYDASTRAADIPARFSGSGSG TDFTLTISSLEPEDFAVYYCQQYYDWPPLSFGGGTKVEIK
386	2H7 HCDR1	GFTFKDYCMT
387	2H7 HCDR2	AIVYSGGSTYYADSVKG
388	2H7 HCDR3	YTRASYFYDAMDV
389	2H7 LCDR1	RASQSIGKSFLA
390	2H7 LCDR2	DASTRAA
391	2H7 LCDR3	QQYYDWPPLS
392	C51E6-5 VH	CAGGTTCAGCTGGTTCAGTCTGGCAGCGAGCTGAAGAAACCTGGCGCCTCTGTGAAGGTGTCCTGCAAG GCCTCTGGCTACAGCCTGTACGGCACCTCTATGCACTGGGTCCGACAGGCTCCAGGACAGGGACTTGAG TGGATGGGCTACATCAGCCCCTTTACCGGCAGAGCCACATACGCCCAGGGCTTCACAGGCAGATTCGTG TTCAGCCTGGACACCAGCGTGTCCACAGCCTACCTGCAGATCAGCTCTCTGAAGGCCGAGGACACCGCC GTGTACTACTGCGCCAGAGACTACGACTACCGGTACTACTATGCCATGGACTACTGGGGCCAGGGCACC ACAGTTACAGTGTCCTCA
393	C51E6-5 VL	GAAATTGTGCTGACACAGAGCCCCGACTTCCAGAGCGTGACCCCTAAAGAAAAAGTGACCATCACCTGT ACCGCCAGCGAGTCCGTGCCTCCTCAGTTCCTGCATTGGTATCAGCAGAAGCCCGATCAGAGCCCCAAG CTGCTGATCTACGCCAGCAGAGAAAGAGCCAGCGGCGTCCCAAGCAGATTTTCTGGCTCTGGCAGCGGC ACCGACTTCACCCTGACAATCAATAGCCTGGAAGCCGAGGACGCCGCCACCTACTACTGCCACCAGTTT CACAGAAGCCCTCTGACCTTTGGCGGAGGCACCAAGCTGGAAATCAAG
394	C51E6-5 VH	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSS
395	C51E6-5 VL	EIVLTQSPDFQSVTPKEKVTITCTASESVPPQFLHWYQQKPDQSPKLLIYASRERASGVPSRFSGSGSG TDFTLTINSLEAEDAATYYCHQFHRSPLTFGGGTKLEIK
396	C51E6-5 HCDR1	GYSLYGTSMH
397	C51E6-5 HCDR2	YISPFTGRATYAQGFTG
398	C51E6-5 HCDR3	DYDYRYYYAMDY
399	C51E6-5 LCDR1	TASESVPPQFLH
400	C51E6-5 LCDR2	ASRERAS

401	C51E6-5 LCDR3	HQFHRSPLT
402	A2 VH	GACGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTCCAGCCCGGCGGCTCTCTGAGACTGAGCTGCGCC GCCAGCGGCTTCACCTTCGACATCAGCGCCATGAGCTGGGTGCGGCAGGCCCCTGGCAAGGGCCTGGAA TGGGTCAGCACAATCAGCGGATCTGCCTACAGCACCTACTACGCCGACAGCGTGAAGGGCAGATTCACC ATCTCAAGAGATAACAGCAAGAGCACCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCC GTGTACTACTGCGCCAGAGAGATCTTCAGCGACTACTGGGGCTTGGGCACCCTGGTGACAGTGTCCTCA
403	A2 VL	CAAAGCGTGCTGACACAGCCCCCCAGCGCTTCTGGCACCCCTGGCCAGAGAGTGACCATCTCATGCAGC GGGTCAACAAGCAACATCGGCAGAGAGAGCGTGTACTGGTACCAGCAGCTGCCTGGAACCGCCCCTAAG CTGCTGATCTACAGCAACGTGCAGCGGCCTAGCGGCGCCCCTAACAGATTCAGCGGCAGCAAGAGCGGC ACCAGCGCCAGCCTGGCCATCAGCGGCCTGCAGAGCGAGGACGAGGCCGACTACTACTGCGGCACATGG GACGACAGCCTGAACGGCTGGGTGTTCGGCGGCGGAACTAAGCTGACCGTCCTA
404	A2 VH	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSS
405	A2 VL (OMC479p1.A2VL)	QSVLTQPPSASGTPGQRVTISCSGSTSNIGRESVYWYQQLPGTAPKLLIYSNVQRPSGAPNRFSGSKSG TSASLAISGLQSEDEADYYCGTWDDSLNGWVFGGGTKLTVL
406	A2 HCDR1	GFTFDISAMS
407	A2 HCDR2	TISGSAYSTYYADSVKG
408	A2 HCDR3	EIFSDY
409	A2 LCDR1	SGSTSNIGRESVY
410	A2 LCDR2	SNVQRPS
411	A2 LCDR3	GTWDDSLNGWV
412	H7-767 HC	GAGGTGCAGCTGCTGGAAAGCGGCGGCGGCCTCGTGCAGCCTGGCGGATCTCTGCGGCTGAGCTGTGCT GCCAGCGGCTTCACATTTAAATCCTACGCCATGCACTGGGTTAGACAAGCCCCCGGAAAGGGCCTGGAA TGGGTGTCCGCCATCGTCTACAGCGGCGGATCTACATACTACGCCGACAGCGTGAAGGGCCGGTTCACC ATCAGCAGAGATAATAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTACTGCGCCAAGTACGACAGAGCTTCTTATTTCTACGATGCCATGGACGTGTGGGGCCAGGGC ACCACCGTGACAGTGTCCTCAGCTAGCACCAAGGGCCCTAGCGTGTTTCCACTGGCCCCTAGCTCTAAA AGCACAAGCGGCGGAACCGCCGCTCTGGGTTGTCTGGTGAAGGACTACTTCCCTGAGCCTGTGACCGTC AGCTGGAACAGCGGCGCCCTGACCAGCGGCGTTCACACATTCCCCGCTGTGCTGCAGAGCTCTGGGCTG TACAGCCTGAGCAGCGTGGTGACCGTGCCTTCTTCTTCTCTGGGCACACAAACATACATCTGCAACGTG AACCACAAGCCCAGTAATACCAAAGTGGATAAGAAGGTGGAACCTAAGTCTTGCGACAAGACCCACACC TGTCCTCCGTGCCCTGCTCCTGAACTGgctGGAgctCCCAGCGTGTTCCTGTTCCCCCCCAAACCTAAA GACACCCTGATGATCAGCCGGACCCCTGAGGTGACCTGCGTGGTCGTCGACGTGTCCCACGAAGATCCT GAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAAGTGCATAATGCCAAGACAAAGCCTAGAGAGGAA CAGTACAACAGCACCTATAGAGTGGTGTCCGTGCTGACAGTGCTGCACCAGGACTGGCTGAACGGCAAG GAATACAAGTGCAAGGTGTCCAACAAGGCCCTCCCCGCCCCTATCGAGAAGACCATCAGCAAGGCAAAG

		GGCCAACCTAGAGAGCCCCAGGTGTACACCCTGCCTCCAAGCAGAGATGAGCTGACCAAGAACCAGGTT AGCCTGACTTGTCTGGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGAGCAACGGCCAG CCTGAGAACAACTACAAGACCACACCTCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTATAGCAAG CTGACAGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTCATGCACGAGGCCCTG CACAACCACTACACCCAGAAGTCTCTGAGCCTGAGCCCTGGAAAGGCCCCTGCTTCTAGCAGCACCAAG AAGACCCAGCTGCAGCTGGAACACCTGCTGCTGGCCCTGCAGATGATCCTGAACGGCATCAACAACTAC AAGAACCCCAAGCTGACCGAGATGCTGACATTTAAGTTCTACATGCCTAAGAAAGCCACCGAGCTGAAG CACCTGCAATGTCTGGAAGAAGAGCTGAAACCTCTGGAAGAGGTGCTGAATCTGGCTCAGTCAAAGAAC TTCCACCTTAGACCTAGAGATCTGATCAGCAACATCAACGTGATCGTGCTGGAACTGAAGGGCAGCGAG ACGACCTTCATGTGCGAGTACGCCGACGAGACAGCCACAATCGTGGAGTTCCTGAACAGATGGATCACC TTCGCCCAGAGCATCATCTCCACCCTGACC
413	H7-767 LC	GAGATCGTGCTGACCCAGTCCCCAGGCACACTGAGCCTGAGCCCCGGCGAGCGGGCCACCCTGAGCTGT AGAGCTAGCCAGAGCATCTCCAGCAGCTTCCTGGCCTGGTACCAGCAGAAACCTGGCCAGGCCCCTAGA CTGCTGATCTACGACGCCTCTGATAGAGCTACAGGCATCCCCGACCGGTTCAGCGGCAGCGGATCTGGC ACCGACTTCACCCTGACCATCAGCAGACTCGAGCCTGAAGATTTCGCCGTGTACTACTGCCAGCAATAC TATGACTGGCCTCCTCTGTCTTTTGGCGGCGGAACAAAGGTGGAAATTAAGCGTACGGTGGCGGCGCCC AGCGTGTTCATCTTCCCACCCAGCGACGAGCAGCTGAAGTCCGGCACAGCCAGCGTGGTGTGCCTGCTG AACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGC CAGGAAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGC AAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTG ACCAAGAGCTTCAACCGGGGCGAGTGC
414	H7-632 HC CDR帶下劃實線 恆定區帶下劃虛線	EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMHWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYDRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
415	H7-632 LC CDR帶下劃實線 恆定區帶下劃虛線	EIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIYDASDRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQYYDWPPLSFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
416	H7-632 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMHWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYDRASYFYDAMDVWGQGTTVTVSS

417	H7-632 VL	EIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIYDASDRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQYYDWPPLSFGGGTKVEIK
418	H7-632 HCDR1	GFTFKSYAMH
419	H7-632 HCDR2	AIVYSGGSTYYADSVKG
420	H7-632 HCDR3	YDRASYFYDAMDV
421	H7-632 LCDR1	RASQSISSSFLA
422	H7-632 LCDR2	DASDRAT
423	H7-632 LCDR3	QQYYDWPPLS
424	2H7-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
425	2H7-hκ LC	EIVLTQSPGTLSLSPGERATLSCRASQSIGKSFLAWYQQKPGQAPRLLIYDASTRAADIPARFSGSGSG TDFTLTISSLEPEDFAVYYCQQYYDWPPLSFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
426	C51E6-5-hIgG4 HC	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
427	C51E6-5-hκ LC	EIVLTQSPDFQSVTPKEKVTITCTASESVPPQFLHWYQQKPDQSPKLLIYASRERASGVPSRFSGSGSG TDFTLTINSLEAEDAATYYCHQFHRSPLTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC

428	A2-hIgG4 HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG
429	A2-hλ LC	QSVLTQPPSASGTPGQRVTISCSGSTSNIGRESVYWYQQLPGTAPKLLIYSNVQRPSGAPNRFSGSKSG TSASLAISGLQSEDEADYYCGTWDDSLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
430	2H7-hIgG4-df-hIL-2 (D20A/R38E)HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNP KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTF MCEYADETATIVEFLNRWITFCQSIISTLT*
431	H7-632-hIgG1-LAGA-df-hIL-2 (T3A/C125A) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMHWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYDRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKAPASSSTKKTQLQLEHLLLDLQMILNGINNY KNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFAQSIISTLT

432	C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)HC 連接子為下劃虛線 hIL-2為斜體	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK<u>SGGGGS</u>*APTSSSTKKTQLQLEHLLLALQMILNGIN* *NYKNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKG* *SETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
433	A2-hIgG4-df-hIL-2 (D20A/R38E)HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
434	1H3-hIgG4-df-hIL-2 (D20A/R38E)HC hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEM* *LTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYA* *DETATIVEFLNRWITFCQSIISTLT*
435	2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*

436	hPD-1胞外域	CCAGGATGGTTCTTAGACTCCCCAGACAGGCCCTGGAACCCCCCCACCTTCTCCCCAGCCCTGCTCGTG GTGACCGAAGGGGACAACGCCACCTTCACCTGCAGCTTCTCCAACACATCGGAGAGCTTCGTGCTAAAC TGGTACCGCATGAGCCCCAGCAACCAGACGGACAAGCTGGCCGCCTTCCCCGAGGACCGCAGCCAGCCC GGCCAGGACTGCCGCTTCCGTGTCACACAACTGCCCAACGGGCGTGACTTCCACATGAGCGTGGTCAGG GCCCGGCGCAATGACAGCGGCACCTACCTCTGTGGGGCCATCTCCCTGGCCCCCAAGGCGCAGATCAAA GAGAGCCTGCGGGCAGAGCTCAGGGTGACAGAGAGAAGGGCAGAAGTGCCCACAGCCCACCCCAGCCCC TCACCCAGGCCAGCCGGCCAGTTCCAA
437	hPD-1胞外域HC	PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQP GQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSP SPRPAGQFQ
438	OMC.1.B6-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVSAISSSGGTIFYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKHKWNAVYYDGMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
439	OMC.1.B6-hλ LC	QSVLTQPPSASGTPGQRVTISCSGSNSNIGRNLVNWYQQLPGTAPKLLIYTIDQRPSGVPDRFSGSKSG TSASLVISGLQSEDEADYYCAAWDGSLNAWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
440	OMC.2.C6-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCTASGFTFSSYEMQWVRQAPGKGLEWVLGITSSSSHIFYADSVKGRFT VSRDNSKNTLYLQMNSLRAEDTAVYYCTKDLNSYYGLDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHK PSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
441	OMC.2.C6-hλ LC	QSVMTQPPSASGTPGQRVTISCSGSTSNLGNNYVSWYQHLPGTAPKLLIYGNDQRPSGVPDRFSGSKSG TSASLAISGLQSDDEADYYCSSWDASLNVWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS

442	OMC.1.D6-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSAISSSGGTIFYADSVKGRFI ISRDNSKNTLYLQMNSLRAEDTAVYYCAKHKWNDVYYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
443	OMC.1.D6-hλ LC	QSVLTQPPSASGTPGQRVTISCSGSNSNIGRNLVNWYQQLPGTAPKLLIYTVDQRPSGVPDRFSGSKSG TSASLAISGLASEDEADYYCAAWDSSLNSWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
444	D12-hIgG4 HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG
445	D12-hλ LC	QSVLTQPPSASGTPGQRVTISCSGNTSNIGRESVYWYQQLPGTAPKLLIYSNVQRPSGVPDRFSGSKSG TSASLAISGLQSEDEADYYCGTWDDSLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
446	G12-hIgG4 HC	DSLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFTI SRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLG
447	G12-hλ LC	QSVLTQPPSASGTPGQRVTISCSGSTSNIGRESVYWYQQLPGTAPKLLIYLNSQRPSGVPDRFSGSKSG TSASLAISGLQSEDVADYYCGTWDDSLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS

448	pCMV6-hygro-HA-cyno-PD-1 (1-185)	aacaaaatattaacgcttacaatttccattcgccattcaggctgcgcaactgttgggaagggcgatcgg tgcgggcctcttcgctattacgccagctggcgaaaggggatgtgctgcaaggcgattaagttgggtaa cgccagggttttcccagtcacgacgttgtaaaacgacggccagtgccaagctgatctatacattgaatc aatattggcaattagccatattagtcattggttatatagcataaatcaatattggctattggccattgc atacgttgtatctatatcataatatgtacatttatattggctcatgtccaatatgaccgccatgttgac attgattattgactagttattaatagtaatcaattacggggtcattagttcatagcccatatatggagt tccgcgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgt caataatgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatt tacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagtccgcccctattgacgtca atgacggtaaatggcccgcctggcattatgcccagtacatgaccttacgggactttcctacttggcagt acatctacgtattagtcatcgctattaccatggtgatgcggttttggcagtacaccaatgggcgtggat agcggtttgactcacggggatttccaagtctccaccccattgacgtcaatgggagtttgttttggcacc aaaatcaacgggactttccaaaatgtcgtaataaccccgccccgttgacgcaaatgggcggtaggcgtg tacggtgggaggtctatataagcagagctcgtttagtgaaccgtcagaattttgtaatacgactcacta tagggcggccgggaattcgtcgactggatccggtaccgaggagatctgccgccgcgatcgccggcgcgc cagatctcaagcttatggacatgcgggtgccagcacaacttctcggattactattgttatggctgcgag gtgcgcgctgttatccttacgacgtgcctgactacgccccaggatggttcttagagtccccagacaggc cctggaacgcccccaccttctccccagccctgctcctggtgaccgaaggggacaacgccaccttcacct gcagcttctccaacgcatcggagagcttcgtgctaaactggtacaggatgagccccagcaaccagacgg acaagctggccgccttccccgaggaccgcagccagcccggccaggactgccgcttccgtgtcacacgcc tgcccaacgggcgtgacttccacatgagcgtggtcagggcccggcgcaatgacagcggcacctacctct gtggggccatctccctggcccccaaggcgcagatcaaagagagcctgcgggcagagctcagggtgacag agagaagggcagaagtgcccacagcccaccccagcccctcacccaggccagccggccagttccaagccc tggtggttggtgtcgtgggcggcctgctgggcagcctggtgctgctagtctgggtcctggccgtcatct gctcccgcgccgcacaagggacaatagaagccaggcgcacctgacgcgttaagcggccgcactcgaggt ttaaacggccggccgcggtcatagctgtttcctgaacagatcccgggtggcatccctgtgacccctccc cagtgcctctcctggccctggaagttgccactccagtgcccaccagccttgtcctaataaaattaagtt gcatcattttgtctgactaggtgtccttctataatattatggggtggaggggggtggtatggagcaagg ggcaagttgggaagacaacctgtagggcctgcggggtctattgggaaccaagctggagtgcagtggcac aatcttggctcactgcaatctccgcctcctgggttcaagcgattctcctgcctcagcctcccgagttgt tgggattccaggcatgcatgaccaggctcagctaatttttgtttttttggtagagacggggtttcacca tattggccaggctggtctccaactcctaatctcaggtgatctacccaccttggcctcccaaattgctgg gattacaggcgtgaaccactgctcccttccctgtccttctgattttaaaataactataccagcaggagg acgtccagacacagcataggctacctggccatgcccaaccggtgggacatttgagttgcttgcttggca ctgtcctctcatgcgttgggtccactcagtagatgcctgttgaattgggtacgcggccagcttggctgt ggaatgtgtgtcagttagggtgtggaaagtccccaggctccccagcaggcagaagtatgcaaagcatgc atctcaattagtcagcaaccaggtgtggaaagtccccaggctccccagcaggcagaagtatgcaaagca

		tgcatctcaattagtcagcaaccatagtcccgcccctaactccgcccatcccgcccctaactccgccca gttccgcccattctccgccccatggctgactaatttttttatttatgcagaggccgaggccgcctcgg cctctgagctattccagaagtagtgaggaggcttttttggaggcctaggcttttgcaaaaagctcccgg gagcttgtatatccattttcggatctgatcaagagacacgtacgaccatgaaaaagcctgaactcaccg cgacgtctgttgagaagtttctgatcgaaaagttcgacagcgtctccgacctgatgcagctctcggagg gcgaagaatctcgtgctttcagcttcgatgtaggagggcgtggatatgtcctgcgggtaaatagctgcg ccgatggtttctacaaagatcgttatgtttatcggcactttgcatcggccgcgctcccgattccggaag tgcttgacattggggaatttagcgagagcctgacctattgcatctcccgccgtgcacagggtgtcacgt tgcaagacctgcctgaaaccgaactgcccgctgttctgcaaccggtcgcggaggccatggatgcaatcg ctgcggccgatcttagccagacgagcgggttcggcccattcggaccgcaaggaatcggtcaatacacta catggcgtgatttcatatgcgcgattgctgatccccatgtgtatcactggcaaactgtgatggacgaca ccgtcagtgcgtccgtcgcgcaggctctcgatgagctgatgctttgggccgaggactgccccgaagtcc ggcacctcgtgcacgcggatttcggctccaacaatgtcctgacggacaatggccgcataacagcggtca ttgactggagcgaggcgatgttcggggattcccaatacgaggtcgccaacatcttcttctggaggccgt ggttggcttgtatggagcagcagacgcgctacttcgagcggaggcatccggagcttgcaggatcgccgc ggctccgggcgtatatgctccgcattggtcttgaccaactctatcagagcttggttgacggcaatttcg atgatgcagcttgggcgcagggtcgatgcgacgcaatcgtccgatccggagccgggactgtcgggcgta cacaaatcgcccgcagaagcgcggccgtctggaccgatggctgtgtagaagtactcgccgatagtggaa accgacgccccagcactcgtccgagggcaaaggaatagctgcagcgggactctggggttcgaaatgacc gaccaagcgacgcccaacctgccatcacgagatttcgattccaccgccgccttctatgaaaggttgggc ttcggaatcgttttccgggacgccggctggatgatcctccagcgcggggatctcatgctggagttcttc gcccaccccaacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcaca aataaagcatttttttcactgcattctagttgtggtttgtccaaactcatcaatgtatcttatcatgtc tgtataccgtcgacctctagctagagcttggcgtaatcatggtcatagctgtttcctgtgtgaaattgt tatccgctcacaattccacacaacatacgagccggaagcataaagtgtaaagcctggggtgcctaatga gtgagctaactcacattaattgcgttgcgctcactgcccgctttccagtcgggaaacctgtcgtgccag ctgcattaatgaatcggccaacgcgcggggagaggcggtttgcgtattgggcgctcttccgcttcctcg ctcactgactcgctgcgctcggtcgttcggctgcggcgagcggtatcagctcactcaaaggcggtaata cggttatccacagaatcaggggataacgcaggaaagaacatgtgagcaaaaggccagcaaaaggccagg aaccgtaaaaaggccgcgttgctggcgtttttccataggctccgcccccctgacgagcatcacaaaaat cgacgctcaagtcagaggtggcgaaacccgacaggactataaagataccaggcgtttcccccctggaagc tccctcgtgcgctctcctgttccgaccctgccgcttaccggatacctgtccgcctttctcccttcggga agcgtggcgctttctcatagctcacgctgtaggtatctcagttcggtgtaggtcgttcgctccaagctg ggctgtgtgcacgaaccccccgttcagcccgaccgctgcgccttatccggtaactatcgtcttgagtcc aacccggtaagacacgacttatcgccactggcagcagccactggtaacaggattagcagagcgaggtat gtaggcggtgctacagagttcttgaagtggtggcctaactacggctacactagaagaacagtatttggt atctgcgctctgctgaagccagttaccttcggaaaaagagttggtagctcttgatccggcaaacaaacc

		accgctggtagcggtggttttttgtttgcaagcagcagattacgcgcagaaaaaaggatctcaagaa gatcctttgatcttttctacggggtctgacgctcagtggaacgaaaactcacgttaagggattttggtc atgagattatcaaaaaggatcttcacctagatccttttaaattaaaaatgaagttttaaatcaatctaa agtatatatgagtaaacttggtctgacagttaccaatgcttaatcagtgaggcacctatctcagcgatc tgtctatttcgttcatccatagttgcctgactccccgtcgtgtagataactacgatacgggagggctta ccatctggccccagtgctgcaatgataccgcgagacccacgctcaccggctccagatttatcagcaata aaccagccagccggaagggccgagcgcagaagtggtcctgcaactttatccgcctccatccagtctatt aattgttgccgggaagctagagtaagtagttcgccagttaatagtttgcgcaacgttgttgccattgct acaggcatcgtggtgtcacgctcgtcgtttggtatggcttcattcagctccggttcccaacgatcaagg cgagttacatgatcccccatgttgtgcaaaaaagcggttagctccttcggtcctccgatcgttgtcaga agtaagttggccgcagtgttatcactcatggttatggcagcactgcataattctcttactgtcatgcca tccgtaagatgcttttctgtgactggtgagtactcaaccaagtcattctgagaatagtgtatgcggcga ccgagttgctcttgcccggcgtcaatacgggataataccgcgccacatagcagaactttaaaagtgctc atcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccgctgttgagatccagttcgatg taacccactcgtgcacccaactgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaa acaggaaggcaaaatgccgcaaaaagggaataagggcgacacggaaatgttgaatactcatactcttc ctttttcaatattattgaagcatttatcagggttattgtctcatgagcggatacatatttgaatgtatt tagaaaaataaacaaatagggttccgcgcacatttccccgaaaagtgccacctgacgcgccctgtagc ggcgcattaagcgcggcgggtgtggtggttacgcgcagcgtgaccgctacacttgccagcgccctagcg cccgctcctttcgctttcttcccttcctttctcgccacgttcgccggctttccccgtcaagctctaaat cgggggctcccttagggttccgatttagtgctttacggcacctcgaccccaaaaaacttgattagggt gatggttcacgtagtgggccatcgccctgatagacggtttttcgccctttgacgttggagtccacgttc tttaatagtggactcttgttccaaactggaacaacactcaaccctatctcggtctattcttttgattta taagggattttgccgatttcggcctattggttaaaaaatgagctgatttaacaaaaatttaacgcgaat ttt
449	Abz1mod-hIgG4 HC	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYAMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
450	Abz1mod-hκ LC	EIVLTQSPDFQSVTPKEKVTITCRASQSIPPQFLHWYQQKPDQSPKLLIKAASQRASGVPSRFSGSGSG TDFTLTINSLEAEDAATYYCHQFHSSPLTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC

451	抗hPD-1 #1-hIgG4-L6-hIL-2 (D20A/R38E) HC 連接子為下劃虛線 hIL-2為斜體	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFT ISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLP PSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGN VFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLT* *EMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCE* *YADETATIVEFLNRWITFCQSIISTLT*
452	抗hPD-1 #1-hκ LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGT DFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
453	OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E) HC 連接子為下劃虛線 hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVSAISSSGGTIFYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKHKWNAVYYDGMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLALQMILNGI* *NNYKNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK* *GSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
454	OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E) HC 連接子為下劃虛線 hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCTASGFTFSSYEMQWVRQAPGKGLEWVLGITSSSSHIFYADSVKGRFT VSRDNSKNTLYLQMNSLRAEDTAVYYCTKDLNSYYGLDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHK PSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLALQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFCQSIISTLT*

455	OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E) HC 連接子為下劃虛線 hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSAISSSGGTIFYADSVKGRFI ISRDNSKNTLYLQMNSLRAEDTAVYYCAKHKWNDVYYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK<u>SGGGGS</u>*APTSSSTKKTQLQLEHLLLALQMILNGI* *NNYKNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK* *GSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
456	D12-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
457	G12-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2為斜體	DSLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFTI SRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLTF* *KFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADET* *ATIVEFLNRWITFCQSIISTLT*
458	2H7-hIgG4-LE HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG

459	2H7-hIgG4-LAGA HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
460	OMC.2-A3-hIgG4/λ HC	EVQLLESGGCLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSAISSSGGTIFYADSVKGRFI ISRDNSKNTLYLQMNSLRAEDTAVYYCAKHKWNDVYYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
461	OMC476pH7-hIgG4 HC	DMQLVESGGGVVRPGESLRLSCTASGFTFSISAMSWVRQAPGKGLEWVSAISGTAYSTYYADSVRGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKDNFFDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG
462	OMC476pB11.H7 LC	QSVMTQPPSASGTPGQRVTISCSGVTSNIGSNSVYWYQQLPGTAPKLLIYLNSQRPSGVPDRFSGSKSG TSASLAISGLQSEDEADYYCGTWDDSLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
463	OMC476pB11-hIgG4 HC	DVQLVESGGGVVRPGESLRLSCTASGFTFSISAMSWVRQAPGKGLEWVSAISGTAYSTYYADSVRGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKDNFFDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG

464	OMC476pG10-hIgG4 HC	DVQLVESGGGVVRPGGSLRLSCAASGFTFSIYAMSWVRQAPGEGLEWVSHISASGGSTYYADSVKGRFA ISRDNSKNTLYLQMNSLRAEDTAVYYCTTNLGSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG
465	OMC476pH10-hIgG4 HC	DVQLVESGGGVVRPGGSLRLSCAASGFTFSIYAVSWVRQAPGEGLEWVSHISASGGSTYYADSVKGRFA ISRDNSKNTLYLQMNSLRAEDTAVYYCTTNLGSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG
466	OMC476pG10.H10 LC	QSVLTQPPSASGTPGQRVTISCSGSYSDIGTNYVYWYQQLPGTAPKLLIFATDRRPSGVPDRFSGSKSG TSASLAISGLQSEDEADYYCGTWDDSLNVWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
467	OMC476pE4-hIgG4 HC	DVQLVESGGGVVRPGESLRLSCAASGFTFSTDAMGWVRQAPGEGLEWVSLISGSGYSTYYADSVKGRFT ISRDNSKNTLYLQMNSLTAEDTAVYYCAKNSLAFFDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLG
468	OMC476pE4 LC	QSVLTQPPSASGTPGQRVTISCSGGSSNIGRESVNWYQQLPGTAPKLLIYSTDRRPSGVPDRFSGSKSG TSASLAISGLQSEDEADYYCGTWDNDLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
469	J110-hIgG1 HC	DVQLQESGPGLVKPSQSLSLTCTVTGHSITSDYAWNWIRQFPGDKLEWMGYISYSGYTTYNPSLKSRVS ITRDTSKNQFFLQLNSVTTEDTATYFCARDLDYGPWFAYWGQGTLVTVSAASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

470	J110-hκ LC	DIQMTQSPASLSASVGETVTLTCRASENIHNYLAWYQQKQGKSPQLLVYNVKTLADGVPSRFSGSGSGT QYSLKINSLQPEDFGSYYCQHFWSSPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
471	2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLALQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
472	2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*
473	2H7-hIgG1-LAGA--df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*

474	2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVKVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
475	2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLDLQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVKVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*
476	2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLDLQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVKVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*
477	2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRKLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*

478	2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLDLQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRKLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*
479	2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLDLQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRKLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*
480	1H3-hIgG4-df-hIL-2 (WT) HC hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRM* *LTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYA* *DETATIVEFLNRWITFCQSIISTLT*
481	1H3-hIgG4-L6-hIL-2 (WT) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK*SGGGGS*<u>*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKN*</u> *PKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*

482	1H3-hIgG4 HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLG
483	1H3-hκ-df-hIL-2 (WT) LC hIL-2為斜體	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEEL* *KPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL* *T*
484	1H3-hκ-L6-hIL-2 (WT) LC 連接子為下劃虛線 hIL-2為斜體	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC<u>SGGGGS</u>*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQ* *CLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ* *SIISTLT*
485	1H3-hIgG4-L6-hIL-2 (D20Y) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK<u>SGGGGS</u>*APTSSSTKKTQLQLEHLLLYLQMILNGINNYKN* *PKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*
486	1H3-hIgG4-df-hIL-2 (D20Y) HC hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLYLQMILNGINNYKNPKLTRM* *LTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYA* *DETATIVEFLNRWITFCQSIISTLT*

487	1H3-hIgG1-df-hIL-2 (D20Y) HC hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APTSSSTKKTQLQLEHLLLYLQMILNGINNYKNPKL* *TRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMC* *EYADETATIVEFLNRWITFCQSIISTLT*
488	1H3-hIgG4-L6-hIL-2 (D20A/R38P) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK*SGGGGS**APTSSSTKKTQLQLEHLLLALQMILNGINNYKN* *PKLTPMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*
489	1H3-hIgG4-L6-hIL-2 (D20A/R38S) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK*SGGGGS**APTSSSTKKTQLQLEHLLLALQMILNGINNYKN* *PKLTSMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*
490	1H3-hIgG4-L6-hIL-2 (D20A/R38D) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK*SGGGGS**APTSSSTKKTQLQLEHLLLALQMILNGINNYKN* *PKLTDMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*

491	1H3-hIgG4-L6-hIL-2 (D20A/R38Q/E95A) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLALQMILNGINNYKN* *PKLTQMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLALKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*
492	1H3-hIgG4-L6-hIL-2 (D20A/F42H/E95A) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLALQMILNGINNYKN* *PKLTRMLTHKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLALKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*
493	1H3-hIgG4-L6-hIL-2 (R38D/I92D) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKN* *PKLTDMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVDVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*
494	1H3-hIgG4-L6-hIL-2 (R38E/I92D) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKN* *PKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVDVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*

495	1H3-hIgG4-L6-hIL-2 (F42H/I92D) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKN* *PKLTRMLTHKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVDVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*
496	1H3-hIgG4-L6-hIL-2 (D20A/R38E) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLALQMILNGINNYKN* *PKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*
497	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APASSSTKKTQLQLEHLLLALQMILNGINNYKN* *PKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT* *FMCEYADETATIVEFLNRWITFCQSIISTLT*
498	1H3-hIgG4-L6-hIL-2 (D20A/R38E/C125A) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKSGGGGS*APTSSSTKKTQLQLEHLLLALQMILNGINNYKN* *PKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT* *FMCEYADETATIVEFLNRWITFAQSIISTLT*

499	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E/C125A) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK<u>SGGGGGS</u>*APASSSTKKTQLQLEHLLLALQMILNGINNYKN* *PKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT* *FMCEYADETATIVEFLNRWITFAQSIISTLT*
500	1H3-hIgG1-L6-hIL-2 (D20A/R38E) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<u>SGGGGGS</u>*APTSSSTKKTQLQLEHLLLALQMILNGINN* *YKNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGS* *ETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
501	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<u>SGGGGGS</u>*APASSSTKKTQLQLEHLLLALQMILNGINN* *YKNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGS* *ETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
502	1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<u>SGGGGGS</u>*APTSSSTKKTQLQLEHLLLALQMILNGINN* *YKNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGS* *ETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

503	1H3-hκ-df-hIL-2 (D20A/R38E) LC hIL-2為斜體	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLTFKFYMPKKATELKHLQCLEEEL* *KPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL* *T*
504	1H3-hκ-L6-hIL-2 (D20A/R38E) LC 連接子為下劃虛線 hIL-2為斜體	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC<u>SGGGGS</u>*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLTFKFYMPKKATELKHLQ* *CLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ* *SIISTLT*
505	OMC476pB11-hIgG4-df-hIL-2 (D20A/R38E)HC hIL-2為斜體	DVQLVESGGGVVRPGESLRLSCTASGFTFSISAMSWVRQAPGKGLEWVSAISGTAYSTYYADSVRGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKDNFFDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
506	OMC476pE4-hIgG4-df-hIL-2 (D20A/R38E)HC hIL-2為斜體	DVQLVESGGGVVRPGESLRLSCAASGFTFSTDAMGWVRQAPGEGLEWVSLISGSGYSTYYADSVKGRFT ISRDNSKNTLYLQMNSLTAEDTAVYYCAKNSLAFFDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEM* *LTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYA* *DETATIVEFLNRWITFCQSIISTLT*

507	OMC476pG10-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2為斜體	DVQLVESGGGVVRPGGSLRLSCAASGFTFSIYAMSWVRQAPGEGLEWVSHISASGGSTYYADSVKGRFA ISRDNSKNTLYLQMNSLRAEDTAVYYCTTNLGSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
508	OMC476pH10-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2為斜體	DVQLVESGGGVVRPGGSLRLSCAASGFTFSIYAVSWVRQAPGEGLEWVSHISASGGSTYYADSVKGRFA ISRDNSKNTLYLQMNSLRAEDTAVYYCTTNLGSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
509	A2-hIgG4-df-hIL-2 (D20A/F42A) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTRMLT* *AKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
510	A2-hIgG4-df-hIL-2 (D20A/F42S) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTRMLT* *SKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*

511	A2-hIgG4-df-hIL-2 (D20S/R38E) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLSLQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
512	A2-hIgG4-df-hIL-2 (F42A/N88R) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT* *AKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISRINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
513	A2-hIgG4-df-hIL-2 (F42I/I92D) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT* *IKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVDVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
514	A2-hIgG4-df-hIL-2 (F42Q/I92D) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT* *QKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVDVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*

515	A2-hIgG4-df-hIL-2 (F42T/I92D) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT* *TKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVDVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
516	A2-hIgG4-df-hIL-2 (F42W/I92D) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT* *WKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVDVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
517	A2-hIgG4-df-hIL-2 (R38E/D84K) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRKLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*
518	A2-hIgG4-df-hIL-2 (R38E/I92K) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVKVLELKGSETTFMCEYADE* *TATIVEFLNRWITFCQSIISTLT*

519	C51E6-5-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2為斜體	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNPK* *LTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFM* *CEYADETATIVEFLNRWITFCQSIISTLT*
520	C51E6-5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNPK* *LTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFM* *CEYADETATIVEFLNRWITFAQSIISTLT*
521	C51E6-5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNPK* *LTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFM* *CEYADETATIVEFLNRWITFAQSIISTLT*
522	1H3-hIgG1-LAGA-L6-hIL-2 (T3A/D20A/R38E/C125A)	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSAPASSSTKKTQLQLEHLLLALQMILNGINN YKNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGS ETTFMCEYADETATIVEFLNRWITFAQSIISTLT

523	2A3-hκ LC	EIVLTQSPGTLSLSPGERATLSCRASQSIGRSFLAWYQQKPGQAPRLLIYDASTRAADIPARFSGSGSG TDFTLTISSLEPEDFAVYYCQQYYDWPPLSFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
524	1H9-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCVGSGFNLKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTRGSYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFCQSIISTLT*
525	1H9-hκ LC	EIVLTQSPGTLSLSPGERATLSCRASQSIGRSFLAWYQQKPGQAPRLLIYDASTRAADIPDRFSGSGSG TDFTLTINRLEPEDFAVYYCQQYYDWPPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
526	1D5-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCVGSGFNFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTRGSYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APTSSSTKKTQLQLEHLLLALQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFCQSIISTLT*
527	1D5-hκ LC	EIVLTQSPGTLSLSPGERATLSCRASQSIGRSFLAWYQQKPGQAPRLLIYDASTRATDIPDRFSGSGSG TEFTLTISSLQSEDFAVYYCQQYYDWPPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC

528	1D5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCVGSGFNFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTRGSYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*
529	1D5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCVGSGFNFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTRGSYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*
530	2H7-hIgG1-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLALQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
531	2H7-hIgG1-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLALQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*

532	H7-767 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMHWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYDRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKAPASSSTKKTQLQLEHLLLALQMILNGINNY KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFAQSIISTLT
533	2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/D84K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRKLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
534	2H7-hIgG4-df-hIL-2 (T3A/R38E/D84K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLDLQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRKLISNINVIVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*
535	2H7-hIgG1-df-hIL-2 (T3A/R38E/I92K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVKVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*

536	2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVKVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
537	2H7-hIgG4-df-hIL-2 (T3A/R38E/I92K/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLDLQMILNGINNYKNP* *KLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVKVLELKGSETTF* *MCEYADETATIVEFLNRWITFAQSIISTLT*
538	2H7-hIgG1-LAGA-df-hIL2 (T3A/D20S/R38E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLSLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
539	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/D84F/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRFLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*

540	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92R/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVRVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
541	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVEVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
542	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92S/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVSVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
543	2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92D/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVDVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*

544	2H7-hIgG1-LAGA-df-hIL2 (T3A/H16E/R38E/C125A) HC hIL-2為斜體	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEELLLDLQMILNGINNY* *KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE* *TTFMCEYADETATIVEFLNRWITFAQSIISTLT*
545	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGS*APASSSTKKTQLQLEHLLLALQMILNGINN* *YKNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGS* *ETTFMCEYADETATIVEFLNRWITFAQSIISTLT*
546	1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNPKL* *TEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMC* *EYADETATIVEFLNRWITFAQSIISTLT*
547	C51E6-5-hIgG4/k-LE HC	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG

548	C51E6-5-hIgG4/k-LAGA HC	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
549	C51E6-5-hIgG4/k-LEPG HC	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLGSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
550	C51E6-5-hIgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG*KAPASSSTKKTQLQLEHLLLALQMILNGINNYKNPK* *LTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFM* *CEYADETATIVEFLNRWITFAQSIISTLT*
551	C51E6-5-hIgG4/k-LEPG-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	QVQLVQSGSELKKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYDYRYYYAMDYWGQGTTVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLGSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG*KAPASSSTKKTQLQLEHLLLALQMILNGINNYKNPK* *LTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFM* *CEYADETATIVEFLNRWITFAQSIISTLT*

552	A2-hIgG4/k-LE HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFeGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG
553	A2-hIgG4/k-LAGA HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFaGaPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG
554	A2-hIgG4/k-LEPG HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFeGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLgSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG
555	A2-hIgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG*KAPASSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFAQSIISTLT*

556	A2-hIgG4/k-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFAQSIISTLT*
557	A2-hIgG4/k-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFAQSIISTLT*
558	A2-hIgG4/k-LEPG-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2為斜體	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLGSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK*APASSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTEMLT* *FKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADE* *TATIVEFLNRWITFAQSIISTLT*
559	抗hPD-1 #1 HC	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFT ISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLP PSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGN VFSCSVMHEALHNHYTQKSLSLSLG

560	抗CD20-hIgG1/k HC	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKAT LTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
561	抗 CD20-hIgG1/k-LAGA HC	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKAT LTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
562	抗CD20-hκ LC	QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGSGTS YSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
563	1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A) HC hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*APASSSTKKTQLQLEHLLLDLQMILNGINNYKNPKL* *TRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMC* *EYADETATIVEFLNRWITFAQSIISTLT*
564	抗 mPD-1 RMP1-14 mIgG2b-N297A HC	EVQLQESGPGLVKPSQSLSLTCSVTGYSITSSYRWNWIRKFPGNRLEWMGYINSAGISNYNPSLKRRIS ITRDTSKNQFFLQVNSVTTEDAATYYCARSDNMGTTPFTYWGQGTLVTVSSAKTTPPSVYPLAPGCGDT TGSSVTLGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHP ASSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVS EDDPDVQISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKEFKCKVNNKDLPSPIERTI SKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYF IYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGK

565	抗 mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) HC 連接子為下劃虛線 hIL-2為斜體	EVQLQESGPGLVKPSQSLSLTCSVTGYSITSSYRWNWIRKFPGNRLEWMGYINSAGISNYNPSLKRRIS ITRDTSKNQFFLQVNSVTTEDAATYYCARSDNMGTTPFTYWGQGTLVTVSSAKTTPPSVYPLAPGCGDT TGSSVTLGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHP ASSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVS EDDPDVQISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKEFKCKVNNKDLPSPIERTI SKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYF IYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGKSGGGGS*APTSSSTKKTQLQLEHLLLDL* *QMILNGINNYKNPKLTRMLTKKFRMPKKATELKHLQCLEEELKPLEERLNLAQSKNFHLRPRDLISNIN* *VIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
566	抗mPD-1 RMP1-14 mκ LC	DIVMTQGTLPNPVPSGESVSITCRSSKSLLYSDGKTYLNWYLQRPGQSPQLLIYWMSTRASGVSDRFSG SGSGTDFTLKISGVEAEDVGIYYCQQGLEFPTFGGGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVC FLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTS PIVKSFNRNEC
567	抗 mPD-1 RMP1-30 mIgG2b-N297A HC	EVQLVESGGGLVQPGRSLKLSCAASGFTFGDYSMAWVRQAPKRGLEWVANIIYDGSRTFYRDSVKGRFT ISRDNAKPTLYLQMDSLRPEDTATYYCATHNYPGYAMEAWGQGTSVTVSSAKTTPPSVYPLAPGCGDTT GSSVTLGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHPA SSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSE DDPDVQISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKEFKCKVNNKDLPSPIERTIS KIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYFI YSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGK
568	抗mPD-1 RMP1-30 mκ LC	DTVLTQSPALPVSLGQRVNISCRATKSVSRYVHWYQQKSGQQPRLLIYTTSNLESGVPSRFSGSGSGTD FTLTIDPVEADDIANYYCQQSNEIPYTFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNF YPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKS FNRNEC
569	抗 mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVESGGGLVQPGRSLKLSCAASGFTFGDYSMAWVRQAPKRGLEWVANIIYDGSRTFYRDSVKGRFT ISRDNAKPTLYLQMDSLRPEDTATYYCATHNYPGYAMEAWGQGTSVTVSSAKTTPPSVYPLAPGCGDTT GSSVTLGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHPA SSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSE DDPDVQISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKEFKCKVNNKDLPSPIERTIS KIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYFI YSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGKSGGGGS*APTSSSTKKTQLQLEHLLLDLQ* *MILNGINNYKNPKLTRMLTkKFrMPKKATELKHLQCLEEELKPLEErLNLAQSKNFHLRPRDLISNINV* *IVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*

570	抗 KLH-C3-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) HC 連接子為下劃虛線 hIL-2為斜體	EVQLVGSGGGLVQPGGSLKLSCAASGFTFSDFYMAWVRQAPTKGLEWVASISTGGGNTHYRDSVKGRFT ISRDNAKSTLYLQMDSLRSEETATYYCARLLSTISTPFDYWGQGVIVTVSSAKTTPPSVYPLAPGCGDT TGSSVTLGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHP ASSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVS EDDPDVQISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKEFKCKVNNKDLPSPIERTI SKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYF IYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGKSGGGGS*APTSSSTKKTQLQLEHLLLDL* *QMILNGINNYKNPKLTRMLTkKFrMPKKATELKHLQCLEEELKPLEErLNLAQSKNFHLRPRDLISNIN* *VIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
571	KLH-C3-mκ LC	DVVLIQSPTTLSVTPGETVSLSCRASHSVGTNLHWYQQRTNESPSLLIKYSSHSTSGIPSRFSATGSGT DFTLNISNVEFDDVASYFCQQSQKWPLTFGSGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNN FYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVK SFNRNEC
572	2D12-hIgG1-L6-hIL-2 HC 連接子為下劃虛線 hIL-2為斜體	EVQLQQSGPELVKPGASVKISCKTSGYTFTEYTMHWVKQSHGKSLEWIGGINPNNGGTTYNQKFKGKAT LTVDKSSSTAYMELRSLTSQDSAVYYCARDYYRYGHYYAMDYWGQGTSVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGS*APTSSSTKKTQLQLEHLLLDLQMIL* *NGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVL* *ELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*
573	2D12-hκ LC	QIVLTQSPAIMSASPGEKVTMTCSVSSSVRFMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTS YSLTISSMEAEDAATYYCQQWSSNPPTFGGGTKLKIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
574	hIL-2 F42A/Y45A/L72G	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLT**A**KF**A**MPKKATELKHLQCLEEELKPLEEV LN**G**AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
575	hIL-2 H16A/F42A	APTSSSTKKTQLQLE**A**LLLDLQMILNGINNYKNPKLTRMLT**A**KFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
576	1H9-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCVGSGFNLKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTRGSYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG

577	1D5-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCVGSGFNFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTRGSYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
578	抗hPD-1 #2 HC	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVT LTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDH KPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
579	抗hPD-1 #2 LC	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPARFSGS GSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC
580	人類PD-1受體慢病毒載體	gtcgacggatcgggagatctcccgatcccctatggtgcactctcagtacaatctgctctgatgccgcat agttaagccagtatctgctccctgcttgtgtgttggaggtcgctgagtagtgcgcgagcaaaatttaag ctacaacaaggcaaggcttgaccgacaattgcatgaagaatctgcttagggttaggcgttttgcgctgc ttcgcgatgtacgggccagatatacgcgttgacattgattattgactagttattaatagtaatcaatta cggggtcattagttcatagcccatatatggagttccgcgttacataacttacggtaaatggcccgcctg gctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatag ggactttccattgacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaagtgt atcatatgccaagtacgcccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagt acatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctattaccatggtga tgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacggggatttccaagtctccacc ccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatgtcgtaacaact ccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcagcgcgttttgcc tgtactgggtctctctggttagaccagatctgagcctgggagctctctggctaactagggaacccactg cttaagcctcaataaagcttgccttgagtgcttcaagtagtgtgtgcccgtctgttgtgtgactctggt aactagagatccctcagacccttttagtcagtgtggaaaatctctagcagtggcgcccgaacagggact tgaaagcgaaagggaaaccagaggagctctctcgacgcaggactcggcttgctgaagcgcgcacggcaa gaggcgaggggcggcgactggtgagtacgccaaaaattttgactagcggaggctagaaggagagagatg ggtgcgagagcgtcagtattaagcgggggagaattagatcgcgatgggaaaaaattcggttaaggccag ggggaaagaaaaaatataaattaaaacatatagtatgggcaagcagggagctagaacgattcgcagtta

		atcctggcctgttagaaacatcagaaggctgtagacaaatactgggacagctacaaccatcccttcaga caggatcagaagaacttagatcattatataatacagtagcaaccctctattgtgtgcatcaaaggatag agataaaagacaccaaggaagctttagacaagatagaggaagagcaaaacaaaagtaagaccaccgcac agcaagcggccgctgatcttcagacctggaggaggagatatgagggacaattggagaagtgaattatat aaatataaagtagtaaaaattgaaccattaggagtagcacccaccaaggcaaagagaagagtggtgcag agagaaaaaagagcagtgggaataggagctttgttccttgggttcttgggagcagcaggaagcactatg ggcgcagcgtcaatgacgctgacggtacaggccagacaattattgtctggtatagtgcagcagcagaac aatttgctgagggctattgaggcgcaacagcatctgttgcaactcacagtctggggcatcaagcagctc caggcaagaatcctggctgtggaaagatacctaaaggatcaacagctcctggggatttggggttgctct ggaaaactcatttgcaccactgctgtgccttggaatgctagttggagtaataaatctctggaacagatt tggaatcacacgacctggatggagtgggacagagaaattaacaattacacaagcttaatacactcctta attgaagaatcgcaaaaccagcaagaaaagaatgaacaagaattattggaattagataaatgggcaagt ttgtggaattggtttaacataacaaattggctgtggtatataaaattattcataatgatagtaggaggc ttggtaggtttaagaatagtttttgctgtactttctatagtgaatagagttaggcagggatattcacca ttatcgtttcagacccacctcccaaccccgaggggacccgacaggcccgaaggaatagaagaagaaggt ggagagagagacagagacagatccattcgattagtgaacggatcggcactgcgtgcgccaattctgcag acaaatggcagtattcatccacaattttaaaagaaaaggggggattgggggtacagtgcaggggaaag aatagtagacataatagcaacagacatacaaactaaagaattacaaaaacaaattacaaaaattcaaaa ttttcgggtttattacagggacagcagagatccagtttggttaattaagtaattcgctagctaggtctt gaaaggagtgggaattggctccggtgcccgtcagtgggcagagcgcacatcgcccacagtccccgagaa gttgggggggagggtcggcaattgatccggtgcctagagaaggtggcgcggggtaaactgggaaagtga tgtcgtgtactggctccgccttttttcccgagggtgggggagaaccgtatataagtgcagtagtcgccgt gaacgttctttttcgcaacgggtttgccgccagaacacaggaccggttctagagcgctgccaccatgca gatcccacaggcgccctggccagtcgtctgggcggtgctacaactgggctggcggccaggatggttctt agactccccagacaggccctggaacccccccaccttctccccagccctgctcgtggtgaccgaagggga caacgccaccttcacctgcagcttctccaacacatcggagagcttcgtgctaaactggtaccgcatgag ccccagcaaccagacggacaagctggccgccttccccgaggaccgcagccagcccggccaggactgccg cttccgtgtcacacaactgcccaacgggcgtgacttccacatgagcgtggtcagggcccggcgcaatga cagcggcacctacctctgtggggccatctccctggcccccaaggcgcagatcaaagagagcctgcgggc agagctcagggtgacagagagaagggcagaagtgcccacagcccaccccagcccctcacccaggccagc cggccagttccaaaccctggtggttggtgtcgtgggcggcctgctgggcagcctggtgctgctagtctg ggtcctggccgtcatctgctcccgggccgcacgagggacaataggagccaggcgcaccggccagcccct gaaggaggacccctcagccgtgcctgtgttctctgtggactatggggagctggatttccagtggcgaga gaagaccccggagcccccgtgccctgtgtccctgagcagacggagtatgccaccattgtctttcctag cggaatgggcacctcatcccccgcccgcaggggctcagctgacggccctcggagtgcccagccactgag gcctgaggatggacactgctcttggcccctctgagcccctctccctcccccccctaacgttactggcc gaagccgcttggaataaggccggtgtgcgtttgtctatatgttattttccaccatattgccgtcttttg

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		acgggagggcttaccatctggccccagtgctgcaatgataccgcgagacccacgctcaccggctccaga tttatcagcaataaaccagccagccggaagggccgagcgcagaagtggtcctgcaactttatccgcctc catccagtctattaattgttgccgggaagctagagtaagtagttcgccagttaatagtttgcgcaacgt tgttgccattgctacaggcatcgtggtgtcacgctcgtcgtttggtatggcttcattcagctccggttc ccaacgatcaaggcgagttacatgatcccccatgttgtgcaaaaaagcggttagctccttcggtcctcc gatcgttgtcagaagtaagttggccgcagtgttatcactcatggttatggcagcactgcataattctct tactgtcatgccatccgtaagatgcttttctgtgactggtgagtactcaaccaagtcattctgagaata gtgtatgcggcgaccgagttgctcttgcccggcgtcaatacgggataataccgcgccacatagcagaac tttaaaagtgctcatcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccgctgttgag atccagttcgatgtaacccactcgtgcacccaactgatcttcagcatcttttactttcaccagcgtttc tgggtgagcaaaaacaggaaggcaaaatgccgcaaaaaagggaataagggcgacacggaaatgttgaat actcatactcttcctttttcaatattattgaagcatttatcagggttattgtctcatgagcggatacat atttgaatgtatttagaaaaataaacaaatagggttccgcgcacatttccccgaaaagtgccacctga c
581	hIL-2 V69R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE**R** LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
582	H7-02-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKAPASSSTKKTQLQLEHLLLALQMILNGINNY KNPKLTEMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFAQSIISTLT
583	H7-02-hκ LC	EIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIYDASTRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQYYDWPPLSFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
584	hPD-L1	MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVH GEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKIN QRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIF YCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQD TNSKKQSDTHLEET

585	KLH-C3-hIgG4 HC	EVQLVGSGGGLVQPGGSLKLSCAASGFTFSDFYMAWVRQAPTKGLEWVASISTGGGNTHYRDSVKGRFT ISRDNAKSTLYLQMDSLRSEETATYYCARLLSTISTPFDYWGQGVIVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDH KPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
586	KLH-C3-hκ LC	DVVLIQSPTTLSVTPGETVSLSCRASHSVGTNLHWYQQRTNESPSLLIKYSSHSTSGIPSRFSATGSGT DFTLNISNVEFDDVASYFCQQSQKWPLTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
587	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLAHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
588	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20I) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLILQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT

589	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLSLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
590	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20H) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLHLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
591	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLWLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT

592	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLYLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
593	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20R) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLRLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
594	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20F) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLFLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT

595	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRKLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
596	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLIANINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
597	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88Y) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISYINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT

598	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISDINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
599	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISRINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
600	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88E) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISEINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT

601	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88F) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISFINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
602	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88I) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISIINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
603	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (I92A) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVAVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT

604	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95A) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLALKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
605	1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDTATYYCARHGSGYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGGSGGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLKLKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
606	hIL-2 D20R/R38E	APTSSSTKKTQLQLEHLLL**R**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
607	hIL-2 D20N/R38E	APTSSSTKKTQLQLEHLLL**N**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
608	hIL-2 D20Q/R38E	APTSSSTKKTQLQLEHLLL**Q**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
609	hIL-2 D20E/R38E	APTSSSTKKTQLQLEHLLL**E**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
610	hIL-2 D20G/R38E	APTSSSTKKTQLQLEHLLL**G**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
611	hIL-2 D20I/R38E	APTSSSTKKTQLQLEHLLL**I**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

612	hIL-2 D20L/R38E	APTSSSTKKTQLQLEHLLL**L**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
613	hIL-2 D20K/R38E	APTSSSTKKTQLQLEHLLL**K**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
614	hIL-2 D20M/R38E	APTSSSTKKTQLQLEHLLL**M**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
615	hIL-2 D20F/R38E	APTSSSTKKTQLQLEHLLL**F**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
616	hIL-2 D20P/R38E	APTSSSTKKTQLQLEHLLL**P**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
617	hIL-2 D20T/R38E	APTSSSTKKTQLQLEHLLL**T**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
618	hIL-2 D20W/R38E	APTSSSTKKTQLQLEHLLL**W**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
619	hIL-2 D20Y/R38E	APTSSSTKKTQLQLEHLLL**Y**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
620	hIL-2 D20V/R38E	APTSSSTKKTQLQLEHLLL**V**LQMILNGINNYKNPKLT**E**MLTFKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
621	hIL-2 F42K/Y45R/V69R	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTKKFRMPKKATELKHLQCLEEELKPLEER LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

實施例

【0251】 以下實施例之清單意欲補充先前之描述，而非替換或替代先前之描述。

實施例1. 一種經修飾之人類介白素-2 (hIL-2)蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代，其中相對於未經修飾之hIL-2，經修飾之hIL-2蛋白質對高親和力hIL-2受體及對中等親和力hIL-2受體兩者展現降低之效力。

實施例2. 如實施例1之經修飾之hIL-2蛋白質，其中在胺基酸位置20處之取代係選自D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代。

實施例3. 如實施例1或2之經修飾之hIL-2蛋白質，其中在胺基酸位置38處之取代係選自R38E、R38N、R38G、R38H、R38I、R38L、R38M、R38F、R38P、R38S、R38T、R38W、R38Y、R38V、R38A、R38Q、R38D及R38K取代。

實施例4. 如前述實施例中任一項之經修飾之hIL-2蛋白質，其進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之缺失或取代。

實施例5. 如實施例4之經修飾之hIL-2蛋白質，其中在胺基酸位置3處之取代為T3A。

實施例6. 如前述實施例中任一項之經修飾之hIL-2蛋白質，其進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。

實施例7. 如實施例6之經修飾之hIL-2蛋白質，其中在胺基酸位置125處之取代為C125A。

實施例8. 如前述實施例中任一項之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質對高親和力IL-2受體(hIL-2Rαβγ)展現約1,000倍之效力降低。

實施例9. 如前述實施例中任一項之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質對中等親和力IL-2受體(hIL-2Rβγ)展現約10,000倍之效力降低。

實施例10. 如實施例1至9中任一項之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質係融合至抗PD-1抗體或其抗原結合片段。

實施例11. 如實施例10之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、抗原結合片段之N端或抗原結合片段之C端處融合至抗體或其抗原結合片段。

實施例12. 如實施例10或11之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質係藉由肽鍵直接融合至抗體或其抗原結合片段。

實施例13. 如實施例12之經修飾之hIL-2蛋白質，其中經修飾之hIL-2係藉由肽鍵直接融合至抗體重鏈之C端胺基酸殘基。

實施例14. 如實施例10或11之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質係經由連接子融合至抗體或其抗原結合片段。

實施例15. 一種經修飾之人類介白素-2 (hIL-2)蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或

D20E取代及在胺基酸位置38處之R38E取代。

實施例16. 如實施例15之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 307、607至611、614、617或620中之任一者的胺基酸序列。

實施例17. 如實施例15或16之經修飾之hIL-2蛋白質，其包含D20A取代及R38E取代。

實施例18. 如實施例17之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 149之胺基酸序列。

實施例19. 如實施例15至18中任一項之經修飾之hIL-2蛋白質，其進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之缺失或取代。

實施例20. 如實施例19之經修飾之hIL-2蛋白質，其中在胺基酸位置3處之取代為T3A。

實施例21. 如實施例20之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 216之胺基酸序列。

實施例22. 如實施例19之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 218之胺基酸序列。

實施例23. 如實施例15至22中任一項之經修飾之hIL-2蛋白質，其進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。

實施例24. 如實施例23之經修飾之hIL-2蛋白質，其中在胺基酸位置125處之取代為C125A。

實施例25. 如實施例24之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 215、217或219之胺基酸序列。

實施例26. 如實施例25之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 217之胺基酸序列。

實施例27. 如實施例15至26中任一項之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質係融合至抗PD-1抗體或其抗原結合片段。

實施例28. 如實施例27之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、抗原結合片段之N端或抗原結合片段之C端處融合至抗體或其抗原結合片段。

實施例29. 如實施例27或28之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質係藉由肽鍵直接融合至抗體或其抗原結合片段。

實施例30. 如實施例29之經修飾之hIL-2蛋白質，其中經修飾之hIL-2係藉由肽鍵直接融合至抗體重鏈之C端胺基酸殘基。

實施例31. 如實施例27或28之經修飾之hIL-2蛋白質，其中經修飾之hIL-2蛋白質係經由連接子融合至抗體或其抗原結合片段。

實施例32. 一種免疫特異性結合至人類計劃性細胞死亡蛋白-1 (hPD-1)之人類抗體分子或其抗原結合片段，其中人類抗體分子或其抗原結合片段包含：

a) 包含SEQ ID NO: 418之胺基酸序列的重鏈互補決定區1 (CDR1)、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3；

b) 包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID

NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3；

c) 包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3；或

d) 包含SEQ ID NO: 406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序列的輕鏈CDR3。

實施例33. 如實施例32之人類抗體分子或其抗原結合片段，其包含：

a) 包含SEQ ID NO: 416之胺基酸序列的重鏈可變區及包含SEQ ID NO: 417之胺基酸序列的輕鏈可變區；

b) 包含SEQ ID NO: 384之胺基酸序列的重鏈可變區及包含SEQ ID NO: 385之胺基酸序列的輕鏈可變區；

c) 包含SEQ ID NO: 394之胺基酸序列的重鏈可變區及包含SEQ ID NO: 395之胺基酸序列的輕鏈可變區；或

d) 包含SEQ ID NO: 404之胺基酸序列的重鏈可變區及包含SEQ ID

NO: 405之胺基酸序列的輕鏈可變區。

實施例34. 如實施例32或33之人類抗體分子或其抗原結合片段，其包含人類IgG1重鏈恆定區。

實施例35. 如實施例34之人類抗體分子或其抗原結合片段，其包含根據EU編號之L235A取代及G237A取代。

實施例36. 如實施例32至35中任一項之人類抗體分子或其抗原結合片段，其包含：

a) 包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415之胺基酸序列的輕鏈；

b) 包含SEQ ID NO: 424之胺基酸序列的重鏈及包含SEQ ID NO: 425之胺基酸序列的輕鏈；

c) 包含SEQ ID NO: 426之胺基酸序列的重鏈及包含SEQ ID NO: 427之胺基酸序列的輕鏈；或

d) 包含SEQ ID NO: 428之胺基酸序列的重鏈及包含SEQ ID NO: 429之胺基酸序列的輕鏈。

實施例37. 如實施例36之人類抗體分子或其抗原結合片段，其包含有包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415之胺基酸序列的輕鏈。

實施例38. 如實施例32至37中任一項之人類抗體分子或其抗原結合片段，其係融合至經修飾之介白素-2 (hIL-2)蛋白質，該蛋白質包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代。

實施例39. 如實施例38之人類抗體分子或其抗原結合片段，其中經

修飾之hIL-2蛋白質包含SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的胺基酸序列。

實施例40. 如實施例39之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 149之胺基酸序列。

實施例41. 如實施例38至40中任一項之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之缺失或取代。

實施例42. 如實施例41之人類抗體分子或其抗原結合片段，其中在胺基酸位置3處之取代為T3A。

實施例43. 如實施例42之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 216之胺基酸序列。

實施例44. 如實施例41之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 218之胺基酸序列。

實施例45. 如實施例38至44中任一項之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。

實施例46. 如實施例45之人類抗體分子或其抗原結合片段，其中在胺基酸位置125處之取代為C125A。

實施例47. 如實施例46之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 215、217或219之胺基酸序列。

實施例48. 如實施例47之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 217之胺基酸序列。

實施例49. 如實施例38至48中任一項之人類抗體分子或其抗原結合

片段，其中經修飾之hIL-2蛋白質在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、抗原結合片段之N端或抗原結合片段之C端處融合至抗體或其抗原結合片段。

實施例50. 如實施例38至49中任一項之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質係藉由肽鍵直接融合至抗體或其抗原結合片段。

實施例51. 如實施例50之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質係藉由肽鍵直接融合至抗體重鏈之C端胺基酸殘基。

實施例52. 如實施例38至49中任一項之人類抗體分子或其抗原結合片段，其中經修飾之hIL-2蛋白質係經由連接子融合至抗體或抗原結合片段。

實施例53. 一種免疫結合物，該免疫結合物包含：

(a) 經修飾之人類介白素-2 (hIL-2)蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代；及

(b) 免疫特異性結合至人類計劃性細胞死亡蛋白-1 (hPD-1)之人類抗體分子或其抗原結合片段，其中人類抗體分子或其抗原結合片段包含：

(i) 包含SEQ ID NO: 418之胺基酸序列的重鏈互補決定區1 (CDR1)、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3；

(ii) 包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID

NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3；

(iii) 包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3；或

(iv) 包含SEQ ID NO: 406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序列的輕鏈CDR3。

實施例54. 如實施例53之免疫結合物，其中經修飾之hIL-2蛋白質之胺基酸位置20處的取代係選自D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代。

實施例55. 如實施例53或54之免疫結合物，其中經修飾之hIL-2蛋白質之胺基酸位置38處的取代係選自R38E、R38N、R38G、R38H、R38I、R38L、R38M、R38F、R38P、R38S、R38T、R38W、R38Y、R38V、R38A、R38Q、R38D及R38K取代。

實施例56. 如實施例53至55中任一項之免疫結合物，其中經修飾之hIL-2蛋白質之胺基酸位置20處的取代係選自D20A、D20S、D20Q、

D20M、D20I、D20V、D20N、D20G、D20T或D20E取代，且經修飾之hIL-2蛋白質之胺基酸位置38處的胺基酸取代為R38E。

實施例57. 如實施例53至56中任一項之免疫結合物，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的胺基酸序列。

實施例58. 如實施例53至56中任一項之免疫結合物，其中經修飾之hIL-2蛋白質包含D20A及R38E取代。

實施例59. 如實施例58之免疫結合物，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 149之胺基酸序列。

實施例60. 如實施例53至57中任一項之免疫結合物，其包含SEQ ID NO: 608、614、611、620、607、610、617、609或307中之任一者的胺基酸序列。

實施例61. 如實施例53至60中任一項之免疫結合物，其中經修飾之hIL-2蛋白質進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之缺失或取代。

實施例62. 如實施例61之免疫結合物，其中經修飾之hIL-2蛋白質之胺基酸位置3處之取代為T3A。

實施例63. 如實施例62之免疫結合物，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 216之胺基酸序列。

實施例64. 如實施例61之免疫結合物，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 218之胺基酸序列。

實施例65. 如實施例53至64中任一項之免疫結合物，其中經修飾之hIL-2蛋白質進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸

序列在胺基酸位置125處之缺失或取代。

實施例66. 如實施例65之免疫結合物，其中在胺基酸位置125處之取代為C125A。

實施例67. 如實施例66之免疫結合物，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 215、217或219之胺基酸序列。

實施例68. 如實施例67之免疫結合物，其中經修飾之hIL-2蛋白質包含SEQ ID NO: 217之胺基酸序列。

實施例69. 如實施例53至68中任一項之免疫結合物，其中經修飾之hIL-2蛋白質在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、抗原結合片段之N端或抗原結合片段之C端處融合至抗體或其抗原結合片段。

實施例70. 如實施例53至69中任一項之免疫結合物，其中經修飾之hIL-2蛋白質係藉由肽鍵直接融合至抗體或其抗原結合片段。

實施例71. 如實施例70之免疫結合物，其中經修飾之hIL-2蛋白質係藉由肽鍵直接融合至抗體重鏈之C端胺基酸殘基。

實施例72. 如實施例53至69中任一項之免疫結合物，其中經修飾之hIL-2蛋白質係經由連接子融合至抗體或其抗原結合片段。

實施例73. 如實施例53至72中任一項之免疫結合物，其中人類抗體分子或其抗原結合片段包含：

a) 包含SEQ ID NO: 416之胺基酸序列的重鏈可變區及包含SEQ ID NO: 417之胺基酸序列的輕鏈可變區；

b) 包含SEQ ID NO: 384之胺基酸序列的重鏈可變區及包含SEQ ID NO: 385之胺基酸序列的輕鏈可變區；

c) 包含SEQ ID NO: 394之胺基酸序列的重鏈可變區及包含SEQ ID NO: 395之胺基酸序列的輕鏈可變區；或

d) 包含SEQ ID NO: 404之胺基酸序列的重鏈可變區及包含SEQ ID NO: 405之胺基酸序列的輕鏈可變區。

實施例74. 如實施例53至73中任一項之免疫結合物，其中人類抗體分子或其抗原結合片段包含IgG1重鏈恆定區。

實施例75. 如實施例74之免疫結合物，其中人類抗體分子或其抗原結合片段包含根據EU編號之L235A取代及G237A取代。

實施例76. 如實施例53至75中任一項之免疫結合物，其中人類抗體分子或其抗原結合片段包含：

a) 包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415之胺基酸序列的輕鏈；

b) 包含SEQ ID NO: 424之胺基酸序列的重鏈及包含SEQ ID NO: 425之胺基酸序列的輕鏈；

c) 包含SEQ ID NO: 426之胺基酸序列的重鏈及包含SEQ ID NO: 427之胺基酸序列的輕鏈；或

d) 包含SEQ ID NO: 428之胺基酸序列的重鏈及包含SEQ ID NO: 429之胺基酸序列的輕鏈。

實施例77. 如實施例76之免疫結合物，其中人類抗體分子或其抗原結合片段包含有包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415之胺基酸序列的輕鏈。

實施例78. 如實施例53至77中任一項之免疫結合物，其包含

包含SEQ ID NO: 415之胺基酸序列的輕鏈；及

包含SEQ ID NO: 532之胺基酸序列的重鏈-經修飾之hIL-2蛋白質融合物。

實施例79. 一種醫藥組合物，其包含如實施例1至31中任一項之經修飾之hIL-2蛋白質、如實施例32至52中任一項之人類抗體分子或其抗原結合片段，或如實施例53至78中任一項之免疫結合物。

實施例80. 一種聚核苷酸，其包含編碼如實施例1至31中任一項之經修飾之hIL-2蛋白質、如實施例32至52中任一項之人類抗體分子或其抗原結合片段，或如實施例53至78中任一項之免疫結合物的核酸序列。

實施例81. 一種載體，其包含聚核苷酸，該聚核苷酸包含編碼如實施例1至31中任一項之經修飾之hIL-2蛋白質、如實施例32至52中任一項之人類抗體分子或其抗原結合片段，或如實施例53至78中任一項之免疫結合物的核酸序列。

實施例82. 一種經轉型之細胞，其包含如實施例81之載體。

實施例83. 一種治療個體中之疾病或病症之方法，該方法包含向個體投與治療有效量之如實施例10至14及27至31中任一項之經修飾之hIL-2蛋白質、如實施例53至78中任一項之免疫結合物，或如實施例79之醫藥組合物，由此治療該疾病或病症。

實施例84. 如實施例83之方法，其中該疾病或病症為癌症。

實施例85. 如實施例84之方法，其中該癌症為黑色素瘤。

實施例86. 如實施例84之方法，其中該癌症為非小細胞肺癌。

實施例87. 一種如實施例10至14及27至31中任一項之經修飾之hIL-2蛋白質、如實施例53至78中任一項之免疫結合物，或如實施例79之醫藥組合物的用途，其係用以製備用於治療疾病或病症之藥物。

實施例88. 如實施例87之用途，其中該疾病或病症為癌症。

實施例89. 如實施例88之用途，其中該癌症為黑色素瘤。

實施例90. 如實施例88之用途，其中該癌症為非小細胞肺癌。

實施例91. 一種如實施例10至14及27至31中任一項之經修飾之hIL-2蛋白質、如實施例53至78中任一項之免疫結合物，或如實施例79之醫藥組合物的用途，其係用於治療疾病或病症。

實施例92. 如實施例91之用途，其中該疾病或病症為癌症。

實施例93. 如實施例92之用途，其中該癌症為黑色素瘤。

實施例94. 如實施例92之用途，其中該癌症為非小細胞肺癌。

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【發明申請專利範圍】

【請求項1】

一種經修飾之人類介白素-2 (hIL-2)蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代，其中相對於未經修飾之hIL-2，該經修飾之hIL-2蛋白質對高親和力hIL-2受體及對中等親和力hIL-2受體兩者展現降低之效力。

【請求項2】

如請求項1之經修飾之hIL-2蛋白質，其中在胺基酸位置20處之該取代係選自D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代。

【請求項3】

如請求項1或2之經修飾之hIL-2蛋白質，其中在胺基酸位置38處之該取代係選自R38E、R38N、R38G、R38H、R38I、R38L、R38M、R38F、R38P、R38S、R38T、R38W、R38Y、R38V、R38A、R38Q、R38D及R38K取代。

【請求項4】

如前述請求項中任一項之經修飾之hIL-2蛋白質，其進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之缺失或取代。

【請求項5】

如請求項4之經修飾之hIL-2蛋白質，其中在胺基酸位置3處之該取代為T3A。

【請求項6】

如前述請求項中任一項之經修飾之hIL-2蛋白質，其進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。

【請求項7】

如請求項6之經修飾之hIL-2蛋白質，其中在胺基酸位置125處之該取代為C125A。

【請求項8】

如前述請求項中任一項之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質對該高親和力IL-2受體(hIL-2Rαβγ)展現降低約1,000倍之效力。

【請求項9】

如前述請求項中任一項之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質對該中等親和力IL-2受體(hIL-2Rβγ)展現降低約10,000倍之效力。

【請求項10】

如請求項1至9中任一項之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質係融合至抗PD-1抗體或其抗原結合片段。

【請求項11】

如請求項10之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、該抗原結合片段之N端或該抗原結合片段之C端處融合至該抗體或其抗原結合片段。

【請求項12】

如請求項10或11之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質係藉由肽鍵直接融合至該抗體或其抗原結合片段。

【請求項13】

如請求項12之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2係藉由肽鍵直接融合至該抗體重鏈之C端胺基酸殘基。

【請求項14】

如請求項10或11之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質係經由連接子融合至該抗體或其抗原結合片段。

【請求項15】

一種經修飾之人類介白素-2 (hIL-2)蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代及在胺基酸位置38處之R38E取代。

【請求項16】

如請求項15之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 307、607至611、614、617或620中之任一者的胺基酸序列。

【請求項17】

如請求項15或16之經修飾之hIL-2蛋白質，其包含D20A取代及R38E取代。

【請求項18】

如請求項17之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 149之胺基酸序列。

【請求項19】

如請求項15至18中任一項之經修飾之hIL-2蛋白質，其進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之缺失或取代。

【請求項20】

如請求項19之經修飾之hIL-2蛋白質，其中在胺基酸位置3處之該取代為T3A。

【請求項21】

如請求項20之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 216之胺基酸序列。

【請求項22】

如請求項19之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 218之胺基酸序列。

【請求項23】

如請求項15至22中任一項之經修飾之hIL-2蛋白質，其進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。

【請求項24】

如請求項23之經修飾之hIL-2蛋白質，其中在胺基酸位置125處之該取代為C125A。

【請求項25】

如請求項24之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 215、217或219之胺基酸序列。

【請求項26】

如請求項25之經修飾之hIL-2蛋白質，其包含SEQ ID NO: 217之胺基酸序列。

【請求項27】

如請求項15至26中任一項之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質係融合至抗PD-1抗體或其抗原結合片段。

【請求項28】

如請求項27之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、該抗原結合片段之N端或該抗原結合片段之C端處融合至該抗體或其抗原結合片段。

【請求項29】

如請求項27或28之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質係藉由肽鍵直接融合至該抗體或其抗原結合片段。

【請求項30】

如請求項29之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2係藉由肽鍵直接融合至該抗體重鏈之C端胺基酸殘基。

【請求項31】

如請求項27或28之經修飾之hIL-2蛋白質，其中該經修飾之hIL-2蛋白質係經由連接子融合至該抗體或其抗原結合片段。

【請求項32】

一種免疫特異性結合至人類計劃性細胞死亡蛋白-1 (hPD-1)之人類抗體分子或其抗原結合片段，其中該人類抗體分子或其抗原結合片段包含：

a) 包含SEQ ID NO: 418之胺基酸序列的重鏈互補決定區1(CDR1)、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3；

b) 包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3；

c) 包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3；或

d) 包含SEQ ID NO: 406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序列的輕鏈CDR3。

【請求項33】

如請求項32之人類抗體分子或其抗原結合片段，其包含：

a) 包含SEQ ID NO: 416之胺基酸序列的重鏈可變區及包含SEQ ID

NO: 417之胺基酸序列的輕鏈可變區；

b) 包含SEQ ID NO: 384之胺基酸序列的重鏈可變區及包含SEQ ID NO: 385之胺基酸序列的輕鏈可變區；

c) 包含SEQ ID NO: 394之胺基酸序列的重鏈可變區及包含SEQ ID NO: 395之胺基酸序列的輕鏈可變區；或

d) 包含SEQ ID NO: 404之胺基酸序列的重鏈可變區及包含SEQ ID NO: 405之胺基酸序列的輕鏈可變區。

【請求項34】

如請求項32或33之人類抗體分子或其抗原結合片段，其包含人類IgG1重鏈恆定區。

【請求項35】

如請求項34之人類抗體分子或其抗原結合片段，其包含根據EU編號之L235A取代及G237A取代。

【請求項36】

如請求項32至35中任一項之人類抗體分子或其抗原結合片段，其包含：

a) 包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415之胺基酸序列的輕鏈；

b) 包含SEQ ID NO: 424之胺基酸序列的重鏈及包含SEQ ID NO: 425之胺基酸序列的輕鏈；

c) 包含SEQ ID NO: 426之胺基酸序列的重鏈及包含SEQ ID NO: 427之胺基酸序列的輕鏈；或

d) 包含SEQ ID NO: 428之胺基酸序列的重鏈及包含SEQ ID NO:

429之胺基酸序列的輕鏈。

【請求項37】

如請求項36之人類抗體分子或其抗原結合片段，其包含有包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415之胺基酸序列的輕鏈。

【請求項38】

如請求項32至37中任一項之人類抗體分子或其抗原結合片段，其融合至經修飾之人類介白素-2 (hIL-2)蛋白質，該蛋白質包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代。

【請求項39】

如請求項38之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的胺基酸序列。

【請求項40】

如請求項39之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 149之胺基酸序列。

【請求項41】

如請求項38至40中任一項之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之缺失或取代。

【請求項42】

如請求項41之人類抗體分子或其抗原結合片段，其中在胺基酸位置3

處之該取代為T3A。

【請求項43】

如請求項42之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 216之胺基酸序列。

【請求項44】

如請求項41之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 218之胺基酸序列。

【請求項45】

如請求項38至44中任一項之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。

【請求項46】

如請求項45之人類抗體分子或其抗原結合片段，其中在胺基酸位置125處之該取代為C125A。

【請求項47】

如請求項46之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 215、217或219之胺基酸序列。

【請求項48】

如請求項47之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 217之胺基酸序列。

【請求項49】

如請求項38至48中任一項之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之

N端、抗體重鏈之C端、該抗原結合片段之N端或該抗原結合片段之C端處融合至該抗體或其抗原結合片段。

【請求項50】

如請求項38至49中任一項之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質係藉由肽鍵直接融合至該抗體或其抗原結合片段。

【請求項51】

如請求項50之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質係藉由肽鍵直接融合至該抗體重鏈之C端胺基酸殘基。

【請求項52】

如請求項38至49中任一項之人類抗體分子或其抗原結合片段，其中該經修飾之hIL-2蛋白質係經由連接子融合至該抗體或抗原結合片段。

【請求項53】

一種免疫結合物，該免疫結合物包含：

(a) 經修飾之人類介白素-2 (hIL-2)蛋白質，其包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置20處之取代及在胺基酸位置38處之取代；及

(b) 免疫特異性結合至人類計劃性細胞死亡蛋白-1 (hPD-1)之人類抗體分子或其抗原結合片段，其中該人類抗體分子或其抗原結合片段包含：

(i) 包含SEQ ID NO: 418之胺基酸序列的重鏈互補決定區1 (CDR1)、包含SEQ ID NO: 419之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 420之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 421

之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 422之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 423之胺基酸序列的輕鏈CDR3；

(ii) 包含SEQ ID NO: 386之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 387之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 388之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 389之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 390之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 391之胺基酸序列的輕鏈CDR3；

(iii) 包含SEQ ID NO: 396之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 397之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 398之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 399之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 400之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 401之胺基酸序列的輕鏈CDR3；或

(iv) 包含SEQ ID NO: 406之胺基酸序列的重鏈CDR1、包含SEQ ID NO: 407之胺基酸序列的重鏈CDR2、包含SEQ ID NO: 408之胺基酸序列的重鏈CDR3、包含SEQ ID NO: 409之胺基酸序列的輕鏈CDR1、包含SEQ ID NO: 410之胺基酸序列的輕鏈CDR2，及包含SEQ ID NO: 411之胺基酸序列的輕鏈CDR3。

【請求項54】

如請求項53之免疫結合物，其中該經修飾之hIL-2蛋白質之胺基酸位置20處的該取代係選自D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代。

【請求項55】

如請求項53或54之免疫結合物，其中該經修飾之hIL-2蛋白質之胺基

酸位置38處的該取代係選自R38E、R38N、R38G、R38H、R38I、R38L、R38M、R38F、R38P、R38S、R38T、R38W、R38Y、R38V、R38A、R38Q、R38D及R38K取代。

【請求項56】

如請求項53至55中任一項之免疫結合物，其中該經修飾之hIL-2蛋白質之胺基酸位置20處的該取代係選自D20A、D20S、D20Q、D20M、D20I、D20V、D20N、D20G、D20T或D20E取代，且該經修飾之hIL-2蛋白質之胺基酸位置38處的該胺基酸取代為R38E。

【請求項57】

如請求項53至56中任一項之免疫結合物，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 134至150、307、344、607至611、614、617或620中之任一者的胺基酸序列。

【請求項58】

如請求項53至56中任一項之免疫結合物，其中該經修飾之hIL-2蛋白質包含D20A及R38E取代。

【請求項59】

如請求項58之免疫結合物，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 149之胺基酸序列。

【請求項60】

如請求項53至57中任一項之免疫結合物，其包含SEQ ID NO: 608、614、611、620、607、610、617、609或307中之任一者的胺基酸序列。

【請求項61】

如請求項53至60中任一項之免疫結合物，其中該經修飾之hIL-2蛋白

質進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置3處之缺失或取代。

【請求項62】

如請求項61之免疫結合物，其中該經修飾之hIL-2蛋白質之胺基酸位置3處的該取代為T3A。

【請求項63】

如請求項62之免疫結合物，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 216之胺基酸序列。

【請求項64】

如請求項61之免疫結合物，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 218之胺基酸序列。

【請求項65】

如請求項53至64中任一項之免疫結合物，其中該經修飾之hIL-2蛋白質進一步包含相對於SEQ ID NO: 345之未經修飾之hIL-2胺基酸序列在胺基酸位置125處之缺失或取代。

【請求項66】

如請求項65之免疫結合物，其中在胺基酸位置125處之該取代為C125A。

【請求項67】

如請求項66之免疫結合物，其中該經修飾之hIL-2蛋白質包含SEQ ID NO: 215、217或219之胺基酸序列。

【請求項68】

如請求項67之免疫結合物，其中該經修飾之hIL-2蛋白質包含SEQ ID

NO: 217之胺基酸序列。

【請求項69】

如請求項53至68中任一項之免疫結合物，其中該經修飾之hIL-2蛋白質在抗體輕鏈之N端、抗體輕鏈之C端、抗體重鏈之N端、抗體重鏈之C端、該抗原結合片段之N端或該抗原結合片段之C端處融合至該抗體或其抗原結合片段。

【請求項70】

如請求項53至69中任一項之免疫結合物，其中該經修飾之hIL-2蛋白質係藉由肽鍵直接融合至該抗體或其抗原結合片段。

【請求項71】

如請求項70之免疫結合物，其中該經修飾之hIL-2蛋白質係藉由肽鍵直接融合至該抗體重鏈之C端胺基酸殘基。

【請求項72】

如請求項53至69中任一項之免疫結合物，其中該經修飾之hIL-2蛋白質係經由連接子融合至該抗體或其抗原結合片段。

【請求項73】

如請求項53至72中任一項之免疫結合物，其中該人類抗體分子或其抗原結合片段包含：

a) 包含SEQ ID NO: 416之胺基酸序列的重鏈可變區及包含SEQ ID NO: 417之胺基酸序列的輕鏈可變區；

b) 包含SEQ ID NO: 384之胺基酸序列的重鏈可變區及包含SEQ ID NO: 385之胺基酸序列的輕鏈可變區；

c) 包含SEQ ID NO: 394之胺基酸序列的重鏈可變區及包含SEQ ID

NO: 395之胺基酸序列的輕鏈可變區；或

d) 包含SEQ ID NO: 404之胺基酸序列的重鏈可變區及包含SEQ ID NO: 405之胺基酸序列的輕鏈可變區。

【請求項74】

如請求項53至73中任一項之免疫結合物，其中該人類抗體分子或其抗原結合片段包含IgG1重鏈恆定區。

【請求項75】

如請求項74之免疫結合物，其中該人類抗體分子或其抗原結合片段包含根據EU編號之L235A取代及G237A取代。

【請求項76】

如請求項53至75中任一項之免疫結合物，其中該人類抗體分子或其抗原結合片段包含：

a) 包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415之胺基酸序列的輕鏈；

b) 包含SEQ ID NO: 424之胺基酸序列的重鏈及包含SEQ ID NO: 425之胺基酸序列的輕鏈；

c) 包含SEQ ID NO: 426之胺基酸序列的重鏈及包含SEQ ID NO: 427之胺基酸序列的輕鏈；或

d) 包含SEQ ID NO: 428之胺基酸序列的重鏈及包含SEQ ID NO: 429之胺基酸序列的輕鏈。

【請求項77】

如請求項76之免疫結合物，其中該人類抗體分子或其抗原結合片段包含有包含SEQ ID NO: 414之胺基酸序列的重鏈及包含SEQ ID NO: 415

之胺基酸序列的輕鏈。

【請求項78】

如請求項53至77中任一項之免疫結合物，其包含

包含SEQ ID NO: 415之胺基酸序列的輕鏈；及

包含SEQ ID NO: 532之胺基酸序列的重鏈-經修飾之hIL-2蛋白質融合物。

【請求項79】

一種醫藥組合物，其包含如請求項1至31中任一項之經修飾之hIL-2蛋白質、如請求項32至52中任一項之人類抗體分子或其抗原結合片段，或如請求項53至78中任一項之免疫結合物。

【請求項80】

一種聚核苷酸，其包含編碼如請求項1至31中任一項之經修飾之hIL-2蛋白質、如請求項32至52中任一項之人類抗體分子或其抗原結合片段，或如請求項53至78中任一項之免疫結合物的核酸序列。

【請求項81】

一種載體，其包含聚核苷酸，該聚核苷酸包含編碼如請求項1至31中任一項之經修飾之hIL-2蛋白質、如請求項32至52中任一項之人類抗體分子或其抗原結合片段，或如請求項53至78中任一項之免疫結合物的核酸序列。

【請求項82】

一種經轉型之細胞，其包含如請求項81之載體。

【請求項83】

一種治療個體中之疾病或病症之方法，該方法包含向該個體投與治

療有效量之如請求項10至14及27至31中任一項之經修飾之hIL-2蛋白質、如請求項53至78中任一項之免疫結合物，或如請求項79之醫藥組合物，由此治療該疾病或病症。

【請求項84】

如請求項83之方法，其中該疾病或病症為癌症。

【請求項85】

如請求項84之方法，其中該癌症為黑色素瘤。

【請求項86】

如請求項84之方法，其中該癌症為非小細胞肺癌。

【請求項87】

一種如請求項10至14及27至31中任一項之經修飾之hIL-2蛋白質、如請求項53至78中任一項之免疫結合物，或如請求項79之醫藥組合物的用途，其係用以製備用於治療疾病或病症之藥物。

【請求項88】

如請求項87之用途，其中該疾病或病症為癌症。

【請求項89】

如請求項88之用途，其中該癌症為黑色素瘤。

【請求項90】

如請求項88之用途，其中該癌症為非小細胞肺癌。

【請求項91】

一種如請求項10至14及27至31中任一項之經修飾之hIL-2蛋白質、如請求項53至78中任一項之免疫結合物，或如請求項79之醫藥組合物的用途，其係用於治療疾病或病症。

【請求項92】

如請求項91之用途，其中該疾病或病症為癌症。

【請求項93】

如請求項92之用途，其中該癌症為黑色素瘤。

【請求項94】

如請求項92之用途，其中該癌症為非小細胞肺癌。

[發明圖式]

圖1
圖2
圖3
圖4
圖5
圖6
圖7
圖8

第二入口
第一入口
出口
入口
3

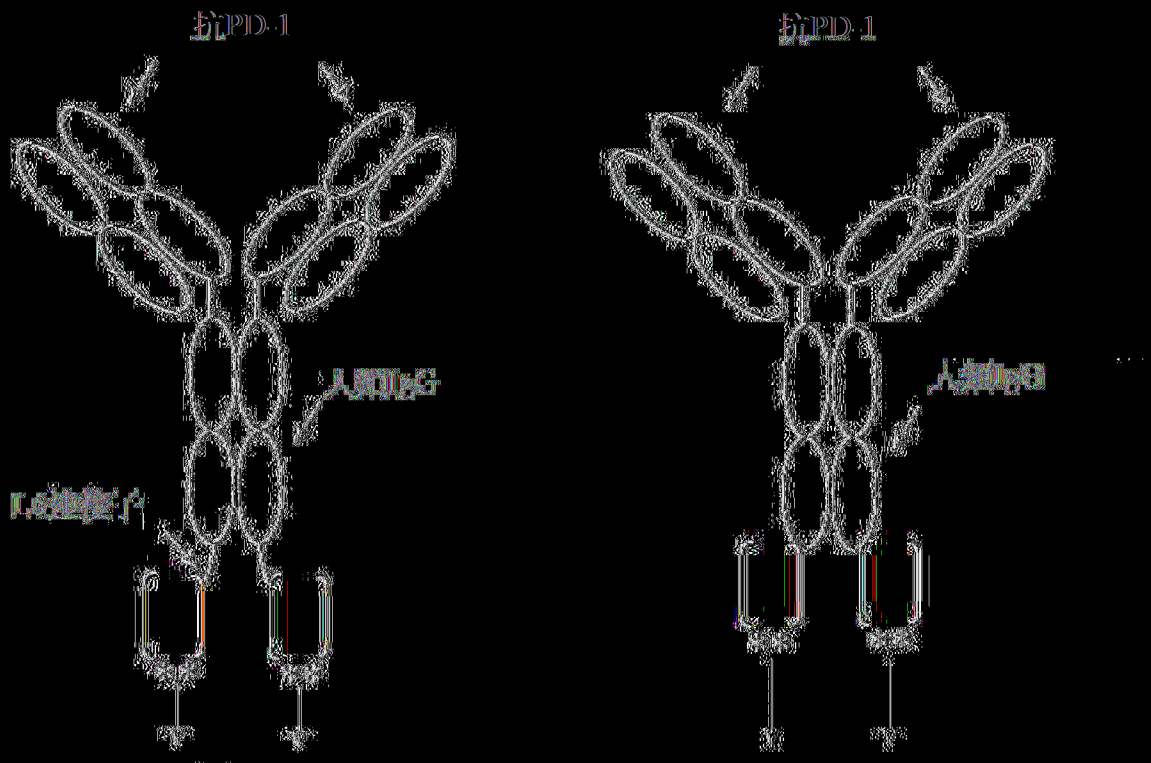
【圖4A】

【圖4B】

(C7C)

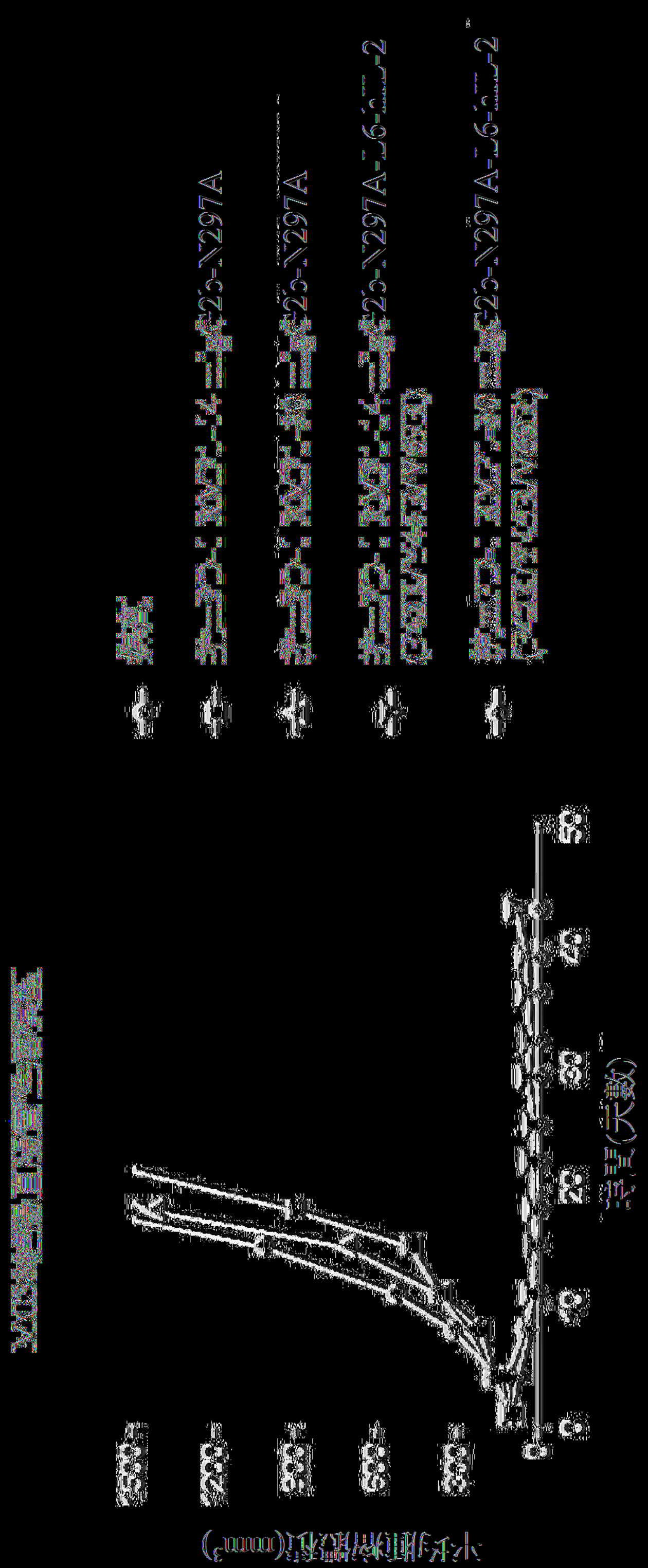
(C7C)

抗hPD-1抗體減弱之hIL-2融合物



[圖5]

圖 7(c3)



【圖8】

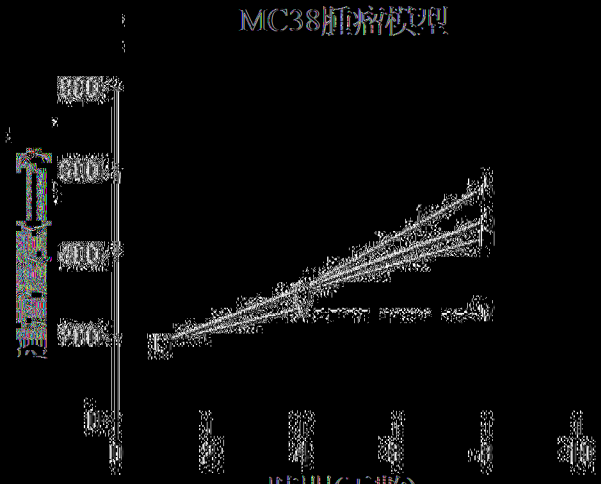
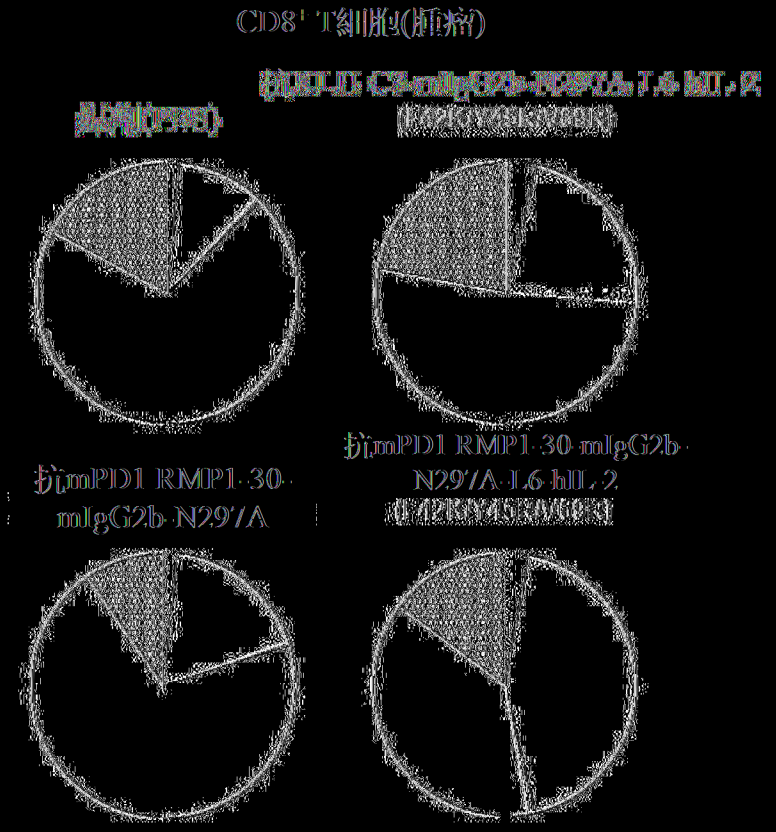
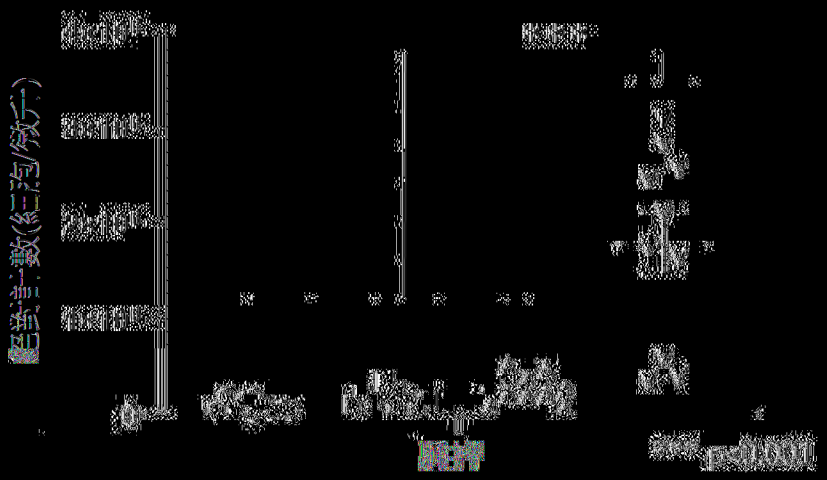

MC38腫瘤模型
腫瘤體積(mm³)
時間(天數)
媒劑(PBS)
抗KLH-C3-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)
抗mPD1 RMP1-30-mIgG2b-N297A
抗mPD1 RMP1-30-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)

圖9A

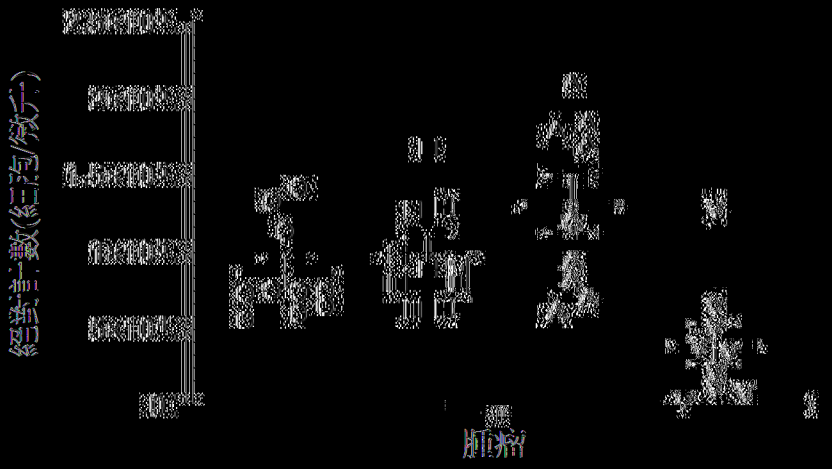

CD8+ T細胞(腫瘤)
抗mPD1 RMP1-30-mIgG2b-N297A, IL-6 和 IL-2
(0.2%)
抗mPD1 RMP1-30-mIgG2b-N297A
(0.2%)
抗mPD1 RMP1-30-mIgG2b-N297A
(42%)
抗mPD1 RMP1-30-mIgG2b-N297A, IL-6 和 IL-2
(45%)
中央記憶T細胞
效應記憶T細胞
常駐記憶T細胞
CD62L+
CD62L-
CD69+
CD69-

[圖式]

MC38腫瘤中之CD8+效應記憶T細胞

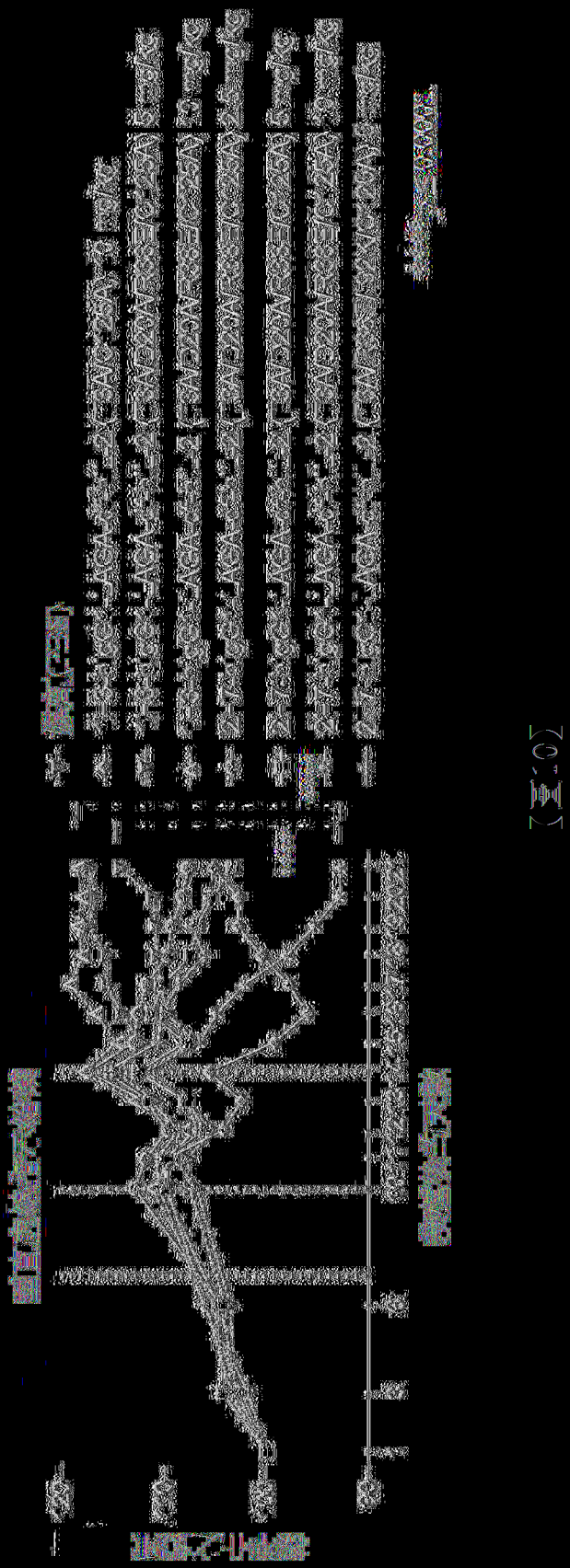


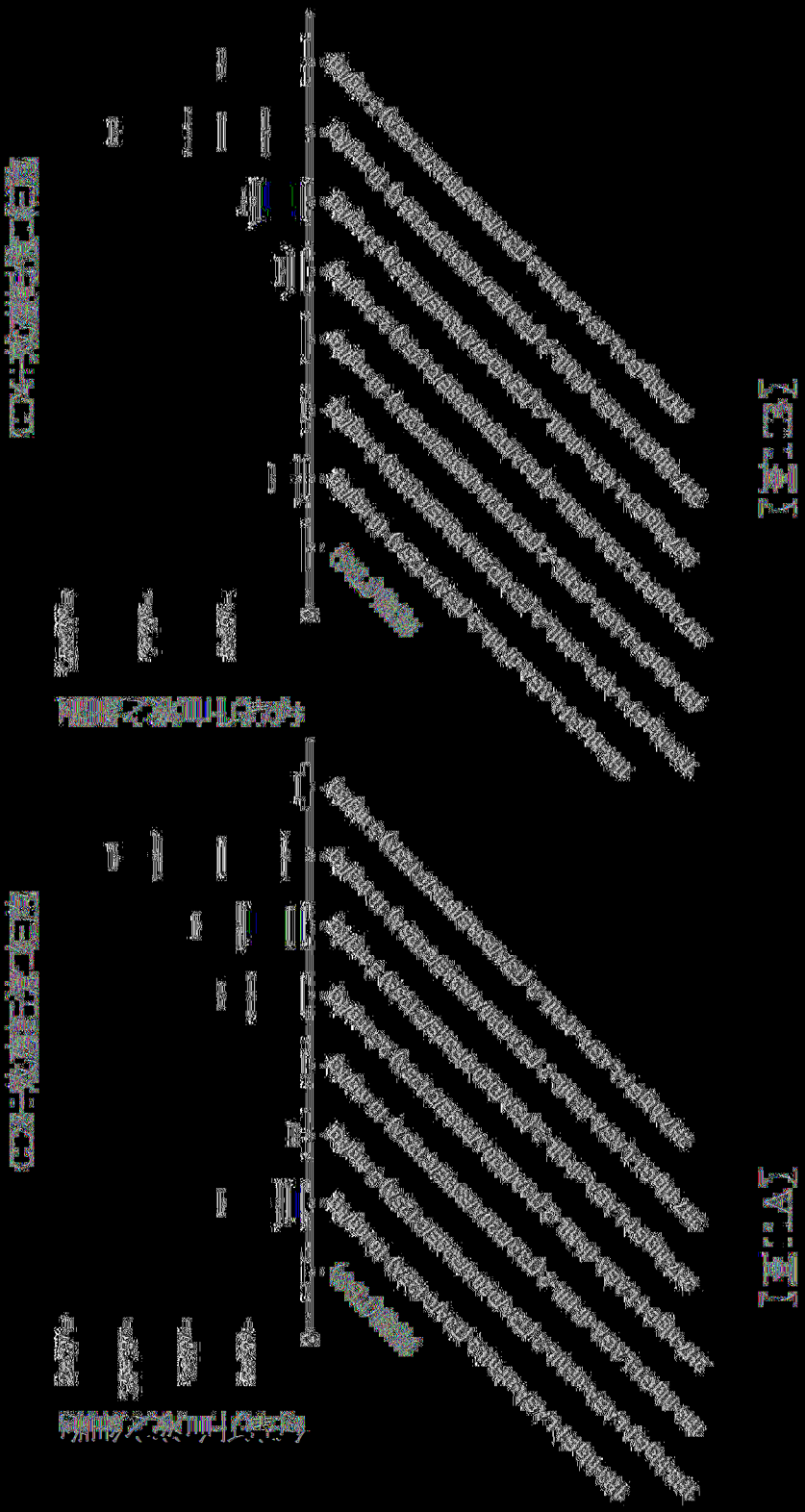
MC38腫瘤中之調節T細胞



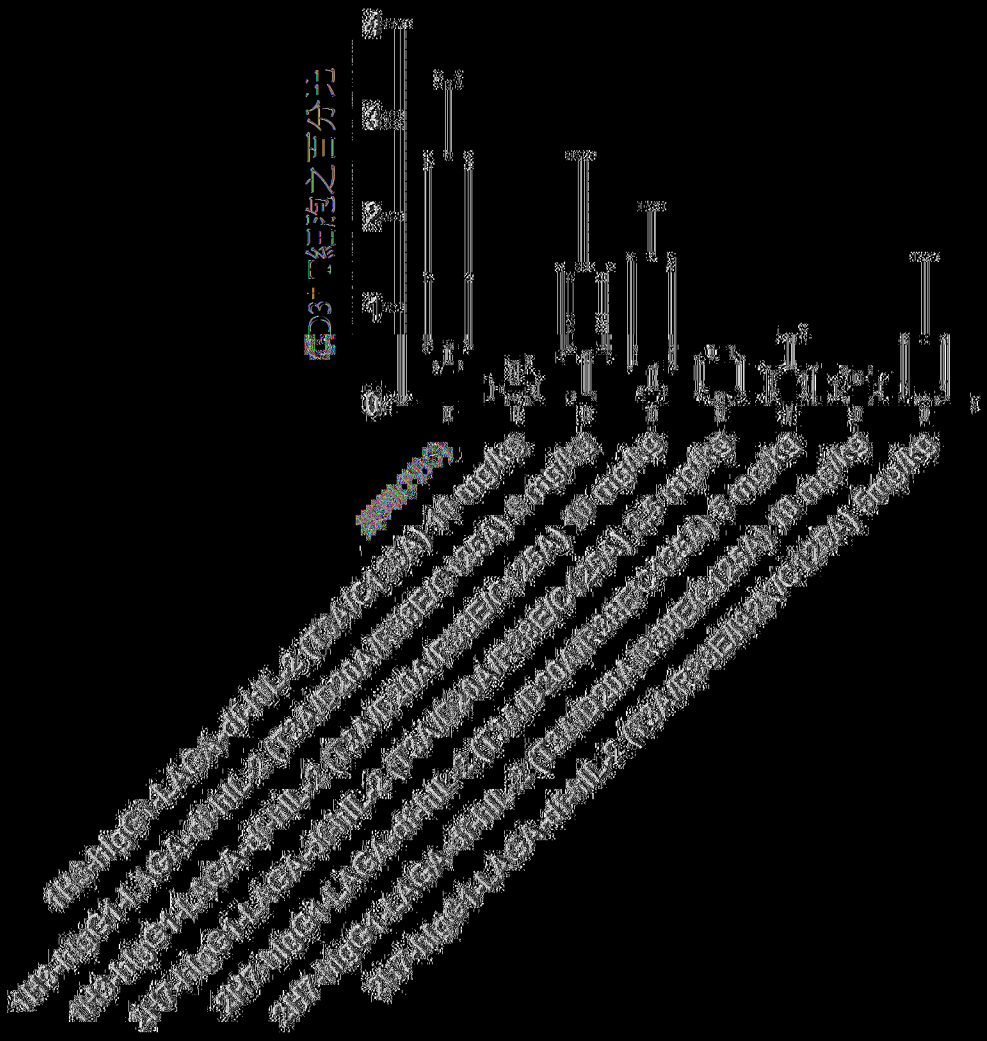
- 媒劑(PBS)
- 抗KLH-C3-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)
- 抗mPD1 RMP1-30-mIgG2b-N297A
- 抗mPD1 RMP1-30-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)

[(圖9C)]





CD3+T細胞之調節T細胞(Treg)百分比



[圖12.]

圖3D

圖3A

（圖4A）

（圖4B）

（圖6B）

（圖6A）

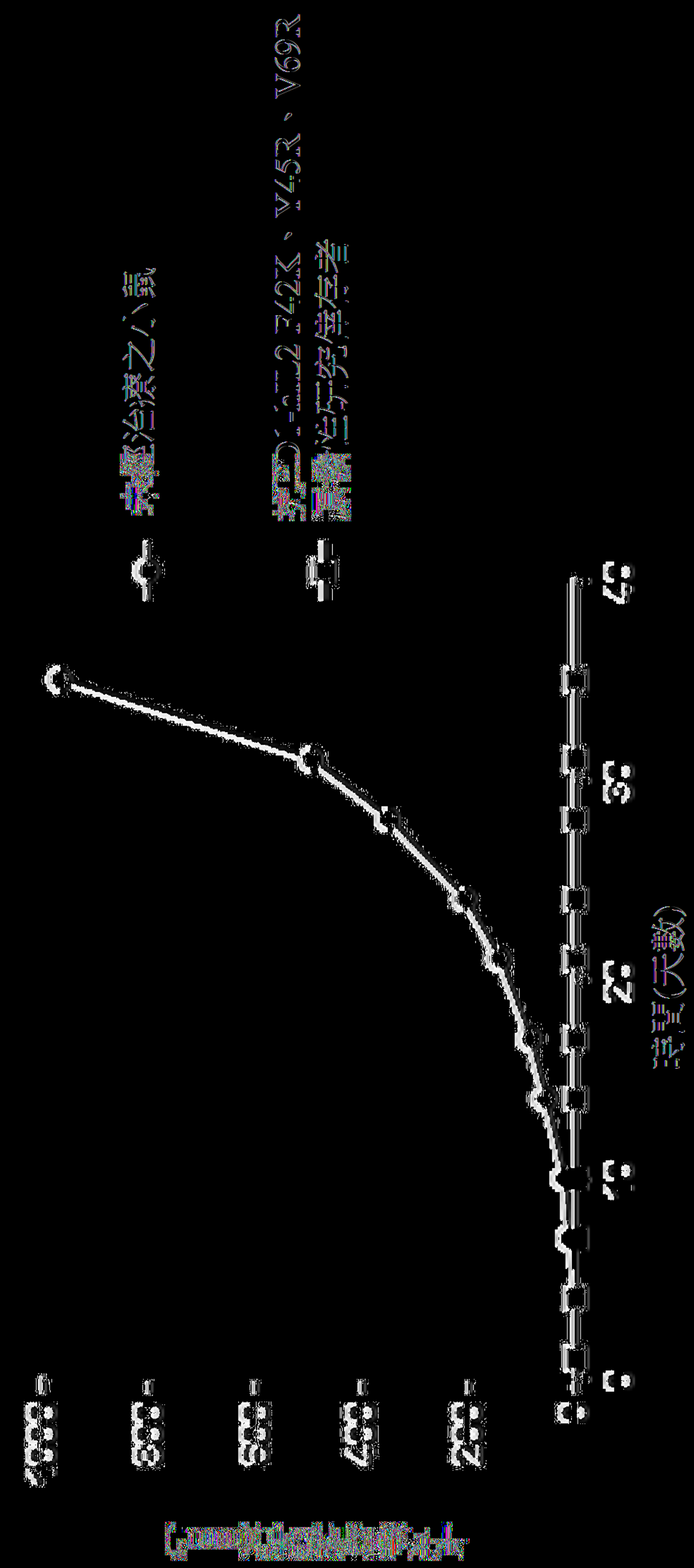
(C9H7)
(C9H7)

(C07D 209/20 (2006.01) I)
(C07D 209/20 (2006.01) I)
(C07D 209/20 (2006.01) I)

光(RUV)
光(RUV)

發光(R,U,V)
發光(R,U,V)

圖1為本發明的流程圖



【圖20】