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(54)名稱

蛋白複合體之組成物及其使用方法

(57)摘要

本文提供包含藉由連接子連接的感測器域及治療域之蛋白複合體，以及其使用方法。在本揭露的方面中，該治療域之活性包含對感測器域與標靶標記物結合的依賴性。

Provided herein are protein complexes comprising a sensor domain and a therapeutic domain linked by a linker, and methods of use thereof. In aspects of the present disclosure, activity of the therapeutic domain comprises a dependence on sensor domain binding to target markers.

【發明摘要】

【中文發明名稱】　蛋白複合體之組成物及其使用方法

【英文發明名稱】　COMPOSITIONS OF PROTEIN COMPLEXES AND METHODS OF USE THEREOF

【中文】本文提供包含藉由連接子連接的感測器域及治療域之蛋白複合體，以及其使用方法。在本揭露的方面中，該治療域之活性包含對感測器域與標靶標記物結合的依賴性。

【英文】Provided herein are protein complexes comprising a sensor domain and a therapeutic domain linked by a linker, and methods of use thereof. In aspects of the present disclosure, activity of the therapeutic domain comprises a dependence on sensor domain binding to target markers.

【指定代表圖】

無

【特徵化學式】

無

【發明說明書】

【中文發明名稱】　蛋白複合體之組成物及其使用方法

【英文發明名稱】　COMPOSITIONS OF PROTEIN COMPLEXES AND METHODS OF USE THEREOF

【技術領域】

【0001】 本發明涉及包含藉由連接子連接的感測器域及治療域之蛋白複合體，以及其使用方法。

【先前技術】

【0002】 介白素 2 (IL-2) 係一種有效的細胞激素，在全身性投予時表現出毒性。需要一種可全身性遞送但可以調節以在有效 T 細胞亞群上表現出治療活性的 IL-2 型式。

【發明內容】

【0003】 在一些態樣中，本揭露提供一種複合體，該複合體包含：(a) 包含 IL-2 肽的治療域及 (b) 包含抗體的感測器域，其中該感測器域經組態為以相互排斥方式結合 PD-1 及 IL-2。在一些實施例中，複合體進一步包含將治療域連接至感測器域的連接子。在一些實施例中，感測器域經組態為：(i) 在不存在 PD-1 的情況下結合 IL-2；以及 (ii) 在存在 PD-1 的情況下不結合 IL-2。在一些實施例中，抗體為抗體片段或抗體衍生物。在一些實施例中，感測器域包含經組態以結合 PD-1 及 IL-2 的單一雙重結合抗體 (DBA)。在一些實施例中，DBA

包含重鏈 CDR3，該重鏈 CDR3 與以下中之任一者具有至少 80%、至少 81%、至少 82%、至少 83%、至少 84%、至少 85%、至少 86%、至少 87%、至少 88%、至少 89%、至少 90%、至少 91%、至少 92%、至少 93%、至少 94%、至少 95%、至少 96%、至少 97%、至少 98%、至少 99% 或 100% 序列同一性：SEQ ID NO: 11 至 20、154 至 156、168 至 173、114 至 119、415、421、433、439、445、451、457、463、469、475、481、487、493、499、505、511、517、523、529、535、541、547、553、559、565、571、577、583、589、595、601、607、613、619、625、631、637、643、649、655、661 或 667。在一些實施例中，DBA 包含重鏈 CDR1、CDR2 或 CDR3，該 CDR1、CDR2 或 CDR3 含有與表 3、表 7、表 8 或表 19 中列舉的序列中之任一者具有至少 80%、至少 81%、至少 82%、至少 83%、至少 84%、至少 85%、至少 86%、至少 87%、至少 88%、至少 89%、至少 90%、至少 91%、至少 92%、至少 93%、至少 94%、至少 95%、至少 96%、至少 97%、至少 98%、至少 99% 或 100% 序列同一性的序列。在一些實施例中，DBA 包含 V_H 或 V_L，該 V_H 或 V_L 包含與表 18 中列舉的序列中之任一者具有至少 80%、至少 81%、至少 82%、至少 83%、至少 84%、至少 85%、至少 86%、至少 87%、至少 88%、至少 89%、至少 90%、至少 91%、至少 92%、至少 93%、至少 94%、至少 95%、至少 96%、至少 97%、至少 98%、至少 99% 或 100% 序列同一性的序列。在一些實施例中，複合體包含 Fc 域。在一些實施例中，Fc 域來自 IgG。在一些實施例中，Fc 域係同二聚體的 (homodimeric)。在一些實施例中，Fc 域係異二聚體的 (heterodimeric)。在一些實施例中，Fc 域包含：(a) 包含杵突變 (knob mutation) 的第一多肽及 (b) 包含臼突變 (hole mutation) 的第二多肽。在一些實

施例中，杵突變或臼突變包含下列相對於 IgG 的殘基對中之任一對之突變：366 與 407、405 與 394、或 407 與 366。在一些實施例中，杵突變包含精胺酸殘基、苯丙胺酸殘基、酪胺酸殘基或色胺酸殘基，且臼突變包含丙胺酸殘基、絲胺酸殘基、蘇胺酸殘基或纈胺酸殘基。在一些實施例中，複合體包含含有全長 DBA 的感測器域，其中該 IL-2 肽與該全長 DBA 之重鏈之 N 端連接，或其中該 IL-2 肽與該全長 DBA 之輕鏈之 N 端連接。在一些實施例中，複合體包含含有全長 DBA 的感測器域，其中該 IL-2 肽與該全長 DBA 之重鏈之 C 端連接。在一些實施例中，複合體包含：(a) 根據 N-[IL-2]-[連接子]-[V_H]-[C_H]-[鉸鏈]-Fc-C 的第一多肽；及根據 N-[V_L]-[C_L]-C 的第二多肽，或 (b) 根據 N-[V_H]-[C_H]-[鉸鏈]-Fc-C 的第一多肽；及根據 N-[IL-2]-[連接子]-[V_L]-[C_L]-C 的第二多肽，其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示該 DBA 之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，V_L 表示該 DBA 之輕鏈可變域，[鉸鏈] 表示免疫球蛋白之鉸鏈區，Fc 表示免疫球蛋白之 Fc 區，且 CL 表示免疫球蛋白之輕鏈恆定域。在一些實施例中，複合體包含 AF003345、AF003243、AF003246、AF003247、AF003341、AF003644、AF003651、AF003657 或 AF003934 中之任一者。在一些實施例中，複合體包含：(a) 根據 N-[IL-2]-[連接子]-[V_H]-[C_H]-[鉸鏈]-Fc[杵]-C 的第一多肽；根據 N-[V_L]-[C_L]-C 的第二多肽；及根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[臼]-C 的第三多肽，或 (b) 根據 N-[IL-2]-[連接子]-[V_H]-[C_H]-[鉸鏈]-Fc[臼]-C 的第一多肽；根據 N-[V_L]-[C_L]-C 的第二多肽；及根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[杵]-C 的第三多肽，其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示該 DBA 之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，V_L 表示該 DBA 之輕鏈可變域，

[鉸鏈] 表示免疫球蛋白之鉸鏈區，Fc[杵] 表示包含杵突變的免疫球蛋白之 Fc，Fc[臼] 表示包含臼突變的免疫球蛋白之 Fc 區，且 C_L 表示免疫球蛋白之輕鏈恆定域。在一些實施例中，杵突變或臼突變包含下列相對於 IgG 的殘基對中之任一對之突變：366 與 407、405 與 394、或 407 與 366。在一些實施例中，複合體包含 AF003229、AF003230、AF003232、AF003740、AF003747、AF003749、AF003753、AF003945、AF003947、AF003951、AF003952、AF003953、AF003955、AF003956 或 AF003941 中之任一者。在一些實施例中，複合體包含：(a) 根據 N-[IL-2]-[連接子]-[V_H]-[C_H]-[鉸鏈]-Fc-[scFv]-C 的第一多肽；及 (b) 根據 N-[V_L]-[C_L]-C 的第二多肽，其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示抗 PD-1 單選擇性 (monoselective) 抗體之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，V_L 表示抗 PD-1 單選擇性抗體之輕鏈可變域，[鉸鏈] 表示免疫球蛋白之鉸鏈區，Fc 表示免疫球蛋白之 Fc 區，C_L 表示免疫球蛋白之輕鏈恆定域，且 [scFv] 表示包含該 DBA 之 V_H 域及 V_L 域的 scFv。在一些實施例中，該 scFv 係根據 N-[V_H]-[連接子2]-[V_L]-C 定向。在一些實施例中，包含該 DBA 的 V_H 及 V_L 域的該 scFv 包含：(a) V_H 域，其包含與 AB002022_2B07v1、AB002328_2B07v4、AB002360_7A04v1、AB002413_2A11v3、AB002342_2B07v5、AB002345_2B07v6 或 AB002365_7A04v2 中之任一者之 V_H 域具有至少 80% 同一性的序列；或 (b) V_L 域，其包含與 AB002022_2B07v1、AB002328_2B07v4、AB002360_7A04v1、AB002413_2A11v3、AB002342_2B07v5、AB002345_2B07v6 或 AB002365_7A04v2 中之任一者之 V_L 域具有至少 80% 同一性的序列。在一些實施例中，包含該 DBA 的 V_H 及 V_L 域的該 scFv 包含：(a) AB002022_2B07v1、

AB002328_2B07v4、AB002360_7A04v1、AB002413_2A11v3、AB002342_2B07v5、AB002345_2B07v6 或 AB002365_7A04v2 中之任一者之重鏈 CDR；或 (b) AB002022_2B07v1、AB002328_2B07v4、AB002360_7A04v1、AB002413_2A11v3、AB002342_2B07v5、AB002345_2B07v6 或 AB002365_7A04v2 中之任一者之輕鏈 CDR。在一些實施例中，複合體包含 AF003864、AF003871、AF003872、AF003913、AF003918、AF003923、AF003927、AF004502、AF004503、AF004504、AF004505、AF004892 或 AF004893 中之任一者。在一些實施例中，複合體包含：(a) 根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[杵]-[連接子]-[IL-2]-C 的第一多肽，根據 N-[V_L]-[C_L]-C 的第二多肽，及根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[臼]-[連接子]-[scFv]-C 的第三多肽；或 (b) 根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[臼]-[連接子]-[IL-2]-C 的第一多肽，根據 N-[V_L]-[C_L]-C 的第二多肽，及根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[杵]-[連接子]-[scFv]-C 的第三多肽；其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示該 DBA 之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，VL 表示該 DBA 之輕鏈可變域，[鉸鏈] 表示免疫球蛋白之鉸鏈區，Fc[杵] 表示包含杵突變的免疫球蛋白之 Fc，Fc[臼] 表示包含臼突變的免疫球蛋白之 Fc 區，C_L 表示免疫球蛋白之輕鏈恆定域，且 [scFv] 表示該 DBA 之 scFv。在一些實施例中，複合體包含 AF004693、AF004695、AF004696、AF005416、AF005418 或 AF005419 中之任一者。在一些實施例中，複合體包含：(a) 根據 N-[V_H]-[C_H]-[het-鉸鏈]-Fc[杵]-[連接子]-[IL-2]-C 的第一多肽，根據 N-[V_L]-[C_L]-C 的第二多肽，及根據 N-[V_H]-[C_H]-[het-鉸鏈]-Fc[臼]-C 的第三多肽；或 (b) 根據 N- [V_H]-[C_H]-[het-鉸鏈]-Fc[臼]-[連接子]-[IL-2]-C 的第一多肽，根據 N-[V_L]-[C_L]-C 的第二多肽，及根據

N-[V_H]-[C_H]-[het-鉸鏈]-Fc[杵]-C 的第三多肽，其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示該 DBA 之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，V_L 表示該 DBA 之輕鏈可變域，[het 鉸鏈] 表示與該 Fc 區異源的鉸鏈區，Fc[杵] 表示包含杵突變的免疫球蛋白之 Fc，Fc[臼] 表示包含臼突變的免疫球蛋白之 Fc 區，且 C_L 表示免疫球蛋白之輕鏈恆定域。在一些實施例中，與該 Fc 區異源的鉸鏈區為：(a) 衍生自 IgG3 抗體的鉸鏈區，或 (b) 基於 G4S 的連接子。在一些實施例中，複合體包含 AF003632 或 AF003634。在一些實施例中，IL-2 肽包含野生型人類 IL-2 肽。在一些實施例中，IL-2 肽包含與人類 IL-2 具有至少約 80%、至少約 81%、至少約 82%、至少約 83%、至少約 84%、至少約 85%、至少約 86%、至少約 87%、至少約 88%、至少約 89%、至少約 90%、至少約 91%、至少約 92%、至少約 93%、至少約 94%、至少約 95%、至少約 96%、至少約 97%、至少約 98%、至少約 99% 或實質上 100% 序列同一性的序列。在一些實施例中，IL-2 肽包含人類 IL-2 的 R38、K43、E61、F42、Y45、L72、T3 或 C125 中之至少一者之突變。在一些實施例中，複合體包含 AF003232、AF003243、AF003246、AF003247、AF003341、AF003345、AF003632、AF003634、AF003644、AF003651、AF003652、AF003653、AF003657、AF003740、AF003744、AF003747、AF003749、AF003753、AF003864、AF003873、AF003876、AF003877、AF003913、AF003918、AF003923、AF003927、AF003930、AF003931、AF003933、AF003934、AF003935、AF003941、AF003945、AF003946、AF003947、AF003948、AF003951、AF003952、AF003953、AF003955、AF003956、AF004262、AF004265、AF004273、AF004276、AF004284、AF004287、

AF004295、AF004298、AF004385、AF004386、AF004387、AF004388、AF004389、AF004404、AF004405、AF004413、AF004414、AF004415、AF004416、AF004504、AF004505、AF004693、AF004695、AF004696、AF004771、AF004773、AF004892 或 AF004893 中之任一者。

【0004】在一些態樣中，本揭露提供一種增強 T 細胞對異源性細胞反應性之方法，該方法包含向有需要之個體投予本文所述之複合體中之任一者。在一些實施例中，異源性細胞為癌細胞。

【0005】在一些態樣中，本揭露提供一種治療有需要之個體之方法，該方法包含向有需要之個體投予請求項 [0162]1 至 [0162]32 中任一項之複合體。在一些實施例中，投予包含靜脈內、肌內或皮下投予。在一些實施例中，有需要之個體患有癌症。在一些實施例中，治療域治療有需要之個體。在一些實施例中，有需要之個體為哺乳動物。在一些實施例中，有需要之個體為人類。

【0006】在一些態樣中，本揭露提供一種組成物，該組成物包含編碼本文所述之複合體中之任一者的重組核酸。在一些態樣中，本揭露提供一種宿主細胞，該宿主細胞包含編碼本文所述之複合體中之任一者的重組核酸中之任一者。

在一些態樣中，本揭露提供一種醫藥組成物，該醫藥組成物包含本文所述之複合體中之任一者及醫藥上可接受之賦形劑。

【0007】在各種態樣中，本揭露提供一種複合體，該複合體包含：a) 治療域；b) 連接子；及 c) 感測器域，其中治療域為 IL-2 促效劑，該治療域藉由連接子與感測器域連接，且其中感測器域為能夠結合治療域 (IL-2 促效劑域) 及標記物的雙重結合抗體 (DBA)，其中標記物為 PD-1。

【0008】在一些態樣中，在不存在標記物的情況下，感測器域結合至治療域。在一些態樣中，在感測器域結合至標記物時，阻斷治療域與感測器域結合。在一些態樣中，在治療域結合至感測器域時，治療域的活性下降。在一些態樣中，在感測器域結合至標記物時，治療域能夠表現出治療活性。在一些態樣中，在感測器域結合至標記物時，治療域具有治療活性。

【0009】在一些態樣中，感測器域包含抗體。在一些態樣中，抗體為抗體片段或抗體衍生物。在一些態樣中，複合體包含 Fc 域。在一些態樣中，複合體包含改善動力學特性的域。在一些態樣中，複合體包括兩條重鏈及兩條輕鏈。

【0010】在一些態樣中，複合體包含兩個治療域。在一些態樣中，複合體包含兩個感測器域。在一些態樣中，複合體為經調節之治療性蛋白質。在一些態樣中，抗體或抗體片段包含 IgG、單域抗體片段、奈米抗體或單鏈可變片段 (scFv)。

【0011】在一些態樣中，治療域為 IL-2 受體促效劑。在一些態樣中，IL-2 受體促效劑為 IL-2、IL-15 或其變異體或融合體。在一些態樣中，治療域與感測器域結合。

【0012】在一些態樣中，連接子為多肽連接子。在一些態樣中，連接子包含 2 至 200 個胺基酸的長度。在一些態樣中，連接子係：接附至感測器域之重鏈，接附至感測器域之輕鏈，係與感測器域之 N 端之融合體，或係與感測器域之 C 端之融合體。在一些態樣中，連接子係：接附至治療域之重鏈、接附至治療域之輕鏈，係與治療域之 N 端之融合體，或係與治療域之 C 端之融合體。

【0013】在一些態樣中，當結合至感測器域時，治療域的活性下降。在一些態樣中，當結合至感測器域時，治療域無活性。在一些態樣中，當結合至治療域時，感測器域阻斷治療域的活性。在一些態樣中，當感測器域結合至標記物時，治療域具有活性。在一些態樣中，感測器域對標記物之親和力等於或大於感測器域對治療域之親和力。

【0014】在一些態樣中，感測器域對標記物之親和力比感測器域對治療域之親和力大至少 2 倍、5 倍、10 倍、100 倍、1000 倍、10000 倍或 100000 倍。

【0015】在一些態樣中，感測器域為抗體或其片段。在一些態樣中，感測器域包含雙特異性抗體之一個或兩個抗原結合域。在一些態樣中，雙特異性抗體包含能夠與治療域結合且能夠與標記物結合的第一抗原結合域，及能夠與標記物結合的第二抗原結合域。在一些態樣中，雙特異性抗體包含單一治療域。

【0016】在一些態樣中，感測抗體與 IL-2 受體促效劑或與 PD-1 結合。在一些態樣中，IL-2 受體促效劑為 IL-2、IL-15 或其變異體或融合體。

【0017】在一些態樣中，感測器域包含選自表 3、表 7、表 8 或表 19 的互補決定區 (CDR)。在一些態樣中，感測器域係選自**表 8 或表 18**。在一些態樣中，複合體係選自**表 15 或表 2A**。在一些態樣中，感測器域包含互補決定區，該互補決定區於選自表 3、表 7、表 8 或表 19 的互補決定區中之任一者具有至少 80%、至少 81%、至少 82%、至少 83%、至少 84%、至少 85%、至少 86%、至少 87%、至少 88%、至少 89%、至少 90%、至少 91%、至少 92%、至少 93%、至少 94%、至少 95%、至少 96%、至少 97%、至少 98%、至少 99%

或 100% 序列同一性。在一些態樣中，感測器域包含 V_H 或 V_L 域，該 V_H 或 V_L 域與表 8 或表 18 中列舉的 V_H 或 V_L 域中之任一者具有至少 80%、至少 81%、至少 82%、至少 83%、至少 84%、至少 85%、至少 86%、至少 87%、至少 88%、至少 89%、至少 90%、至少 91%、至少 92%、至少 93%、至少 94%、至少 95%、至少 96%、至少 97%、至少 98%、至少 99% 或 100% 序列同一性。在一些態樣中，感測器域包含互補決定區，該互補決定區與 SEQ ID NO: 1 至 SEQ ID NO: 20 或 SEQ ID NO: 142 至 SEQ ID NO: 173 或 SEQ ID NO: 238-252 中之任一者具有至少 80%、至少 81%、至少 82%、至少 83%、至少 84%、至少 85%、至少 86%、至少 87%、至少 88%、至少 89%、至少 90%、至少 91%、至少 92%、至少 93%、至少 94%、至少 95%、至少 96%、至少 97%、至少 98%、至少 99% 或 100% 序列同一性。在一些態樣中，感測器域與 SEQ ID NO: 21 至 SEQ ID NO: 27、SEQ ID NO: 31 至 SEQ ID NO: 39 或 SEQ ID NO: 127 至 SEQ ID NO: 141 中之任一者具有至少 80%、至少 85%、至少 90%、至少 95%、至少 97%、至少 99% 或 100% 序列同一性。在一些態樣中，蛋白複合體與 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181 至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至 261、SEQ ID NO: 266 至 282、SEQ ID NO: 289 至 293 中之任一者或其片段具有至少 80%、至少 85%、至少 90%、至少 95%、至少 97%、至少 99% 或 100% 序列同一性。

【0018】 在各種態樣中，本揭露提供一種方法，該方法包含向有需要之個體投予上述複合體中之任一者。在各種態樣中，本揭露提供一種治療有需要

之個體之方法，該方法包含向有需要之個體投予上述複合體中之任一者。在一些態樣中，投予包含靜脈內、肌內或皮下投予。在一些態樣中，有需要之個體患有癌症。在一些態樣中，治療域治療有需要之個體。在一些態樣中，有需要之個體為哺乳動物。在一些態樣中，有需要之個體為人類。

【0019】 在一些態樣中，本揭露提供可全身性遞送但可表現出減弱的全身性毒性的 IL-2 結合物。

【圖式簡單說明】

【0020】 本揭露之新穎特徵特別闡述於隨附申請專利範圍中。藉由參考以下闡述利用了本揭露之原理的說明性實施例的詳細描述，將獲得對本揭露之特徵和優點的更好理解，並且在附圖中：

圖 1A 及 1B 示出本揭露之蛋白複合體之示意圖。**圖 1A** 示出處於無活性狀態之示例性雙重結合蛋白複合體。該蛋白複合體具有感測器域及治療域。該感測器域及該治療域藉由連接子連接。該感測器域顯示為結合至治療域，使治療域無活性。**圖 1B** 示出處於活性狀態之示例性雙重結合蛋白複合體。該蛋白複合體具有感測器域及治療域。該感測器域及該治療域藉由連接子連接。該感測器域顯示為結合至標記物，使治療域具有活性。

圖 2 示出包含一個或多個感測器域及一個或多個治療域的本揭露之蛋白複合體。**圖 2A、2B、2C、2D、2E、2F、2G、2H 及 2I** 示出實例中所詳述之蛋白複合體之排列之示例示意圖。

圖 3 示出五種示例性 PD-1/IL-2 DBA-細胞激素蛋白複合體 (2_A08、2_A11、2_B05、2_B07 及 7_A04，分別為 SEQ ID NO: 67 至 SEQ ID NO: 68、SEQ ID NO: 69 至 SEQ ID NO: 70、SEQ ID NO: 71 至 SEQ ID NO: 72、SEQ ID NO: 73

至 SEQ ID NO: 74 及 SEQ ID NO: 75 至 SEQ ID NO: 76) 之 IL-2 傳訊與對照 IL-2-抗 HER2 蛋白複合體 (SEQ ID NO: 65 至 SEQ ID NO: 66) 相比有所下降。

圖 4A、4B、4C、4D、4E 及 4F 提供在用 PD-1-Fc 或 IgG1 對照蛋白塗覆的孔中，包含**圖 2B** 中所示之結構的蛋白複合體之 IL-2 活性。活性係作為來自 HEK-Blue™ IL-2 報導子細胞之 630 nm 訊息的增長來測量。**圖 4A 至 C** 提供三種不同 PD-1/IL-2 DBA-IL-2 複合體之 IL-2 活性。**圖 4D** 提供抗 PD-1 抗體-IL-2 複合體之活性。**圖 4E** 提供抗 Her-2 抗體-IL-2 複合體之活性。**圖 4F** 提供抗 IL-2 抗體-IL-2 複合體之活性。

圖 5A、5B、5C、5D、5E、5F、5G 及 5H 提供在用 PD-1-Fc 或 IgG1 對照蛋白塗覆的孔中，包含**圖 2H** 中所示之結構的蛋白複合體之 IL-2 活性。活性係作為來自 HEK-Blue™ IL-2 報導子細胞之 630 nm 訊息的增長來測量。**圖 5B 至 5D** 提供在 Fab 臂中包含抗 PD-1 域且在 Fc 臂上包含 PD-1/IL-2 DBA scFv 的兩種 PD-1/IL-2 DBA 複合體之結果。**圖 5A、5C** 及 **5E 至 5H** 提供對照蛋白複合體之結果。

圖 6 提供在野生型小鼠之血液中，PD-1/IL-2 DBA-細胞激素複合體 (2B07 IL-2 mut) 及兩種對照複合體之血清濃度下降之速率。

圖 7A、7B、7C 及 7D 提供從用 PD-1/IL-2 DBA-細胞激素複合體 (2B07 IL-2 mut) 及兩種對照複合體治療 5 天後的野生型小鼠中收集之血液及脾臟組織中之 $CD8^+$ T 細胞及 NK 細胞計數。

圖 8 提供小鼠中腫瘤體積測量結果作為在細胞植入後天數的函數。小鼠接受各種靜脈內劑量的 PD-1/IL-2 DBA-IL-2 複合體、缺乏 IL-2 的 PD-1/IL-2 DBA 複合體或同型對照。

圖 9 提供 IL-2RBG 與包含**圖 2E** 中所示之結構的對稱複合體之結合。

圖 10 提供 IL-2RBG 與包含**圖 2B** 中所示之結構的不對稱複合體之結合。

圖 11 示出描繪顯示了藉由 PD-1/IL-2 DBA-細胞激素複合體及未經調節之對照複合體結合的*活體外* IL-2RBG 的圖，並比較了用兩種不同形式的IL-2 (包括 WT IL-2 及 IL-2 3x) 製成的複合體。**圖 11A** 示出 IL-2RBG 與具有野生型 IL-2 的複合體之結合，且**圖 11B** 示出 IL-2RBG 與具有 IL-2 3x 突變體的複合體之結合。

圖 12A、12B、13A、13B、14A、14B、15 及 16 示出描繪在用 PD-1-Fc 或 IgG1 對照蛋白處理的細胞中包含**圖 2E、2B、2H、2G 及 2I** 中所示之結構的 IL-2-連接蛋白複合體之 IL-2 活性的圖。活性係作為來自 HEK-Blue™ IL-2 報導子細胞 (一種經工程化改造的人類腎細胞株，在其 IL-2 受體活化後產生可偵測之顏色變化) 之 630 nm 訊息的增長來測量。

圖 17 示出描繪在用 PD-1-Fc 或 IgG1 對照蛋白處理的細胞中包含**圖 2H** 中所示之結構與人類 Fc 域的 IL-2-連接蛋白複合體之 IL-2 活性的圖。活性係作為來自 HEK-Blue™ IL-2 報導子細胞 (一種經工程化改造的人類腎細胞株，在其 IL-2 受體活化後產生可偵測之顏色變化) 之 630 nm 訊息的增長來測量。

圖 18 示出描繪包含**圖 2B** 中所示之結構與 IL-2 3x 變異體的蛋白複合體中之 IL-2 活性的圖。

圖 19A、19B 及 19C 示出描繪在接種於用 PD-1-Fc 或 IgG1 對照蛋白塗覆的孔中之細胞中包含**圖 2H 中所示之結構與三種不同抗 PD-1 Fab 臂 (分別為納武利尤單抗、4C10 及 Knd)** 的 IL-2-3x-連接蛋白複合體之 IL-2 活性的圖。活性係作為來自 HEK-Blue™ IL-2 報導子細胞 (一種經工程化改造的人類腎細胞株，在其 IL-2 受體活化後產生可偵測之顏色變化) 之 630 nm 訊息的增長來測量。

圖 20 示出描繪包含**圖 2B** 中所示之結構與具有變化的長度的連接子的 IL-2-連接蛋白複合體之 IL-2 活性的圖。複合體係於用 PD-1-Fc 或 IgG1 對照蛋白塗覆的孔中測試。活性係作為來自 HEK-Blue™ IL-2 報導子細胞 (一種經工程化改造

的人類腎細胞株，在其 IL-2 受體活化後產生可偵測之顏色變化) 之 630 nm 訊息的增長來測量。

圖 21A 及 21B 示出描繪如藉由流式細胞分析技術所測量之 PD-1/IL-2 DBA-細胞激素複合體在人類初代 CD8+ T 細胞中對 STAT5 磷酸化之 PD-1 依賴性誘導的圖。

圖 22A 及 22B 示出描繪如藉由顆粒酶 B 釋放所評定之混合淋巴球反應中 PD-1/IL-2 DBA-細胞激素複合體對人類 T 細胞活化之調節的圖。

圖 23A 及 23B 示出描繪同基因腫瘤模型中 PD-1/IL-2 DBA-細胞激素複合體對抗腫瘤免疫之調節的圖。將 500,000 個 MC38 腫瘤細胞皮下植入人類 PD-1 剔入小鼠體內，並將小鼠用複合體進行靜脈內治療，並評估腫瘤體積。

【實施方式】

藉由引用方式併入

【0021】 本說明書中提及的所有出版物、專利及專利申請案均藉由引用方式併入本文，其程度就如同每個單獨的出版物、專利或專利申請案被具體地和單獨地指示為藉由引用方式併入一樣。

序列表

【0022】 本申請包含序列表，該序列表已經以 XML 格式以電子方式提交，並以引用方式以其全部內容併入本文。該 XML 複本創建於 2022 年 11 月 14 日，命名為 51177-046TW2_Sequence_Listing_11_14_22，且大小為 634,137 位元組。

【0023】 本揭露提供蛋白複合體之組成物及其使用方法。介白素 2 治療藥物往往由於全身性靶向毒性而無法實現。本文提供蛋白複合體，其特異性地

表現出對 PD-1 陽性細胞、具體地為經歷過抗原的 T 細胞之治療功效。此外，本揭露之蛋白複合體為自調節的，在不存在 PD-1 的情況下保持無活性，並在結合至 PD-1 時活化。本文所揭露之蛋白複合體可包括經由連接子與 IL-2 受體促效劑 (治療域) 連接的感測器域 (例如，抗體、Fab 或 scFv)。感測器域可以為雙重結合抗體，該雙重結合抗體具有對治療域及對 PD-1 的親和力，使得 PD-1 及治療域競爭結合感測器域。在不存在 PD-1 的情況下，感測器域結合治療域，使該治療域在 IL-2 受體上無法發揮活性。當感測器域結合至 PD-1 時，治療域係未結合的，並且可以發揮活性。在一些實施例中，藉由複合體對 IL-2 受體促效劑活性之調節可以為可逆的，亦即，當感測器域從 PD-1 解離時，該感測器域可以結合治療域，使該治療域再次無法發揮活性。因此，本揭露之蛋白複合體包含感測器域，該感測器域在存在 PD-1 的情況下調節 IL-2 受體促效劑域、結合 PD-1 並使 IL-2 受體促效劑域具有活性。本文揭示了蛋白複合體的各種結構及組成物，包括醫藥調配物。再者，本文提供藉由向有需要之個體投予蛋白複合體來治療該個體之方法。

【0024】 如本文所用，「感測器域」通常係指能夠結合 PD-1 並結合 IL-2 受體促效劑的雙重結合抗體。

【0025】 如本文所用，「治療域」通常係指 IL-2 受體促效劑。治療域的非限制性實例包括 IL-2、IL-15 或以類似於 IL-2 的方式作用於 IL-2 受體的任何其他分子。

【0026】 如本文所用，「標記物」通常係指 PD-1 蛋白。

【0027】 如本文所用，「抗體」通常係指抗體、抗體衍生物、或其含有抗體可變域的一部分或全部的一個或多個片段。

【0028】術語「重組核酸」通常係指具有非天然存在之核苷酸序列的合成核酸。重組核酸可以在實驗室中合成。重組核酸係藉由使用重組 DNA 技術藉由使用 DNA 之酶修飾諸如酶限制性酶切、連接、DNA 選殖來製備。如本文所用之重組核酸可為 DNA 或 RNA。重組 DNA 可以在活體外轉錄，以產生信使 RNA (mRNA)，重組 mRNA 可以被分離、純化並用於轉染細胞。重組核酸可以編碼蛋白質或多肽。重組核酸在合適的條件下可被摻入活細胞中，並且可在活細胞內表現。如本文所用，核酸之「表現」通常係指核酸之轉錄及/或翻譯。核酸表現之產物通常為蛋白質，但亦可以為 mRNA。在摻入重組核酸的細胞中偵測由重組核酸編碼之 mRNA，被視為核酸在細胞中「表現」的確證。

【0029】如本文所用，術語「治療域」通常係指具有最小序列特徵以活化細胞或生物體中給定治療活性的蛋白質域。在其中治療域為配體-受體對中之配體的情況下，該配體具有最小序列和/或結構特徵以允許結合至或活化受體。

【0030】將核酸插入或摻入細胞的過程可經由轉化、轉染或轉導進行。轉化係由細菌細胞吸收外來核酸的過程。該過程適用於質粒 DNA 之增殖、蛋白質生產及其他應用。轉化將重組質粒 DNA 引入有能力的細菌細胞中，這些細菌細胞從環境中吸收細胞外 DNA。一些細菌物種在某些環境條件下具有天然能力，但在實驗室環境中人工誘導其能力。轉染係將小分子諸如 DNA、RNA 或抗體強行引入真核細胞中。容易混淆的是，「轉染」亦指將噬菌體引入細菌細胞中。「轉導」主要用於描述將重組病毒載體顆粒引入標靶細胞中，而「感染」係指人類或動物自然感染野生型病毒。

蛋白複合體

【0031】本揭露提供可自調節 IL-2 受體促效劑活性的複合體。本揭露之蛋白複合體可包括具有對 PD-1 之親和力及對 IL-2 受體促效劑 (「感測器域」) 及 IL-2 受體促效劑 (「治療域」) 之親和力的雙重結合抗體。感測器域及治療域可藉由連接子連接。感測器域可調節治療域之活性。對治療域之活性之調節亦可包括感測器域與治療域結合，使該治療域無法對 IL-2 受體發揮活性。對治療域之活性之調節亦可包括在感測器域與 PD-1 結合時由感測器域脫離治療域或釋放治療域。因此，本揭露之蛋白複合體係優異的候選藥物，因為 IL-2 受體促效劑之感測器域依賴性活性支持細胞特異性活性，即使在全身性投予該蛋白複合體時亦如此。與以其自身投予之 IL-2 受體促效劑相比，本揭露之蛋白複合體表現出經調節之治療活性。因此，與以其自身投予之游離 IL-2 受體促效劑相比，本揭露之蛋白複合體表現出降低之全身性靶向毒性。

【0032】本揭露之蛋白複合體可具有 Fc 區。本揭露之蛋白複合體可具有改善動力學特性的域。例如，本揭露之蛋白複合體可進一步連接至半衰期延長劑，諸如 Fc 區、白蛋白、PEG 或另一種兩性離子性聚合物。本揭露之蛋白複合體可具有兩條重鏈及兩條輕鏈。本揭露之蛋白複合體可具有兩條重鏈及一條輕鏈。本揭露之蛋白複合體可包括多個感測器域及多個治療域。例如，本揭露之蛋白複合體可包括兩個感測器域及兩個治療域，其全部連接且其中該等兩個治療域結合至該等兩個感測器域。在一些實施例中，本揭露之蛋白複合體可包括兩個感測器域及一個治療域，其全部連接且其中治療域可結合至兩個感測器域或該等兩個感測器域中僅一者。

【0033】在一些實施例中，PD-1 可以為表面蛋白，諸如細胞表面蛋白。在一些實施例中，PD-1 可以在經歷過抗原的 T 細胞上表現。

【0034】在一些實施例中，IL-2 受體促效劑可以為 IL-2、IL-2 之變異體或 IL-2 之截短型式。在一些實施例中，IL-2 受體促效劑可以為 IL-15、IL-15-sushi、Il-15 之變異體或 IL-15-sushi 之變異體。在一些實施例中，IL-2 受體促效劑可以為經工程化改造或設計之肽，其結合 IL2 受體 β 及 IL-2 受體 γ。在一些實施例中，IL-2 受體促效劑可以為結合 IL2 受體 β 及 IL-2 受體 γ 的抗體。

【0035】在一些實施例中，感測器域與治療域之結合相比於感測器域與 PD-1 之結合係藉由感測器域對治療域之相對親和力來調節。在一些實施例中，感測器域具有的與 PD-1 之解離常數 (Kd) 可低於該感測器域與治療域之解離常數 (Kd)。因此，感測器具有的對 PD-1 的親和力可高於對治療域的親和力 (更低之的 Kd)。本揭露之感測器域可以經工程化改造，例如藉由親和力成熟，以對 PD-1 具有比對治療域更高之親和力 (更低之解離常數)。在不存在標記物的情況下，本揭露之感測器域可以對治療域具有足夠高的親和力，使得該治療域由感測器域結合。在存在標記物的情況下，感測器域對 PD-1 之親和力足夠高 (低解離常數)，使得 PD-1 在結合至感測器域方面勝過治療域。因此，平衡結合從其中感測器域結合至 IL-2 受體促效劑域的狀態轉變為其中 IL-2 受體促效劑域未結合且感測器域結合 PD-1 的狀態。

【0036】感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 2 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 5 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 10 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 15 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 20 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 25 倍。感測器域具有

的對 PD-1 之親和力可以為對治療域之親和力的至少 30 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 35 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 40 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 45 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 50 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 60 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 70 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 80 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 90 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 100 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 150 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 200 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 250 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 300 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 350 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 400 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 450 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 500 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 1000 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 10000 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的至少 100000 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 2 至 10 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 10 至 20 倍。感

測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 20 至 30 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 30 至 40 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 40 至 50 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 50 至 100 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 100 至 150 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 150 至 200 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 200 至 250 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 250 至 300 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 300 至 350 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 350 至 400 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 400 至 450 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 450 至 500 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 500 至 1000 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 10 至 80 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 30 至 70 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 40 至 60 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 20 至 50 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 10 至 1000 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 70 至 500 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 100 至 500 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 500 至 750 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 250 至 750 倍。感測器域具有的對 PD-1 之

親和力可以為對治療域之親和力的 1000 至 100000 倍。感測器域具有的對 PD-1 之親和力可以為對治療域之親和力的 2 至 100000 倍。

【0037】本揭露之蛋白複合體或其片段可包含一個或多個與本文所揭露之 CDR 中之任一者具有至少約 80%、至少約 81%、至少約 82%、至少約 83%、至少約 84%、至少約 85%、至少約 86%、至少約 87%、至少約 88%、至少約 89%、至少約 90%、至少約 91%、至少約 92%、至少約 93%、至少約 94%、至少約 95%、至少約 96%、至少約 97%、至少約 98%、至少約 99% 或實質上 100% 序列同一性的互補決定區 (CDR)。本揭露之蛋白複合體或其片段可包含一個或多個與本文所述之重鏈或輕鏈可變區中之任一者具有至少約 80%、至少約 81%、至少約 82%、至少約 83%、至少約 84%、至少約 85%、至少約 86%、至少約 87%、至少約 88%、至少約 89%、至少約 90%、至少約 91%、至少約 92%、至少約 93%、至少約 94%、至少約 95%、至少約 96%、至少約 97%、至少約 98%、至少約 99% 或實質上 100% 序列同一性的重鏈或輕鏈可變區。例如，本揭露之蛋白複合體或其片段可包含一個或多個與 SEQ ID NO: 1 至 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 中之任一者具有至少 80% 序列同一性的 CDR。本揭露之蛋白複合體或其片段可包含一個或多個與 SEQ ID NO: 1 至 SEQ ID NO: 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 中之任一者具有至少 85% 序列同一性的 CDR。本揭露之蛋白複合體或其片段可包含一個或多個與 SEQ ID NO: 1 至 SEQ ID NO: 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 中之任一者具有至少 90% 序列同一性的 CDR。本揭露之蛋白複合體或其片段可包含一個或多個與 SEQ ID NO: 1 至 SEQ ID NO: 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 中之任一者

具有至少 92% 序列同一性的 CDR。本揭露之蛋白複合體或其片段可包含一個或多個與 SEQ ID NO: 1 至 SEQ ID NO: 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 中之任一者具有至少 95% 序列同一性的 CDR。本揭露之蛋白複合體或其片段可包含一個或多個與 SEQ ID NO: 1 至 SEQ ID NO: 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 中之任一者具有至少 97% 序列同一性的 CDR。本揭露之蛋白複合體或其片段可包含一個或多個與 SEQ ID NO: 1 至 SEQ ID NO: 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 中之任一者具有至少 99% 序列同一性的 CDR。本揭露之蛋白複合體或其片段可包含一個或多個具有 SEQ ID NO: 1 至 SEQ ID NO: 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 中之任一者的 CDR。

【0038】 蛋白複合體或其片段可與 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181 至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至 261、SEQ ID NO: 266 至 282 或 SEQ ID NO: 289 至 293 中之任一者或其片段具有至少 80% 序列同一性。蛋白複合體可與 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181 至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至 261、SEQ ID NO: 266 至 282 或 SEQ ID NO: 289 至 293 中之任一者或其片段具有至少 85% 序列同一性。蛋白複合體可與 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181

至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至 261、SEQ ID NO: 266 至 282 或 SEQ ID NO: 289 至 293 中之任一者或其片段具有至少 90% 序列同一性。蛋白複合體可與 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181 至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至 261、SEQ ID NO: 266 至 282 或 SEQ ID NO: 289 至 293 中之任一者或其片段具有至少 92% 序列同一性。蛋白複合體可與 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181 至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至 261、SEQ ID NO: 266 至 282 或 SEQ ID NO: 289 至 293 中之任一者或其片段具有至少 95% 序列同一性。蛋白複合體可與 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181 至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至 261、SEQ ID NO: 266 至 282 或 SEQ ID NO: 289 至 293 中之任一者或其片段具有至少 97% 序列同一性。蛋白複合體可與 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181 至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至

261、SEQ ID NO: 266 至 282 或 SEQ ID NO: 289 至 293 中之任一者或其片段具有至少 99% 序列同一性。蛋白複合體為 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181 至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至 261、SEQ ID NO: 266 至 282 或 SEQ ID NO: 289 至 293 中之任一者或其片段。

【0039】 本揭露之蛋白複合體可與 SEQ ID NO: 41、SEQ ID NO: 44、SEQ ID NO: 80 至 SEQ ID NO: 112、SEQ ID NO: 174 至 175、SEQ ID NO: 181 至 182、SEQ ID NO: 195 至 196、SEQ ID NO: 205 至 206、SEQ ID NO: 210 至 212、SEQ ID NO: 220 至 223、SEQ ID NO: 226 至 231、SEQ ID NO: 259 至 261、SEQ ID NO: 266 至 282 或 SEQ ID NO: 289 至 293 中之任一者或其片段具有至少 95% 序列同一性，並具有一個或多個與任一 SEQ ID NO: 1 至 SEQ ID NO: 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 具有至少 80% 序列同一性的 CDR。本揭露之蛋白複合體可具有選自以任意組合或順序排列之 SEQ ID NO: 1 至 SEQ ID NO: 20、SEQ ID NO: 142 至 173 或 SEQ ID NO: 238 至 252 的 CDR。

【0040】 以上任一者之片段可保留感測器之功能結合域或治療域或治療藥物之任意功能治療域。例如，雙重結合抗體蛋白複合體可包括整個抗體或具有能夠結合至標記物及治療域的抗體之區域的片段。在後一種情況下，該片段可以為可結合至標記物及治療域的 scFv。本揭露之蛋白複合體之示例性序列如以下**表 1** 中所示。

表 1 – 示例性蛋白複合體

SEQ ID NO	序列	說明
SEQ ID NO: 769	QVQLVESGGGVVQPGRSLRLDCKASGITFSN SGMHWVRQAPGKGLEWVAVIWYDGSKRYY ADSVKGRFTISRDNSKNTLFLQMNSLRAEDT AVYYCATNDDYWGQGTLVTVSSAKTTAPSV YPLAPVCGDTTGSSVTLGCLVKGYFPEPVTL TWNSGSLSSGVHTFPAVLQSDLYTLSSSVTV TSSTWPSQSITCNVAHPASSTKVDKKIEPRGP TIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLM ISLSPIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQDWM SGKEFKCKVNNKDLGAPIERTISKPKGSVRAP QVYVLPPPEKEMTKKQVSLTCLVKDFMPEDI YVEWTNNGKTELNYKNTEPVLKSDGSYFMY SKLTVEKKNWVERNSYSCSVVHEGLHNHHT TKSFSRTPGGGGGSGGGGSGGGGSGGGGSQ VQLVQSGAEVKKPGASVKVSCKASGDTFTR YYVHWVRQAPGQGLEWMGIINPSGGYASYA QKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCAAGLFIWGQGTLVTVSSASGGGGSGG GGSGGGGSHASDIQMTQSPSSLSASVGDRVTI TCRASQSIGRWLAWYQQKPGKAPKLLIYSAS NLETGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIK	PD1-IL2_3x_Cterm_Nivo_2B07_H_H37Y_L_A107Y_S109R； AF4695_pep2
SEQ ID NO: 759	QVQLVESGGGVVQPGRSLRLDCKASGITFSN SGMHWVRQAPGKGLEWVAVIWYDGSKRYY ADSVKGRFTISRDNSKNTLFLQMNSLRAEDT AVYYCATNDDYWGQGTLVTVSSAKTTAPSV YPLAPVCGDTTGSSVTLGCLVKGYFPEPVTL TWNSGSLSSGVHTFPAVLQSDLYTLSSSVTV TSSTWPSQSITCNVAHPASSTKVDKKIEPRGP TIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLM ISLSPIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQDWM SGKEFKCKVNNKDLGAPIERTISKPKGSVRAP QVYVLPPPEEEMTKKQVTLTCMVTDFMPEDI YVEWTNNGKTELNYKNTEPVLDSDGSYFMY SDLRVEKKNWVERNSYSCSVVHEGLHNHHT TESFSRTPGGGGGSGGGGSGGGGSAPTSSST KKTQLQLEHLLLDLQMILNGINNYKNPKLTD MLTFEFYMPKKATELKHLQCLERELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVEFLNRWITFCQSIISTLT	PD1-IL2_3x_Cterm_Nivo_2B07_H_H37Y_L_A107Y_S109R； AF4695_pep1 及 AF4696_pep1

SEQ ID NO	序列	說明
SEQ ID NO: 745	EIVLTQSPATLSLSPGERATLSCRASQSVSSYL AWYQQKPGQAPRLLIYDASNRATGIPARFSG SGSGTDFTLTISSLEPEDFAVYYCQQSSNWPR TFGQGTKVEIKRADAAPTVSIFPPSSEQLTSG GASVVCFLNNFYPKDINVKWKIDGSERQNG VLNSWTDQDSKDSTYSMSSTLTLTKDEYERH NSYTCEATHKTSTSPIVKSFNRNEC	PD1-IL2_3x_Cterm_Nivo_2B07_H_H37Y_L_A107Y_S109R； AF4695_pep3 及 AF4695_pep3
SEQ ID NO: 770	QVQLVESGGGVVQPGRSLRLDCKASGITFSN SGMHWVRQAPGKGLEWVAVIWYDGSKRYY ADSVKGRFTISRDNSKNTLFLQMNSLRAEDT AVYYCATNDDYWGQGTLVTVSSAKTTAPSV YPLAPVCGDTTGSSVTLGCLVKGYFPEPVTL TWNSGSLSSGVHTFPAVLQSDLYTLSSSVTV TSSTWPSQSITCNVAHPASSTKVDKKIEPRGP TIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLM ISLSPIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQDWM SGKEFKCKVNNKDLGAPIERTISKPKGSVRAP QVYVLPPPEKEMTKKQVSLTCLVKDFMPEDI YVEWTNNGKTELNYKNTEPVLKSDGSYFMY SKLTVEKKNWVERNSYSCSVVHEGLHNHHT TKSFSRTPGGGGSGGGGSGGGGSGGGGSQ VQLVQSGAEVKKPGASVKVSCKASGYTFTR YYMHWVRQAPGQGLEWMGIINPRAGYTSY ALKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCTSGWDVWGQGTLVTVSSASGGGGS GGGGSGGGGSHASDIQMTQSPSSLSASVGDR VTITCRASQSISTWLAWYQQKPGKAPKLLIY AASSLDSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSYSFPVTFGQGTKVEIK	PD1-IL2_3x_Cterm_Nivo_704var AF4696_pep2
SEQ ID NO: 181	APTSSSTKKTQLQLEHLLLDLQMILNGINNYK NPKLTDMLTFEFYMPKKATELKHLQCLEREL KPLEEVLNLAQSKNFHLRPRDLISNINVIVLEL KGSETTFMCEYADETATIVEFLNRWITFCQSII STLTGGGGSGGGGSGGGGSGGGGSQVQLVQ SGAEVKKPGASVKVSCKASGDTFTRYYVHW VRQAPGQGLEWMGIINPSGGYASYAQKFQG RVTMTRDTSTSTVYMELSSLRSEDTAVYYCA AGLFIWGQGTLVTVSSAKTTAPSVYPLAPVC GDTTGSSVTLGCLVKGYFPEPVTLTWNSGSL	PD1-IL2_3x_Asym_PD1-IL2_2B07_H_H37Y_L_W38Y_A107Y AF4386_pep1

SEQ ID NO	序列	說明
	SSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQ SITCNVAHPASSTKVDKKIEPRGPTIKPCPPCK CPAPNAAGGPSVFIFPPKIKDVLMISLSPIVTC VVVDVSEDDPDVQISWFVNNVEVHTAQTQT HREDYNSTLRVVSALPIQHQDWMSGKEFKC KVNNKDLGAPIERTISKPKGSVRAPQVYVLPP PEEEMTKKQVTLTCMVTDFMPEDIYVEWTN NGKTELNYKNTEPVLDSDGSYFMYSDLRVE KKNWVERNSYSCSVVHEGLHNHHTTESFSR TPGK	
SEQ ID NO: 182	QVQLVQSGAEVKKPGASVKVSCKASGDTFT RYYVHWVRQAPGQGLEWMGIINPSGGYASY AQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCAAGLFIWGQGTLVTVSSAKTTAPSVY PLAPVCGDTTGSSVTLGCLVKGYFPEPVTLT WNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTS STWPSQSITCNVAHPASSTKVDKKIEPRGPTI KPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMIS LSPIVTCVVVDVSEDDPDVQISWFVNNVEVH TAQTQTHREDYNSTLRVVSALPIQHQDWMS GKEFKCKVNNKDLGAPIERTISKPKGSVRAP QVYVLPPPEKEMTKKQVSLTCLVKDFMPEDI YVEWTNNGKTELNYKNTEPVLKSDGSYFMY SKLTVEKKNWVERNSYSCSVVHEGLHNHHT TKSFSRTPGGGGSGGGSHHHHHH	PD1-IL2_3x_Asym_PD1-IL2_2B07_H_H37Y_L_W38Y_A107Y AF4386_pep2
SEQ ID NO: 212	DIQMTQSPSSLSASVGDRVTITCRASQSIGRY LAWYQQKPGKAPKLLIYSASNLETGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQYNSFP VTFGPGTKVDIKRADAAPTVSIFPPSSEQLTS GGASVVCFLNNFYPKDINVKWKIDGSERQN GVLNSWTDQDSKDSTYSMSSTLTLTKDEYER HNSYTCEATHKTSTSPIVKSFNRNEC	PD1-IL2_3x_Asym_PD1-IL2_2B07_H_H37Y_L_W38Y_A107Y AF4386_pep3
SEQ ID NO: 183	APTSSSTKKTQLQLEHLLLDLQMILNGINNYK NPKLTDMLTFEFYMPKKATELKHLQCLEREL KPLEEVLNLAQSKNFHLRPRDLISNINVIVLEL KGSETTFMCEYADETATIVEFLNRWITFCQSII STLTGGGGSGGGGSGGGGSGGGGSQVQLVQ SGAEVKKPGASVKVSCKASGYTFTDYYMH WVRQAPGQGLEWMGIINPRAGYTSYALKFQ	PD1-IL2_3x_Asym_PD1-IL2_7A04_H_M115W_L_Q68D AF4387_pep1

SEQ ID NO	序列	說明
	GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC TSGWDVWGQGTLVTVSSAKTTAPSVYPLAP VCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWP SQSITCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIV TCVVVDVSEDDPDVQISWFVNNVEVHTAQT QTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYV LPPPEEEMTKKQVTLTCMVTDFMPEDIYVEW TNNGKTELNYKNTEPVLDSDGSYFMYSDLR VEKKNWVERNSYSCSVVHEGLHNHHTTESF SRTPGK	
SEQ ID NO: 184	QVQLVQSGAEVKKPGASVKVSCKASGYTFT DYYMHWVRQAPGQGLEWMGIINPRAGYTS YALKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCTSGWDVWGQGTLVTVSSAKTTAPS VYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVT VTSSTWPSQSITCNVAHPASSTKVDKKIEPRG PTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVL MISLSPIVTCVVVDVSEDDPDVQISWFVNNV EVHTAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPKGSV RAPQVYVLPPPEKEMTKKQVSLTCLVKDFM PEDIYVEWTNNGKTELNYKNTEPVLKSDGSY FMYSKLTVEKKNWVERNSYSCSVVHEGLHN HHTTKSFSRTPGGGGSGGGSHHHHHH	PD1- IL2_3x_Asym_PD1- IL2_7A04_H_M115 W_L_Q68D AF4387_pep2
SEQ ID NO: 185	DIQMTQSPSSLSASVGDRVTITCRASQSISTW LAWYQQKPGKAPKLLIYAASSLDSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQSYSFP VTFGQGTKVEIKRADAAPTVSIFPPSSEQLTS GGASVVCFLNNFYPKDINVKWKIDGSERQN GVLNSWTDQDSKDSTYSMSSTLTLTKDEYER HNSYTCEATHKTSTSPIVKSFNRNEC	PD1- IL2_3x_Asym_PD1- IL2_7A04_H_M115 W_L_Q68D AF4387_pep3

A. 感測器域

【0041】本揭露之蛋白複合體包括感測器域，該感測器域包含具有對 PD-1 之親和力及對 IL-2 受體促效劑之親和力的雙重結合抗體。感測器域可以為能

夠感測第一部分之存在並調節第二部分的任何蛋白質，其中第一部分為 PD-1 且第二部分為 IL-2 受體促效劑。例如，本揭露提供感測器域，該感測器域可以為能夠結合第一部分並結合且阻斷第二部分之活性的抗體或抗體片段，其中第一部分為 PD-1 且第二部分為 IL-2 或其他 IL-2 受體促效劑。在不存在第一部分的情況下，感測器域結合第二部分。如果將第一部分引入該系統中，則感測器域結合第一部分且脫離第二部分。因此，第二部分之結合及脫離係可逆的。感測器域藉由結合 IL-2 受體促效劑域並阻止其結合至其標靶 (IL-2 受體) 來去活化或阻斷 IL-2 受體促效劑域之活性。感測器域藉由在結合 PD-1 時釋放 IL-2 受體促效劑域以作用於其標靶來調節該 IL-2 受體促效劑域。

【0042】 在一些實施例中，感測器域為雙重結合抗體。雙重結合抗體可能能夠結合 PD-1 及 IL-2 受體促效劑域。本揭露之雙重結合抗體可經選擇或經工程化改造為結合 PD-1 及治療域。與 IL-2 受體促效劑域相比，雙重結合蛋白質對 PD-1 可具有更高之親和力。雙重結合蛋白質可以為親和力成熟的，以與 IL-2 受體促效劑域相比，對 PD-1 具有更高之親和力。

【0043】 在一些實施例中，感測器域為抗體。感測器域亦可為抗體之片段。符合本文所揭露之感測器域的抗體之片段保留其表現出對 PD-1 及 IL-2 受體促效劑域兩者的雙重結合的能力。雙特異性抗體的域中之一者或兩者可以為本揭露之蛋白複合體之感測器域。在使用雙特異性抗體的情況下，雙特異性抗體可包括可以結合 IL-2 受體促效劑域及 PD-1 的第一抗原結合域，並且亦可包括能夠結合 PD-1 的第二抗原結合域。

【0044】 在一些實施例中，感測器域為抗 PD1 抗體或其片段 (例如，結合 PD1 或 PD-L1 的 scFv)。

B. 治療域

【0045】 本揭露之蛋白複合體包括包含 IL-2 受體促效劑的治療域。本揭露之治療域經由連接子連接至感測器域以形成蛋白複合體。治療域可藉由結合至 IL-2 受體來發揮治療活性。

【0046】 在一些實施例中，本揭露之蛋白複合體包含治療域，該治療域包含 IL-2 或該細胞激素的變異體或融合體。治療域亦可為上述部分之片段。片段保留結合至其標靶 (例如，IL-2 受體) 所需之部分之功能區及活性所需之任何功能區。

【0047】 在一些實施例中，本揭露之蛋白複合體包含治療域，該治療域包含 IL-15 或該細胞激素的變異體或融合體。治療域亦可為上述部分之片段。片段保留結合至其標靶 (例如，IL-2 受體) 所需之部分之功能區及活性所需之任何功能區。

【0048】 在一些實施例中，本揭露之蛋白複合體包含治療域，該治療域包含能夠結合 IL-2 受體 β 及 IL-2 受體 γ 的肽及經工程化改造之蛋白質或抗體。治療域亦可為上述部分之片段。片段保留結合至其標靶 (例如，IL-2 受體) 所需之部分之功能區及活性所需之任何功能區。

C. 連接子

【0049】 本文所揭露之蛋白複合體可包含連接子。該連接子可連接兩個域，諸如感測器域及治療域。各種連接子符合本揭露之蛋白複合體。在一些實施例中，連接子可以為胺基酸連接子或化學連接子。

【0050】 連接子可以為穩定的連接子。例如，連接子可以維持治療域與感測器域之間的連接，即使在感測器域與標記物結合的情況下，從而使治療域

脫離感測器域。例如，儘管感測器域可能脫離治療域，但治療域可保持經由連接子連接至感測器域。符合該活性的連接子的實例可包括不可切割連接子。

【0051】 連接子亦可為可撓性連接子。可撓性連接子為足夠長以允許治療域在其脫離感測器域時結合至 IL-2 受體。連接子之可撓性可能影響治療功效。例如，在感測器域與 PD-1 結合並脫離治療域時，治療域需要能夠遭遇並結合其標靶 IL-2 受體。若連接子之可撓性不足以允許治療域結合 IL-2 受體，則治療功效可能下降或無法發揮。當連接子具有可撓性時，治療域可能能夠結合 IL-2 受體並發揮高治療功效。連接子之可撓性可以由連接子的長度引起。例如，短連接子可以在空間上阻礙治療域與 IL-2 受體結合。較長之連接子可使蛋白複合體具有更高之可撓性，並允許治療域結合 IL-2 受體。在一些實施例中，過長之連接子可能影響感測器域結合治療域之活性並在不存在 PD-1 的情況下抑制活性。在一些實施例中，過長之連接子可能影響蛋白質治療域之穩定性或蛋白質治療域在*活體內*之半衰期。

【0052】 在一些實施例中，連接子可接附至感測器域之重鏈或感測器域之輕鏈。連接子可融合至感測器域之 N 端或 C 端。在一些實施例中，連接子可以與 IL-2 受體促效劑域之 N 端或 C 端融合。例如，連接子可接附至 scFV 或 ScFab 之 N 端或 C 端。

【0053】 **胺基酸連接子。**胺基酸連接子可包含任何胺基酸殘基。在一些實施例中，有利的胺基酸殘基為熵可撓性的胺基酸殘基。本揭露之胺基酸連接子中有利的個胺基酸殘基可包括甘胺酸及絲胺酸。其他有利的個胺基酸殘基可包括丙胺酸、脯胺酸、蘇胺酸及麩胺酸。在較佳的實施例中，胺基酸連接子可包含 3 至 60 個胺基酸殘基的長度。在一些實施例中，胺基酸連接子可包含 20

個胺基酸殘基。在一些實施例中，胺基酸連接子可包含 40 個胺基酸殘基。在一些實施例中，胺基酸連接子可包含 60 個胺基酸殘基。在一些實施例中，胺基酸連接子可包含 80 個胺基酸殘基。胺基酸連接子可包含至少 5 個胺基酸殘基。胺基酸連接子可包含至少 10 個胺基酸殘基。胺基酸連接子可包含至少 15 個胺基酸殘基。胺基酸連接子可包含至少 20 個胺基酸殘基。胺基酸連接子可包含至少 25 個胺基酸殘基。胺基酸連接子可包含至少 30 個胺基酸殘基。胺基酸連接子可包含至少 35 個胺基酸殘基。胺基酸連接子可包含至少 40 個胺基酸殘基。胺基酸連接子可包含至少 45 個胺基酸殘基。胺基酸連接子可包含至少 50 個胺基酸殘基。胺基酸連接子可包含至少 55 個胺基酸殘基。胺基酸連接子可包含至少 60 個胺基酸殘基。胺基酸連接子可包含至少 65 個胺基酸殘基。胺基酸連接子可包含至少 70 個胺基酸殘基。胺基酸連接子可包含至少 75 個胺基酸殘基。胺基酸連接子可包含至少 80 個胺基酸殘基。胺基酸連接子可包含至少 85 個胺基酸殘基。胺基酸連接子可包含至少 90 個胺基酸殘基。胺基酸連接子可包含至少 95 個胺基酸殘基。胺基酸連接子可包含至少 100 個胺基酸殘基。胺基酸連接子可包含至少 110 個胺基酸殘基。胺基酸連接子可包含至少 120 個胺基酸殘基。胺基酸連接子可包含至少 130 個胺基酸殘基。胺基酸連接子可包含至少 140 個胺基酸殘基。胺基酸連接子可包含至少 150 個胺基酸殘基。胺基酸連接子可包含至少 160 個胺基酸殘基。胺基酸連接子可包含至少 170 個胺基酸殘基。胺基酸連接子可包含至少 180 個胺基酸殘基。胺基酸連接子可包含至少 190 個胺基酸殘基。胺基酸連接子可包含至少 200 個胺基酸殘基。胺基酸連接子可包含至少 300 個胺基酸殘基。胺基酸連接子可包含至少 400 個胺基酸殘基。胺基酸連接子可包含至少 500 個胺基酸殘基。胺基酸連接

子可包含 5 至 10 個胺基酸殘基。胺基酸連接子可包含 10 至 15 個胺基酸殘基。胺基酸連接子可包含 15 至 20 個胺基酸殘基。胺基酸連接子可包含 20 至 25 個胺基酸殘基。胺基酸連接子可包含 25 至 30 個胺基酸殘基。胺基酸連接子可包含 30 至 35 個胺基酸殘基。胺基酸連接子可包含 35 至 40 個胺基酸殘基。胺基酸連接子可包含 40 至 45 個胺基酸殘基。胺基酸連接子可包含 45 至 50 個胺基酸殘基。胺基酸連接子可包含 50 至 55 個胺基酸殘基。胺基酸連接子可包含 55 至 60 個胺基酸殘基。胺基酸連接子可包含 60 至 65 個胺基酸殘基。胺基酸連接子可包含 65 至 70 個胺基酸殘基。胺基酸連接子可包含 70 至 75 個胺基酸殘基。胺基酸連接子可包含 75 至 80 個胺基酸殘基。胺基酸連接子可包含 80 至 85 個胺基酸殘基。胺基酸連接子可包含 85 至 90 個胺基酸殘基。胺基酸連接子可包含 90 至 95 個胺基酸殘基。胺基酸連接子可包含 95 至 100 個胺基酸殘基。胺基酸連接子可包含 5 至 80 個胺基酸殘基。胺基酸連接子可包含 20 至 40 個胺基酸殘基。胺基酸連接子可包含 20 至 80 個胺基酸殘基。胺基酸連接子可包含 30 至 60 個胺基酸殘基。胺基酸連接子可包含 40 至 50 個胺基酸殘基。胺基酸連接子可包含 10 至 30 個胺基酸殘基。胺基酸連接子可包含 10 至 20 個胺基酸殘基。胺基酸連接子可包含 5 至 25 個胺基酸殘基。胺基酸連接子可包含 25 至 75 個胺基酸殘基。胺基酸連接子可包含 100 至 500 個胺基酸殘基。胺基酸連接子可包含 100 至 300 個胺基酸殘基。胺基酸連接子可包含 5 至 500 個胺基酸殘基。胺基酸連接子可包含不多於 100 個胺基酸殘基。胺基酸連接子可包含不多於 90 個胺基酸殘基。胺基酸連接子可包含不多於 80 個胺基酸殘基。胺基酸連接子可包含不多於 70 個胺基酸殘基。胺基酸連接子可包含不多於 60 個胺基酸殘基。胺基酸連接子可包含不多於 50 個胺基酸殘基。胺基酸連接子

可包含不多於 40 個胺基酸殘基。胺基酸連接子可包含不多於 30 個胺基酸殘基。胺基酸連接子可包含不多於 20 個胺基酸殘基。胺基酸連接子可包含不多於 10 個胺基酸殘基。胺基酸連接子可包含不多於 95 個胺基酸殘基。胺基酸連接子可包含不多於 90 個胺基酸殘基。胺基酸連接子可包含不多於 85 個胺基酸殘基。胺基酸連接子可包含不多於 80 個胺基酸殘基。胺基酸連接子可包含不多於 75 個胺基酸殘基。胺基酸連接子可包含不多於 70 個胺基酸殘基。胺基酸連接子可包含不多於 65 個胺基酸殘基。胺基酸連接子可包含不多於 60 個胺基酸殘基。胺基酸連接子可包含不多於 55 個胺基酸殘基。胺基酸連接子可包含不多於 50 個胺基酸殘基。胺基酸連接子可包含不多於 45 個胺基酸殘基。胺基酸連接子可包含不多於 40 個胺基酸殘基。胺基酸連接子可包含不多於 35 個胺基酸殘基。胺基酸連接子可包含不多於 30 個胺基酸殘基。胺基酸連接子可包含不多於 25 個胺基酸殘基。胺基酸連接子可包含不多於 20 個胺基酸殘基。胺基酸連接子可包含不多於 15 個胺基酸殘基。胺基酸連接子可包含不多於 10 個胺基酸殘基。胺基酸連接子可包含不多於 200 個胺基酸殘基。胺基酸連接子可包含不多於 300 個胺基酸殘基。胺基酸連接子可包含不多於 400 個胺基酸殘基。胺基酸連接子可包含不多於 500 個胺基酸殘基。

不可切割連接子。

【0054】不可切割連接子可包括不可經由蛋白水解切割之肽。不可經由蛋白水解切割之肽可以對給定樣品或生物體中存在之蛋白酶呈惰性。例如，肽可以對所有人類蛋白酶切割序列呈惰性，從而在人類及人類樣品內可具有高穩定性。此類肽亦可包含使蛋白酶切割位點對蛋白酶呈惰性或無法接觸的二級結構。本揭露之不可切割連接子可包含在 pH 7 緩衝劑中於 25°C 在存在人類蛋白

酶的情況下的至少 1 小時、至少 2 小時、至少 4 小時、至少 8 小時、至少 12 小時、至少 16 小時、至少 1 天、至少 2 天、至少 3 天、至少 1 週、至少 2 週或至少 1 個月的切割半衰期。

D. 蛋白複合體結構

【0055】 本揭露提供涵蓋各種結構的多種蛋白複合體。本揭露之蛋白複合體可包含以單一單位表現的 IL-2 受體促效劑域及感測器域。IL-2 受體促效劑域可表現為感測器域之 N 端延伸或感測器域之 C 端延伸、或佈置在感測器域內。例如，蛋白複合體可包含肽，該肽從 N 端至 C 端包含 IL-2 受體促效劑域、肽連接子、scFv 域及視情況而定的標籤諸如純化標籤 (例如，V5 或 myc 標籤) 或定位訊息。

【0056】 蛋白複合體可包含複數個蛋白次單元。該等複數個蛋白次單元 (例如，IL-2 受體促效劑域及感測器域、兩個感測器域、或感測器域之兩個次單元) 可以在表現後以化學或物理方式連接。該等複數個蛋白次單元可包含複數個感測器及/或治療域。感測器及/或治療域可包含多個蛋白次單元中之單一蛋白次單元、或其部分。例如，感測器域可包含抗體 Fab 區，該抗體 Fab 區包含免疫球蛋白輕鏈及免疫球蛋白重鏈的部分。

【0057】 複數個蛋白次單元可包含促進其選擇性偶合的物理柄部。物理柄部可實現蛋白次單元之間的自發、不可逆及/或非媒介 (例如，不需要伴護蛋白或催化複合體) 偶合，從而得到複合體及不對稱蛋白複合體。例如，在單一中國倉鼠卵巢 (CHO) 細胞中表現的兩個不同的蛋白複合體次單元可包含在細胞輸出之前自發且不可逆偶合的物理柄部。此類物理柄部可包含「杵臼」(KIH) 構建體或電荷交換構建體，其中兩個蛋白次單元包含具有相互結合親和力及特

異性的物理結構。此類物理柄部可包含共價結合對，諸如複數個經組態為形成二硫鍵的硫醇。物理柄部可以使包含相同或不同的域的蛋白複合體之生產變得容易。

【0058】 蛋白複合體可包含兩個或更多個相同的域。此類蛋白複合體的一個實例提供於**圖 2E** 中，其中示出連接至 IL-2 治療域的抗體 (多個感測器域)。在該實例中，蛋白複合體包含複合以形成有能力的抗體的兩個蛋白質免疫球蛋白輕鏈次單元及倆個免疫球蛋白重鏈次單元。該等兩個免疫球蛋白重鏈次單元包含連接至 IL-2 治療域的 N 端連接子。每個免疫球蛋白重鏈連接至免疫球蛋白輕鏈，使得蛋白複合體包含兩個 Fab 區，該等 Fab 區各自單獨地藉由連接子連接至治療域。此類蛋白複合體的第二實例提供於**圖 2D** 中，其中示出連接至 IL-2 治療域的抗體 (多個感測器域)。在該實例中，蛋白複合體包含複合以形成有能力的抗體的兩個蛋白質免疫球蛋白輕鏈次單元及倆個免疫球蛋白重鏈次單元。該等兩個免疫球蛋白輕鏈次單元包含連接至 IL-2 治療域的 N 端連接子。每個免疫球蛋白重鏈連接至免疫球蛋白輕鏈，使得蛋白複合體包含兩個 Fab 區，該等 Fab 區各自單獨地藉由連接子連接至治療域。此類蛋白複合體的第三實例提供於**圖 2G** 中，其中示出連接至 IL-2 治療域及四個感測器域的抗體 (多個感測器域)。在該實例中，蛋白複合體包含複合以形成有能力的抗體的兩個蛋白質免疫球蛋白輕鏈次單元及倆個免疫球蛋白重鏈次單元。該等兩個免疫球蛋白重鏈次單元包含連接至 IL-2 治療域的 N 端連接子，並包含連接至不靶向治療域 (抗 PD-1 scFv 域) 的感測器域的 C 端連接子。每個免疫球蛋白重鏈連接至免疫球蛋白輕鏈，使得蛋白複合體包含兩個 Fab 區及兩個 Fc 域，該等 Fab

區各自單獨地藉由連接子連接至治療域，該等 Fc 域各自單獨地藉由連接子連接至感測器。

【0059】 儘管上述實例提供了具有兩個相同的感測器域及兩個相同的治療域的對稱蛋白複合體，但蛋白複合體亦可包含複數個不同的感測器及/或治療域。此類蛋白複合體可包含免疫球蛋白單元，該免疫球蛋白單元具有包含重鏈-輕鏈對的第一臂及包含抗體片段諸如 scFv、scFab、VH 或其片段的第二臂。在此類情況下，重鏈、抗體片段或輕鏈可包含具有連接子及治療域的 N 端延伸，分別如**圖 2A、2C 及 2F** 所示。替代性地，重鏈、抗體片段或輕鏈可包含具有連接子及治療域的 C 端延伸。蛋白複合體亦可包含具有單一治療域的對稱免疫球蛋白單元。例如，如**圖 2B** 所示，免疫球蛋白單元可包含在單一重鏈上之 N 端連接子及治療單元。替代性地，免疫球蛋白單元可包含在單一輕鏈上之 N 端連接子及治療單元。免疫球蛋白單元亦可包含一堆連接至單一 Fc 區的抗體片段。免疫球蛋白單元可包含奈米抗體。免疫球蛋白單元可包含雙抗體。

【0060】 蛋白複合體可包含在有能力的抗體之 Fab 臂與 Fc 域之間的可撓性連接子，使得 Fab 感測器域能夠結合連接至 Fc 域之 C 端的治療域，如圖 5I 所示。在該實例中，蛋白複合體包含複合以形成感測器抗體域的兩個蛋白質免疫球蛋白輕鏈次單元及倆個免疫球蛋白重鏈次單元。

【0061】 蛋白複合體可包含不靶向治療域的感測器域。此類感測器域可有助於標靶定位，或可以增強單獨感測器域與 PD-1 之結合。包含不靶向治療域的感測器域的蛋白複合體的一個實例提供於**圖 2H** 中。該系統包含單特異性抗 PD-1 抗體，其中第一重鏈包含連接至治療域的 C 端連接子，且第二重鏈包

含連接至感測器域的 C 端連接子，其具有對 IL-2 受體促效劑域及 PD-1 之雙重特異性。

【0062】 蛋白複合體可包含多種感測器對治療域比率。蛋白複合體可包含相等數量的感測器域及治療域，其實例由**圖 2D 及 2E** 提供，其中示出具有 2 個感測器域及 2 個治療域的蛋白複合體。蛋白複合體包含的感測器域的數量可多於治療域的數量，諸如**圖 2A、2B、2C、2F 及 2I** 之蛋白複合體，其各自包含兩個感測器域及一個治療域，或諸如**圖 2G**，其包含四個感測器域及兩個治療域，及**圖 2H**，其包含三個感測器域及一個治療域。在此類情況下，治療域可能能夠與多個感測器域交互作用，或者可能受限於與多於一個感測器域交互作用。感測器域可與其交互作用的治療域的數量可取決於其連接子。連接子可以足夠短，從而阻止治療域與感測器域交互作用，或可以足夠長，從而允許治療域與多個感測器域交互作用。

【0063】 在具體情況下，蛋白複合體可包含具有 Fc 偶合之治療域及感測器域的抗體。如**圖 2H** 所示，蛋白複合體可包含抗體，該抗體具有包含連接子及治療域的第一重鏈 C 端延伸及包含連接子及感測器域的第二重鏈 C 端延伸。這種設計的抗體可包含在其 Fab 及 C 端延伸感測器域上的共同標靶。例如，抗體 Fab 區及 C 端延伸感測器域可各自靶向 PD-1 上的相同表位。相反，這種設計的抗體可包含在其 Fab 區及 C 端延伸感測器域上的單獨的標靶。例如，抗體 Fab 區及 C 端延伸感測器域可各自靶向 PD-1 上的不同表位。如**圖 2I** 所示，蛋白複合體可包含抗體，該抗體具有包含可撓性連接子 CH1 及 CH2 域 (在 Fab 臂與 Fc 域之間) 及包含連接子及治療域的重鏈 C 端延伸的第一重鏈、及包含可撓

性連接子 CH1 及 CH2 域 (在 Fab 臂與 Fc 域之間) 且無 C 端延伸的第二第一重鏈。

【0064】在一些實施例中，本文所述之蛋白複合體中之胺基酸可包含保守性取代。保守性取代可包含一個胺基酸經具有相似生物化學特性 (例如，電荷、疏水性及大小) 的不同胺基酸取代。下表 2 提供了保守性取代以及可能但不一定較佳的取代的實例。

表 2 – 示例性保守性取代

原始殘基	示例性取代	較佳取代
Ala (A)	Val；Leu；Ile	Val
Arg (R)	Lys；Gln；Asn	Lys
Asn (N)	Gln；His；Lys；Arg	Gln
Asp (D)	Glu	Glu
Cys (C)	Ser	Ser
Gln (Q)	Asn	Asn
Glu (E)	Asp	Asp
Gly (G)	Pro；Ala	Ala
His (H)	Asn；Gln；Lys；Arg	Arg
Ile (I)	Leu；Val；Met；Ala；Phe；正白胺酸	Leu
Leu (L)	正白胺酸；Ile；Val；Met；Ala；Phe	Ile
Lys (K)	Arg；Gln；Asn	Arg
Met (M)	Leu；Phe；Ile	Leu
Phe (F)	Leu；Val；Ile；Ala；Tyr	Leu
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr；Phe	Tyr
Tyr (Y)	Trp；Phe；Thr；Ser	Phe
Val (V)	Ile；Leu；Met；Phe；Ala；正白胺酸	Leu

【0065】在一些實施例中，本揭露描述一種重組核酸，該重組核酸本文所揭露之蛋白複合體。在一些實施例中，重組核酸包含編碼整個蛋白複合體的質粒或載體。在一些實施例中，重組核酸包含分別編碼治療域、感測器域及連

接子的質粒或載體。在一些實施例中，重組核酸包含一起編碼治療域、感測器域及連接子中之任意兩者的質粒或載體。

醫藥製劑

【0066】 蛋白複合體或編碼本揭露之蛋白複合體的重組核酸可配製為醫藥組成物。醫藥組成物可包含醫藥上可接受之載劑或賦形劑。如本文所用之「醫藥上可接受之」或「藥理學上可接受之」包括向個體投予個體時不產生不良反應、過敏或其他不良反應 (視情況而定) 的分子實體及組成物。「醫藥上可接受之載劑」包括任何及所有溶劑、分散介質、包衣、抗菌及滅真菌劑、等滲及吸收延遲劑等。此類介質及用於醫藥上活性物質之試劑的用途在本領域中係熟知的。除非任何習知介質或試劑與活性成分不相容，否則設想到其在治療組成物中之使用。通常亦補充活性成分摻入組成物中。

應用

【0067】 本揭露之蛋白複合體可用於各種應用中。本揭露之蛋白複合體可用作向有需要之個體投予的治療藥物。個體可以為人類或非人類哺乳動物。個體可患有疾病。該疾病可以為癌症。癌症可以為急性淋巴母細胞性白血病 (ALL)；急性骨髓性白血病 (AML)；青少年癌症；腎上腺皮質癌；愛滋病相關癌症；卡波西肉瘤 (Kaposi sarcoma) (軟組織肉瘤)；愛滋病相關淋巴瘤 (淋巴瘤)；原發性中樞神經系統淋巴瘤 (淋巴瘤)；肛門癌；闌尾癌 (見胃腸道類癌腫瘤)；兒童星形細胞瘤 (腦癌)；兒童中樞神經系統非典型畸胎瘤/橫紋肌瘤 (腦癌)；皮膚基底細胞癌 (見皮膚癌)；膽管癌；膀胱癌；骨癌 (包括 尤恩氏肉瘤 (Ewing sarcoma) 及骨肉瘤及惡性纖維組織細胞瘤)；腦腫瘤；乳癌；支氣管腫瘤 (肺癌)；伯奇氏淋巴瘤 (Burkitt lymphoma) (見非何杰金氏淋巴瘤 (non-

Hodgkin lymphoma))；類癌瘤 (胃腸道)；原發灶不明的癌；兒童心臟 (心) 腫瘤；中樞神經系統；兒童非典型畸胎瘤/橫紋肌瘤 (腦癌)；兒童髓母細胞瘤及其他中樞神經系統胚胎腫瘤 (腦癌)；兒童生殖細胞腫瘤 (腦癌)；原發性中樞神經系統淋巴瘤；子宮頸癌；兒童期癌症；兒童期不常見癌症；膽管癌 (見膽管癌)；兒童脊索瘤 (骨癌)；慢性淋巴球白血病 (CLL)；慢性骨髓性白血病 (CML)；慢性骨髓增殖性腫瘤；大腸直腸癌；兒童顱咽管瘤 (腦癌)；皮膚 T 細胞淋巴瘤 (見淋巴瘤 (蕈樣黴菌病及 Sezary 症候群))；導管原位癌 (DCIS) (見乳癌)；兒童胚胎腫瘤、髓母細胞瘤及其他中樞神經系統癌症 (腦癌)；子宮內膜癌 (子宮癌)；兒童室管膜瘤 (腦癌)；食道癌；感覺神經母細胞瘤 (頭頸癌)；尤恩氏肉瘤 (骨癌)；兒童顱外生殖細胞腫瘤；性腺外生殖細胞腫瘤；眼癌；眼內黑色素瘤；視網膜母細胞瘤；輸卵管癌；惡性骨纖維組織細胞瘤及骨肉瘤；膽囊癌；胃癌；胃腸道類癌瘤；胃腸道間質瘤 (GIST) (軟組織肉瘤)；生殖細胞腫瘤；兒童中樞神經系統生殖細胞腫瘤 (腦癌)；兒童顱外生殖細胞腫瘤；性腺外生殖細胞腫瘤；卵巢生殖細胞腫瘤；睪丸癌；妊娠滋養細胞疾病；毛細胞白血病；頭頸癌；兒童心臟腫瘤；肝細胞 (肝) 癌；組織細胞增多症，Langerhans 氏細胞；何杰金氏淋巴瘤；下咽癌 (頭頸癌)；眼內黑色素瘤；胰島細胞腫瘤、胰腺神經內分泌腫瘤；Kaposi 氏肉瘤 (軟組織肉瘤)；腎 (腎細胞) 癌；Langerhans 氏細胞組織細胞增多症；喉癌 (頭頸癌)；白血病；唇部及口腔癌 (頭頸癌)；肝癌；肺癌 (非小細胞、小細胞、胸膜肺母細胞瘤及氣管與支氣管腫瘤)；淋巴瘤；男性乳癌；骨惡性纖維組織細胞瘤及骨肉瘤；黑色素瘤；眼內黑色素瘤 (眼)；Merkel氏細胞癌 (皮膚癌)；惡性間皮瘤；轉移性癌症；轉移性鱗狀頸癌伴隱匿原發性 (頭頸癌)；NUT 基因改變的中線束癌；口腔癌 (頭頸癌)；多發性

內分泌腫瘤症候群；多發性骨髓瘤/漿細胞腫瘤；蕈樣黴菌病 (淋巴瘤)；骨髓增生異常症候群、骨髓增生異常/骨髓增殖性腫瘤；慢性骨髓性白血病 (CML)；急性骨髓性白血病 (AML)；慢性骨髓增殖性腫瘤；鼻腔及鼻旁竇癌 (頭頸癌)；鼻咽癌 (頭頸癌)；神經母細胞瘤；非何杰金氏淋巴瘤；非小細胞肺癌；口腔癌、唇部及口腔癌及口咽癌 (頭頸癌)；骨肉瘤及骨惡性纖維組織細胞瘤；卵巢癌；胰腺癌；胰腺神經內分泌腫瘤 (胰島細胞腫瘤)；狀瘤病 (兒童喉頭癌)；副神經節瘤；鼻旁竇及鼻腔癌 (頭頸癌)；副甲狀腺癌；陰莖癌；咽癌 (頭頸癌)；嗜鉻細胞瘤；垂體瘤；漿細胞腫瘤/多發性骨髓瘤；胸膜肺母細胞瘤 (肺癌)；妊娠合併乳癌；原發性中樞神經系統 (CNS) 淋巴瘤；原發性腹膜癌；前列腺癌；直腸癌；復發性癌症；腎細胞 (腎) 癌；視網膜母細胞瘤；兒童橫紋肌肉瘤 (軟組織肉瘤)；唾液腺癌 (頭頸癌)；肉瘤；兒童橫紋肌肉瘤 (軟組織肉瘤)；兒童血管腫瘤 (軟組織肉瘤)；Ewing 氏肉瘤 (骨癌)；卡波西肉瘤 (軟組織肉瘤)；骨肉瘤 (骨癌)；軟組織肉瘤；子宮肉瘤；Sezary 氏症候群 (淋巴瘤)；皮膚癌；小細胞肺癌；小腸癌；軟組織肉瘤；皮膚鱗狀細胞癌 (見皮膚癌)；隱匿、原發性、轉移性鱗狀頸癌 (頭頸癌)；胃癌；皮膚 T 細胞淋巴瘤 (見淋巴瘤 (蕈樣黴菌病及 Sezary 氏症候群))；睾丸癌；喉癌 (頭頸癌)；鼻咽癌；口咽癌；下咽癌；胸腺瘤及胸腺癌；甲狀腺癌；氣管與支氣管腫瘤 (肺癌)；腎盂及輸尿管移行細胞癌 (腎 (腎細胞) 癌)；未知原發癌；兒童期不常見癌症；輸尿管及腎盂移行細胞癌 (腎 (腎細胞) 癌)；尿道癌；子宮癌，子宮內膜；子宮肉瘤；陰道癌；血管腫瘤 (軟組織肉瘤)；陰門癌；威爾姆氏瘤 (Wilms tumor) 及其他兒童腎腫瘤；或年輕人癌症或 https://www.cancer.gov/types 中提及的任何癌症。

【0068】蛋白複合體可作為醫藥組成物投予。本揭露之醫藥組成物可為本文所述之任何蛋白複合體與其他化學組分諸如載劑、穩定劑、稀釋劑、分散劑、懸浮劑、增稠劑及/或賦形劑的組合。醫藥組成物促進本文所述之蛋白複合體向生物體中之投予。醫藥組成物可藉由各種形式的醫藥組成物及途徑以治療有效量的形式投予，該等途徑為例如靜脈內、皮下、肌內、直腸、氣化噴霧劑、腸胃外、經眼、經肺、透皮、陰道、經眼部、經鼻、經口、吸入、皮膚、關節內、鞘內、鼻內和局部投予。醫藥組成物可以局部或全身性方式投予，例如，經由將本文所述之蛋白複合體直接注入器官中，視情況在儲庫中。

【0069】腸胃外注射液可配製為推注或連續輸注液。醫藥組成物可為適合腸胃外注射的形式，作為油性或水性載體中之無菌混懸劑、溶液或乳劑，並可含有配製劑諸如懸浮劑、穩定劑及/或分散劑。用於腸胃外投予的醫藥調配物包括水溶性形式的本文所述之蛋白複合體之水溶液。本文所述之蛋白複合體之混懸劑可製備為油性注射混懸劑。適當的親脂性溶劑或載劑包括脂肪油 (諸如芝麻油) 或合成脂肪酸酯 (諸如油酸乙酯或甘油三酯) 或脂質體。水性注射混懸劑可含有提高混懸劑黏度的物質，諸如羧甲基纖維素鈉、山梨糖醇或葡聚醣。該混懸劑亦可含有適當的穩定劑或增加溶解度及/或減少本文所述之蛋白複合體之聚集以允許製備高濃度溶液的試劑。替代性地，本文所述之蛋白複合體可凍乾或呈粉末形式，以便在使用前用適當的載體 (例如無菌無熱原水) 復溶。在一些實施例中，經純化之蛋白複合體係經靜脈內投予。本揭露之蛋白複合體可包含足夠長的血清半衰期 (例如，如本文所示，例如，在實例 7 中)，以使給藥方案包含每日、隔天、每週兩次、每週、每兩週或每月給藥頻率。本揭露之蛋白複合體可包含至少 12 小時、至少 24 小時、至少 36 小時、至少 48 小時、至少

72 小時、至少 96 小時、至少 120 小時、至少 168 小時、至少 250 小時、至少 320 小時或至少 400 小時的血清半衰期。血清半衰期可以為人類血清半衰期、鼠血清半衰期、豬血清半衰期、牛血清半衰期、犬血清半衰期、貓血清半衰期或兔血清半衰期。

【0070】 本揭露之蛋白複合體可在外科手術期間直接應用於器官或器官組織或細胞或經由透皮、皮下、肌內、腫瘤內、鞘內、外用或局部遞送。在一些實施例中，蛋白複合體可以直接應用於癌組織 (例如，腫瘤)。本文所述之蛋白複合體可局部投予，並可配製成各種可局部投予的組成物，諸如溶液、混懸劑、洗劑、凝膠、糊劑、藥棒、香膏、乳膏及軟膏。此類醫藥組成物可含有增溶劑、穩定劑、張力增強劑、緩衝劑及防腐劑。蛋白複合體可以在螺旋藻中表現並經口遞送。

【0071】 在實踐本文提供的治療或用途時，向罹患癌症的個體投予在醫藥組成物中的治療有效量的本文所述之蛋白複合體。在一些實施例中，個體為哺乳動物，諸如人類。治療有效量可能因疾病之嚴重程度、個體之年齡及相對健康情況、所使用之化合物之效力及其他因素而有很大差異。

【0072】 可使用一種或多種促進將活性化合物加工成可藥用製劑的生理上可接受之載劑 (包含賦形劑及助劑) 配製醫藥組成物。配製可根據所選擇的投予途徑來修改。包含本文所述之蛋白複合體的醫藥組成物可例如藉由在重組系統中表現蛋白複合體、純化蛋白複合體、凍乾蛋白複合體、混合或溶解來製造。醫藥組成物可包括至少一種醫藥上可接受之載劑、稀釋劑或賦形劑及呈游離鹼或醫藥上可接受之鹽形式的本文所述之化合物。

【0073】 用於製備本文所述之蛋白複合體的方法包括用一種或多個惰性、醫藥上可接受之賦形劑或載劑配製本文所述之蛋白複合體以形成固體、半固體或液體組成物。固體組成物包括例如粉末、片劑、可分散顆粒、膠囊、扁囊劑及栓劑。這些組成物亦可含有少量無毒輔助物質，諸如潤濕劑或乳化劑、pH 緩衝劑及其他醫藥上可接受之添加劑。

【0074】 本文所述之某些方法包含個體投予包含本揭露之蛋白複合體的靜脈內醫藥組成物 (例如，如本文所述)。蛋白複合體之靜脈內醫藥組成物包括任何適合經由任何靜脈內方法 (包括推注、隨時間發生的輸注液或本領域已知的任何其他靜脈內方法) 向個體投予的調配物。在一些態樣中，輸注速率使得劑量在少於五分鐘、多於五分鐘但少於 15 分鐘或長於 15 分鐘的時段內投予。在其他態樣中，輸注速率使得劑量在少於 5 分鐘的時段內投予。在其他態樣中，輸注速率使得劑量在長於 5 分鐘且少於 15 分鐘的時段內投予。在一些其他態樣中，輸注速率使得劑量在長於 15 分鐘的時段內投予。

【0075】 如本文所用之「產品」或「劑型」係指用於投予的任何固體、半固體、凍乾、水性、液體或冷凍調配物或製劑。在投予時，產品中活性部分的釋放速率通常受到構成產品本身的賦形劑及/或產品特性的巨大影響。例如，片劑上的腸溶衣旨在將該片劑的內容物與胃內容物分開，以防止例如胃降解，其通常引起胃腸道不適或損傷。根據目前公認的習知理解，活性部分的全身性暴露將對調配物的微小變化相對不敏感。

【0076】 醫藥上可接受之賦形劑的非限制性實例可參見例如：Remington: The Science and Practice of Pharmacy, 第十九版 (Easton, Pa.: Mack Publishing Company, 1995)；Hoover, John E., Remington's Pharmaceutical Sciences, Mack

Publishing Co., Easton, Pennsylvania 1975；Liberman, H. A. 及 Lachman, L. 編輯, Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980；及 Pharmaceutical Dosage Forms and Drug Delivery Systems, 第七版 (Lippincott Williams & Wilkins1999)，其各自藉由引用方式整體併入。

【0077】本揭露之蛋白複合體可以以有效量向患者投予。如本文所用，術語「有效量」可指所投予的化合物的足夠量，其將在某種程度上緩解所治療的疾病或病況的一種或多種症狀。其結果可以是降低及/或緩和疾病的徵象、症狀或原因、或生物系統的任何其他所預期的改變。可投予含有此類藥劑或化合物的組成物以用於預防性、增強性及/或治療性治療。可使用如劑量遞增研究之類的技術以確定在任何個別案例下的適當「有效」量。

【0078】本揭露之方法、組成物及套組可包含預防、治療、阻止、逆轉或改善病況之症狀的方法。治療可包含用本揭露之蛋白複合體治療個體 (例如，患有疾病或病況的受試者、家畜、野生動物或實驗動物)。可以投予本揭露之蛋白複合體以治療個體之疾病。個體可為人類。個體可為人類；非人類靈長類動物，諸如黑猩猩或其他猿或猴子物種；農場動物，諸如牛、馬、綿羊、山羊、豬；家畜，諸如兔、狗及貓；實驗動物，包括嚙齒動物，諸如大鼠、小鼠及豚鼠等。個體可具有任何年齡。個體可為例如老年人、成人、青少年、青春期前、兒童、幼兒、嬰兒、或子宮內的胎兒。

【0079】可在臨床發病前向個體提供治療。可在臨床發病後向個體提供治療。可在臨床發病後 1 天、1 週、6 個月、12 個月、或 2 年或更長以上後向個體提供治療。可在臨床發病後 1 天、1 週、1 個月、6 個月、12 個月、2 年或更長以上後向個體提供治療。可在臨床發病後 1 天、1 週、1 個月、6 個月、12

個月或 2 年後向個體提供治療。治療亦可包括在臨床試驗中治療人類。治療可包含向個體投予醫藥組成物，諸如在本揭露全文中所述之醫藥組成物中之一者或多者。治療可包含每日給藥一次。治療可包含將本揭露之蛋白複合體遞送給個體，其經靜脈內、皮下、肌內、藉由吸入、經皮膚、關節內注射、經口、鞘內、透皮、鼻內、經腹膜途徑遞送，或直接遞送到病變組織上或病變組織中，例如，經由外用、關節內注射途徑或注射應用途徑。

【0080】 在一些實施例中，本揭露提供一種用於治療癌症之方法，該方法包含向有需要之個體投予有效量之本揭露之蛋白複合體。

【0081】 在一些實施例中，本揭露一種用於治療癌症之方法，該方法包含向有需要之患者投予有效量之包含本揭露之蛋白複合體及醫藥上可接受之載劑的醫藥組成物。

套組

【0082】 本揭露之蛋白複合體可以在各種套組中提供。在一些實施例中，包含本揭露之蛋白複合體的醫藥組成物可以作為套組提供。套組可包含容器，該容器包含蛋白複合體。治療性蛋白複合體可以單劑量或多劑量的注射液的形式提供，或作為將在注射前復溶的無菌粉末提供。替代性地，此類套組可包括用於投予治療性蛋白複合體的乾粉分散器、液體氣化噴霧劑發生器或霧化器。此類套組可進一步包含有關藥物組成物的適應症和用法的書面資訊。

【0083】 除非另有定義，否則本文所使用之技術術語具有與一般熟習本發明所屬技術者通常所理解相同的含義。除非上下文另外明確指示，否則本說明書及隨附申請專利範圍中所用之單數形式「一 (a/an)」及「該 (the)」包括複

數個指示物。除非另有說明，否則本文中對「或」之任何引用皆旨在包含「及/或」。

【0084】 當術語「至少」、「大於」或「大於或等於」在兩個或多個數值的序列中的第一個數值之前時，該術語「至少」、「大於」或「大於或等於」適用於該數值系列中之數值中之各者。例如，大於或等於 1、2 或 3 相當於大於或等於 1、大於或等於 2、或大於或等於 3。

【0085】 當術語「不多於」、「少於」、「少於或等於」或「至多」在兩個或多個數值的序列中的第一個數值之前時，該術語「不多於」、「少於」、「少於或等於」或「至多」適用於該數值系列中之數值中之各者。例如，少於或等於 3、2 或 1 相當於少於或等於 3、少於或等於 2、或少於或等於 1。

【0086】 在值被描述為範圍的情況下，應當理解，此類揭露包括此類範圍內所有可能的子範圍之揭露，以及落在此類範圍內的具體數值，而不論是否明確提及具體數值或具體子範圍。

【0087】 表 2A – 本文所述之多肽免疫細胞激素之示例性肽組分

肽 ID	序列	註釋	SEQ ID NO:
PEP000113	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLY SGVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		671
PEP000169	DIQMTQSPSSLSASVGDRVTITCRASQSI SSWLAWYQQKPGKAPKLLIYAASTLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPLTFGGGTKLEIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK		672

肽 ID	序列	註釋	SEQ ID NO:
	DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		
PEP000243	DIVMTQSPDSLAVSLGERATINCKASES VDTSDNSFIHWYQQKPGQSPKLLIYRSS TLESGVPDRFSGSGSGTDFTLTISSLQAE DVAVYYCQQNYDVPWTFGQGTKVEIK RADAAPTVSIFPPSSEQLTSGGASVVCFL NNFYPKDINVKWKIDGSERQNGVLNSW TDQDSKDSTYSMSSTLTLTKDEYERHNS YTCEATHKTSTSPIVKSFNRNEC		673
PEP000244	DIVMTQSPDSLAVSLGERATINCKASES VDTSDNSFIHWYQQKPGQSPKLLIYRSS TLESGVPDRFSGSGSGTDFTLTISSLQAE DVAVYYCQQNYDVPWTFGQGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNRGEC		674
PEP000245	DIVMTQSPDSLAVSLGERATINCKASQS LLHSSSNKNYLAWYQQKPGQPPKLLIY WASTRESGVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCQQYYSTPITFGPGTKVDI KRADAAPTVSIFPPSSEQLTSGGASVVCF LNNFYPKDINVKWKIDGSERQNGVLNS WTDQDSKDSTYSMSSTLTLTKDEYERH NSYTCEATHKTSTSPIVKSFNRNEC		675
PEP000288	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGGGGGSGGGGSGGGGSAPASS STKKTQLQLEHLLLDLQMILNGINNYKN PKLTRMLTAKFAMPKKATELKHLQCLE EELKPLEEVLNGAQSKNFHLRPRDLISNI NVIVLELKGSETTFMCEYADETATIVEFL NRWITFAQSIISTLT		676

肽 ID	序列	註釋	SEQ ID NO:
PEP001315	MSTSTEQKLISEEDLQVQLVQSGAEVKK PGASVKVSCKASGYTFTTYYMHWVRQ APGQGLEWMGIINPSGGGTLYAQKFQG RVTMTRDTSTSTVYMELSSLRSEDTAVY YCAAGLFIWGQGTTVTVSSASGGGGSG GGGSGGGGSHASDIVMTQSPDSLAVSLG ERATINCKASQSLLHSSSNKNYLAWYQ QKPGQPPKLLIYWASTRESGVPDRFSGS GSGTDFTLTISSLQAEDVAVYYCQQYYS TPITFGPGTKVDIKGSGLNDIFEAQKIEW HEGKPIPNPLLGLDST	PD1_R04_C10 - 內部抗 PD1 mAb	677
PEP003213	MSTSTEQKLISEEDLQVQLVQSGAEVKK PGASVKVSCKASGDTFTRHYVHWVRQA PGQGLEWMGIINPSGGYASYAQKFQGR VTMTRDTSTSTVYMELSSLRSEDTAVYY CAAGLFIWGQGTLVTVSSASGGGGSGG GGSGGGGSHASDIQMTQSPSSLSASVGD RVTITCRASQSIGRWLAWYQQKPGKAP KLLIYSASNLETGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQYESFPVTFGPGT KVDIKGKPIPNPLLGLDST	AB002022_2B07v1	678
PEP003626	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSAKTTAPSVYPLAPVCGDT TGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSST WPSQSITCNVAHPASSTKVDKKIEPRGPT IKPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFV NNVEVHTAQTQTHREDYNSTLRVVSAL PIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEEEMTKK QVTLTCMVTDFMPEDIYVEWTNNGKTE LNYKNTEPVLDSDGSYFMYSDLRVEKK NWVERNSYSCSVVHEGLHNHHTTESFS RTPGGGGGSGGGGSGGGGSAPASSSTK KTQLQLEHLLLDLQMILNGINNYKNPKL TRMLTAKFAMPKKATELKHLQCLEEEL KPLEEVLNGAQSKNFHLRPRDLISNINVI VLELKGSETTFMCEYADETATIVEFLNR WITFAQSIISTLT		679
PEP003639	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGDTFTRHYVHWVRQAPG QGLEWMGIINPSGGYASYAQKFQGRVT		680

肽 ID	序列	註釋	SEQ ID NO:
	MTRDTSTSTVYMELSSLRSEDTAVYYC AAGLFIWGQGTLVTVSSAKTTAPSVYPL APVCGDTTGSSVTLGCLVKGYFPEPVTL TWNSGSLSSGVHTFPAVLQSDLYTLSSS VTVTSSTWPSQSITCNVAHPASSTKVDK KIEPRGPTIKPCPPCKCPAPNAAGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVSEDDP DVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNN KDLGAPIERTISKPKGSVRAPQVYVLPPP EEEMTKKQVTLTCMVTDFMPEDIYVEW TNNGKTELNYKNTEPVLDSDGSYFMYS DLRVEKKNWVERNSYSCSVVHEGLHNH HTTESFSRTPGK		
PEP003641	DIQMTQSPSSLSASVGDRVSITCKASQN VGTNVGWYQQKPGKAPKALIYSASFRY SGVPSRFSGSGSGTDFTLTISSLQPEDFAT YFCQQYYTYPYTFGGGTKLEIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		681
PEP003642	DIQMTQSPSSLSASVGDRVTITCRASQSI GRWLAWYQQKPGKAPKLLIYSASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYESFPVTFGPGTKVDIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		682
PEP003648	QVQLVQSGAEVKKPGASVKVSCKASGD TFTRHYVHWVRQAPGQGLEWMGIINPS GGYASYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTLV TVSSAKTTAPSVYPLAPVCGDTTGSSVT LGCLVKGYFPEPVTLTWNSGSLSSGVHT FPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNAAGGPSVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPK GSVRAPQVYVLPPPEKEMTKKQVSLTCL VKDFMPEDIYVEWTNNGKTELNYKNTE PVLKSDGSYFMYSKLTVEKKNWVERNS YSCSVVHEGLHNHHTTKSFSRTPGGGGS GGGSHHHHHH		683
PEP003654	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA		684

肽 ID	序列	註釋	SEQ ID NO:
	TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSEVQLVESGGGLVKPG GSLRLSCAASGFTFSSYTLAWVRQAPGK GLEWVAAIDSSSYTYSPDTVRGRFTISRD NAKNSLYLQMNSLRAEDTAVYYCARDS NWDALDYWGQGTLVTVSSAKTTAPSV YPLAPVCGDTTGSSVTLGCLVKGYFPEP VTLTWNSGSLSSGVHTFPAVLQSDLYTL SSSVTVTSSTWPSQSITCNVAHPASSTKV DKKIEPRGPTIKPCPPCKCPAPNAAGGPS VFIFPPKIKDVLMISLSPIVTCVVVDVSED DPDVQISWFVNNVEVHTAQTQTHREDY NSTLRVVSALPIQHQDWMSGKEFKCKV NNKDLGAPIERTISKPKGSVRAPQVYVL PPPEEEMTKKQVTLTCMVTDFMPEDIYV EWTNNGKTELNYKNTEPVLDSDGSYFM YSKLRVEKKNWVERNSYSCSVVHEGLH NHHTTKSFSRTPGK		
PEP003655	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSEVQLVESGGGLVQPG GSLRLSCAASGFNIKDTYIHWVRQAPGK GLEWVARIYPTNGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGY FPEPVTLTWNSGSLSSGVHTFPAVLQSD LYTLSSSVTVTSSTWPSQSITCNVAHPAS STKVDKKIEPRGPTIKPCPPCKCPAPNAA GGPSVFIFPPKIKDVLMISLSPIVTCVVVD VSEDDPDVQISWFVNNVEVHTAQTQTH REDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQ VYVLPPPEEEMTKKQVTLTCMVTDFMP EDIYVEWTNNGKTELNYKNTEPVLDSD GSYFMYSKLRVEKKNWVERNSYSCSVV HEGLHNHHTTKSFSRTPGK		685
PEP003657	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGDTFTRHYVHWVRQAPG QGLEWMGIINPSGGYASYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYC AAGLFIWGQGTLVTVSSAKTTAPSVYPL APVCGDTTGSSVTLGCLVKGYFPEPVTL		686

肽 ID	序列	註釋	SEQ ID NO:
	TWNSGSLSSGVHTFPAVLQSDLYTLSSS VTVTSSTWPSQSITCNVAHPASSTKVDK KIEPRGPTIKPCPPCKCPAPNAAGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVSEDDP DVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNN KDLGAPIERTISKPKGSVRAPQVYVLPPP EEEMTKKQVTLTCMVTDFMPEDIYVEW TNNGKTELNYKNTEPVLDSDGSYFMYS KLRVEKKNWVERNSYSCSVVHEGLHNH HTTKSFSRTPGK		
PEP003780	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGDTFTRHYVHWVRQAPG QGLEWMGIINPSGGYASYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYC AAGLFIWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK		687
PEP003782	DIQMTQSPSSLSASVGDRVTITCRASQSI GRWLAWYQQKPGKAPKLLIYSASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYESFPVTFGPGTKVDIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC		688
PEP003786	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSDIQMTQSPSSLSASVG DRVTITCRASQSIGRWLAWYQQKPGKA PKLLIYSASNLETGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQYESFPVTFGPG TKVDIKRTVAAPSVFIFPPSDEQLKSGTA		689

肽 ID	序列	註釋	SEQ ID NO:
	SVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRG EC		
PEP003791	QVQLVQSGAEVKKPGASVKVSCKASGD TFTRHYVHWVRQAPGQGLEWMGIINPS GGYASYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK		690
PEP004129	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTSPPSPEPKSSDTPPPSPRSPEPKSS DTPPPSPRSPEPKSCDTPPPCPRAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALGAPIEKTISKAKGQPREP QVCTLPPSRDELTKNQVSLSCAVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDG SFFLVSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSP		691
PEP004130	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTSPPSPEPKSSDTPPPSPRSPEPKSS DTPPPSPRSPEPKSCDTPPPCPRAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE		692

肽 ID	序列	註釋	SEQ ID NO:
	YKCKVSNKALGAPIEKTISKAKGQPREP QVYTLPPCRDELTKNQVSLWCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGGGGGSGGGG SGGGGSAPASSSTKKTQLQLEHLLLDLQ MILNGINNYKNPKLTRMLTAKFAMPKK ATELKHLQCLEEELKPLEEVLNGAQSKN FHLRPRDLISNINVIVLELKGSETTFMCE YADETATIVEFLNRWITFAQSIISTLT		
PEP004133	QVQLVQSGAEVKKPGASVKVSCKASGD TFTRHYVHWVRQAPGQGLEWMGIINPS GGYASYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTS PPSPEPKSSDTPPPSPRSPEPKSSDTPPPSP RSPEPKSCDTPPPCPRAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVS NKALGAPIEKTISKAKGQPREPQVCTLPP SRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSK LTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSP		693
PEP004134	QVQLVQSGAEVKKPGASVKVSCKASGD TFTRHYVHWVRQAPGQGLEWMGIINPS GGYASYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTS PPSPEPKSSDTPPPSPRSPEPKSSDTPPPSP RSPEPKSCDTPPPCPRAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVS NKALGAPIEKTISKAKGQPREPQVYTLPP CRDELTKNQVSLWCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGGGGGSGGGGSGGGGS APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLT		694

肽 ID	序列	註釋	SEQ ID NO:
PEP004153	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGDTFTRYYVHWVRQAPG QGLEWMGIINPSGGYASYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYC AAGLFIWGQGTLVTVSSAKTTAPSVYPL APVCGDTTGSSVTLGCLVKGYFPEPVTL TWNSGSLSSGVHTFPAVLQSDLYTLSSS VTVTSSTWPSQSITCNVAHPASSTKVDK KIEPRGPTIKPCPPCKCPAPNAAGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVSEDDP DVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNN KDLGAPIERTISKPKGSVRAPQVYVLPPP EEEMTKKQVTLTCMVTDFMPEDIYVEW TNNGKTELNYKNTEPVLDSDGSYFMYS KLRVEKKNWVERNSYSCSVVHEGLHNH HTTKSFSRTPGK		695
PEP004158	DIQMTQSPSSLSASVGDRVTITCRASQSI GRWLAWYQQKPGKAPKLLIYSASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIKRADAA PTVSIFPPSSEQLTSGGASVVCFLNNFYP KDINVKWKIDGSERQNGVLNSWTDQDS KDSTYSMSSTLTLTKDEYERHNSYTCEA THKTSTSPIVKSFNRNEC		696
PEP004159	DIQMTQSPSSLSASVGDRVTITCRASQSI GRWLAWYQQKPGKAPKLLIYSASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNSFPVTFGPGTKVDIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		697
PEP004161	DIQMTQSPSSLSASVGDRVTITCRASQSI GRYLAWYQQKPGKAPKLLIYSASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIKRADAA PTVSIFPPSSEQLTSGGASVVCFLNNFYP KDINVKWKIDGSERQNGVLNSWTDQDS KDSTYSMSSTLTLTKDEYERHNSYTCEA THKTSTSPIVKSFNRNEC		698
PEP004162	DIQMTQSPSSLSASVGDRVTITCRASQSI GRYLAWYQQKPGKAPKLLIYSASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNSFPVTFGPGTKVDIKRADAAP		699

肽 ID	序列	註釋	SEQ ID NO:
	TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		
PEP004163	DIQMTQSPSSLSASVGDRVTITCRASQSI GRYLAWYQQKPGKAPKLLIYYASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNSFPVTFGPGTKVDIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		700
PEP004191	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SIGRWLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYERFPVTFGPGTKVDIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST	AB002342_2B07v5	701
PEP004192	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SIGRWLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYESFPVTFGPGTKVDIKAAAGSG SEQKLISEEDLGKPIPNPLLGLDST	AB002353_2B07v9	702
PEP004195	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SIGRWLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST	AB002328_2B07v4	703
PEP004198	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SIGRWLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT	AB002293_2B07v2	704

肽 ID	序列	註釋	SEQ ID NO:
	YYCQQYNSFPVTFGPGTKVDIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST		
PEP004207	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SIGRYLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST	AB002347_2B07v7	705
PEP004208	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SIGRYLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNSFPVTFGPGTKVDIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST	AB002345_2B07v6	706
PEP004210	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SIGRYLAWYQQKPGKAPKLLIYYASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNSFPVTFGPGTKVDIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST	AB002348_2B07v8	707
PEP004211	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SIGSWLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNSFPVTFGPGTKVDIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST	AB002326_2B07v3	708
PEP004243	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGDTFTRYYVHWVRQAPG QGLEWMGIINPSGGYASYAQKFQGRVT		709

肽 ID	序列	註釋	SEQ ID NO:
	MTRDTSTSTVYMELSSLRSEDTAVYYC AAGLFIWGQGTLVTVSSAKTTAPSVYPL APVCGDTTGSSVTLGCLVKGYFPEPVTL TWNSGSLSSGVHTFPAVLQSDLYTLSSS VTVTSSTWPSQSITCNVAHPASSTKVDK KIEPRGPTIKPCPPCKCPAPNAAGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVSEDDP DVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNN KDLGAPIERTISKPKGSVRAPQVYVLPPP EEEMTKKQVTLTCMVTDFMPEDIYVEW TNNGKTELNYKNTEPVLDSDGSYFMYS DLRVEKKNWVERNSYSCSVVHEGLHNH HTTESFSRTPGK		
PEP004247	QVQLVQSGAEVKKPGASVKVSCKASGD TFTRYYVHWVRQAPGQGLEWMGIINPS GGYASYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTLV TVSSAKTTAPSVYPLAPVCGDTTGSSVT LGCLVKGYFPEPVTLTWNSGSLSSGVHT FPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNAAGGPSVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPK GSVRAPQVYVLPPPEKEMTKKQVSLTCL VKDFMPEDIYVEWTNNGKTELNYKNTE PVLKSDGSYFMYSKLTVEKKNWVERNS YSCSVVHEGLHNHHTTKSFSRTPGK		710
PEP004251	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGYTFTKNYMHWVRQAP GQGLEWLGWVSPDSGYTGYAQKFQGR VTMTRDTSTSTVYMELSSLRSEDTAVYY CTTDLLSLELDDAFDIWGQGTMVTVSSA KTTAPSVYPLAPVCGDTTGSSVTLGCLV KGYFPEPVTLTWNSGSLSSGVHTFPAVL QSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAP NAAGGPSVFIFPPKIKDVLMISLSPIVTCV VVDVSEDDPDVQISWFVNNVEVHTAQT QTHREDYNSTLRVVSALPIQHQDWMSG KEFKCKVNNKDLGAPIERTISKPKGSVR APQVYVLPPPEEEMTKKQVTLTCMVTD FMPEDIYVEWTNNGKTELNYKNTEPVL		711

肽 ID	序列	註釋	SEQ ID NO:
	DSDGSYFMYSDLRVEKKNWVERNSYSC SVVHEGLHNHHTTESFSRTPGK		
PEP004261	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTDYYMHWVRQAPGQGLEW MGIINPRAGYTSYALKFQGRVTMTRDTS TSTVYMELSSLRSEDTAVYYCTSGWDV WGQGTLVTVSSASGGGGSGGGGSGGG GSHASDIQMTQSPSSLSASVGDRVTITCR ASQSISTWLAWYQQKPGKAPKLLIYAAS SLDSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSYSFPVTFGQGTKVEIKAAA GSGSEQKLISEEDLGKPIPNPLLGLDST	AB002381_7A04v4	712
PEP004271	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQGLEWM GIINPSGGYATYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCASGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SINSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYRFPVTFGQGTKVEIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST	AB002427_2A11v5	713
PEP004272	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQGLEWM GIINPSGGYATYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCASGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SINSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYYRFPVTFGQGTKVEIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST	AB002413_2A11v3	714
PEP004273	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQGLEWM GIINPSGGYATYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCASGLFIWG QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SINSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYYSFPVTFGQGTKVEIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST	AB002417_2A11v4	715
PEP004281	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQGLEWM GIINPSGGYATYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCASGWFVW GQGTLVTVSSASGGGGSGGGGSGGGGS HASDIQMTQSPSSLSASVGDRVTITCRAS QSINSWLAWYQQKPGKAPKLLIYDTSTL ESGVPSRFSGSGSGTDFTLTISSLQPEDFA	AB002410_2A11v2	716

肽 ID	序列	註釋	SEQ ID NO:
	TYYCQQSYSFPVTFGQGTKVEIKAAAGS GSEQKLISEEDLGKPIPNPLLGLDST		
PEP004299	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGYTFTDYYMHWVRQAPGQGLEW MGIINPRAGYTSYALKFQGRVTMTRDTS TSTVYMELSSLRSEDTAVYYCTSGWDV WGQGTLVTVSSASGGGGSGGGGSGGG GSHASDIQMTQSPSSLSASVGDRVTITCR ASQSISTWLAWYQQKPGKAPKLLIYAAS SLDSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSYSFPVTFGQGTKVEIKAAA GSGSEQKLISEEDLGKPIPNPLLGLDST	AB002360_7A04v1	717
PEP004340	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGYTFTRYYMHWVRQAPGQGLEWM GIINPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCTSGWDVW GQGTLVTVSSASGGGGSGGGGSGGGGS HASDIQMTQSPSSLSASVGDRVTITCRAS QSISTWLAWYQQKPGKAPKLLIYAASSL DSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSFPVTFGQGTKVEIKAAAG SGSEQKLISEEDLGKPIPNPLLGLDST	AB002365_7A04v2	718
PEP004349	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGYTFTTYYMHWVRQAPGQGLEWM GIINPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCTSGWDVW GQGTLVTVSSASGGGGSGGGGSGGGGS HASDIQMTQSPSSLSASVGDRVTITCRAS QSISTWLAWYQQKPGKAPKLLIYAASSL DSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSFPVTFGQGTKVEIKAAAG SGSEQKLISEEDLGKPIPNPLLGLDST	AB002370_7A04v3	719
PEP004356	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSAKTTAPSVYPLAPVCGDT TGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSST WPSQSITCNVAHPASSTKVDKKIEPRGPT IKPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFV NNVEVHTAQTQTHREDYNSTLRVVSAL PIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEKEMTKK QVSLTCLVKDFMPEDIYVEWTNNGKTE LNYKNTEPVLKSDGSYFMYSKLTVEKK NWVERNSYSCSVVHEGLHNHHTTKSFS RTPGGGGGSGGGGSGGGGSGGGGSEVQ LVESGGGLVKPGGSLRLSCAASGFTFSS YTLAWVRQAPGKGLEWVAAIDSSSYTY		720

肽 ID	序列	註釋	SEQ ID NO:
	SPDTVRGRFTISRDNAKNSLYLQMNSLR AEDTAVYYCARDSNWDALDYWGQGTL VTVSSASGGGGSGGGGSGGGGSHASDI QMTQSPSSLSASVGDRVSITCKASQNVG TNVGWYQQKPGKAPKALIYSASFRYSG VPSRFSGSGSGTDFTLTISSLQPEDFATYF CQQYYTYPYTFGGGTKLEIKGGGSGGG SHHHHHH		
PEP004361	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGDTFTRHYVHWVRQAPG QGLEWMGIINPSGGYASYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYC AAGLFIWGQGTLVTVSSAKTTAPSVYPL APVCGDTTGSSVTLGCLVKGYFPEPVTL TWNSGSLSSGVHTFPAVLQSDLYTLSSS VTVTSSTWPSQSITCNVAHPASSTKVDK KIEPRGPTIKPCPPCKCPAPNAAGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVSEDDP DVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNN KDLGAPIERTISKPKGSVRAPQVYVLPPP EEEMTKKQVTLTCMVTDFMPEDIYVEW TNNGKTELNYKNTEPVLDSDGSYFMYS KLRVEKKNWVERNSYSCSVVHEGLHNH HTTKSFSRTPGGGGGSGGGGSGGGGSG GGGSQVQLVQSGAEVKKPGASVKVSCK ASGYTFTTYYMHWVRQAPGQGLEWMG IINPSGGGTLYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAAGLFIWG QGTTVTVSSASGGGGSGGGGSGGGGSH ASDIVMTQSPDSLAVSLGERATINCKAS QSLLHSSSNKNYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISS LQAEDVAVYYCQQYYSTPITFGPGTKV DIK		721
PEP004363	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGDTFTRYYVHWVRQAPG QGLEWMGIINPSGGYASYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYC AAGLFIWGQGTLVTVSSAKTTAPSVYPL APVCGDTTGSSVTLGCLVKGYFPEPVTL		722

肽 ID	序列	註釋	SEQ ID NO:
	TWNSGSLSSGVHTFPAVLQSDLYTLSSS VTVTSSTWPSQSITCNVAHPASSTKVDK KIEPRGPTIKPCPPCKCPAPNAAGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVSEDDP DVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNN KDLGAPIERTISKPKGSVRAPQVYVLPPP EEEMTKKQVTLTCMVTDFMPEDIYVEW TNNGKTELNYKNTEPVLDSDGSYFMYS KLRVEKKNWVERNSYSCSVVHEGLHNH HTTKSFSRTPGGGGGSGGGGSGGGGSG GGGSQVQLVQSGAEVKKPGASVKVSCK ASGYTFTTYYMHWVRQAPGQGLEWMG IINPSGGGTLYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAAGLFIWG QGTTVTVSSASGGGGSGGGGSGGGGSH ASDIVMTQSPDSLAVSLGERATINCKAS QSLLHSSSNKNYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISS LQAEDVAVYYCQQYYSTPITFGPGTKV DIK		
PEP004395	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSAKTTAPSVYPLAPVCGDT TGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSST WPSQSITCNVAHPASSTKVDKKIEPRGPT IKPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFV NNVEVHTAQTQTHREDYNSTLRVVSAL PIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEKEMTKK QVSLTCLVKDFMPEDIYVEWTNNGKTE LNYKNTEPVLKSDGSYFMYSKLTVEKK NWVERNSYSCSVVHEGLHNHHTTKSFS RTPGGGGGSGGGGSGGGGSGGGGSQVQ LVQSGAEVKKPGASVKVSCKASGDTFT RHYVHWVRQAPGQGLEWMGIINPSGGY ASYAQKFQGRVTMTRDTSTSTVYMELS SLRSEDTAVYYCAAGLFIWGQGTLVTVS SASGGGGSGGGGSGGGGSHASDIQMTQ SPSSLSASVGDRVTITCRASQSIGRWLA WYQQKPGKAPKLLIYSASNLETGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQY ESFPVTFGPGTKVDIKGGGSGGGSHHHH HH		723
PEP004398	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM		724

肽 ID	序列	註釋	SEQ ID NO:
	NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSAKTTAPSVYPLAPVCGDT TGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSST WPSQSITCNVAHPASSTKVDKKIEPRGPT IKPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFV NNVEVHTAQTQTHREDYNSTLRVVSAL PIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEKEMTKK QVSLTCLVKDFMPEDIYVEWTNNGKTE LNYKNTEPVLKSDGSYFMYSKLTVEKK NWVERNSYSCSVVHEGLHNHHTTKSFS RTPGGGGGSGGGGSGGGGSGGGGSQVQ LVQSGAEVKKPGASVKVSCKASGDTFT RYYVHWVRQAPGQGLEWMGIINPSGGY ASYAQKFQGRVTMTRDTSTSTVYMELS SLRSEDTAVYYCAAGLFIWGQGTLVTVS SASGGGGSGGGGSGGGGSHASDIQMTQ SPSSLSASVGDRVTITCRASQSIGRWLA WYQQKPGKAPKLLIYSASNLETGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQY NRFPVTFGPGTKVDIKGGGSGGGSHHH HHH		
PEP004404	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSAKTTAPSVYPLAPVCGDT TGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSST WPSQSITCNVAHPASSTKVDKKIEPRGPT IKPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFV NNVEVHTAQTQTHREDYNSTLRVVSAL PIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEKEMTKK QVSLTCLVKDFMPEDIYVEWTNNGKTE LNYKNTEPVLKSDGSYFMYSKLTVEKK NWVERNSYSCSVVHEGLHNHHTTKSFS RTPGGGGGSGGGGSGGGGSGGGGSQVQ LVQSGAEVKKPGASVKVSCKASGHTFT RYYMHWVRQAPGQGLEWMGIINPSGG YATYAQKFQGRVTMTRDTSTSTVYMEL SSLRSEDTAVYYCASGLFIWGQGTLVTV SSASGGGGSGGGGSGGGGSHASDIQMT QSPSSLSASVGDRVTITCRASQSINSWLA WYQQKPGKAPKLLIYATSTLESGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQY YRFPVTFGQGTKVEIKGGGSGGGSHHH HHH		725

肽 ID	序列	註釋	SEQ ID NO:
PEP004406	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSAKTTAPSVYPLAPVCGDT TGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSST WPSQSITCNVAHPASSTKVDKKIEPRGPT IKPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFV NNVEVHTAQTQTHREDYNSTLRVVSAL PIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEKEMTKK QVSLTCLVKDFMPEDIYVEWTNNGKTE LNYKNTEPVLKSDGSYFMYSKLTVEKK NWVERNSYSCSVVHEGLHNHHTTKSFS RTPGGGGGSGGGGSGGGGSGGGGSQVQ LVQSGAEVKKPGASVKVSCKASGYTFT DYYMHWVRQAPGQGLEWMGIINPRAG YTSYALKFQGRVTMTRDTSTSTVYMEL SSLRSEDTAVYYCTSGWDVWGQGTLVT VSSASGGGGSGGGGSGGGGSHASDIQM TQSPSSLSASVGDRVTITCRASQSISTWL AWYQQKPGKAPKLLIYAASSLDSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQ SYSFPVTFGQGTKVEIKGGGSGGGSHHH HHH		726
PEP004416	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGYTFTDYYMHWVRQAP GQGLEWMGIINPRAGYTSYALKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYC TSGWDVWGQGTLVTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSS SVTVTSSTWPSQSITCNVAHPASSTKVD KKIEPRGPTIKPCPPCKCPAPNAAGGPSV FIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVN NKDLGAPIERTISKPKGSVRAPQVYVLPP PEEEMTKKQVTLTCMVTDFMPEDIYVE WTNNGKTELNYKNTEPVLDSDGSYFMY SKLRVEKKNWVERNSYSCSVVHEGLHN HHTTKSFSRTPGK		727
PEP004418	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH		728

肽 ID	序列	註釋	SEQ ID NO:
	LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGYTFTRYYMHWVRQAP GQGLEWMGIINPRAGYTSYALKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYC TSGWDVWGQGTLVTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSS SVTVTSSTWPSQSITCNVAHPASSTKVD KKIEPRGPTIKPCPPCKCPAPNAAGGPSV FIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVN NKDLGAPIERTISKPKGSVRAPQVYVLPP PEEEMTKKQVTLTCMVTDFMPEDIYVE WTNNGKTELNYKNTEPVLDSDGSYFMY SKLRVEKKNWVERNSYSCSVVHEGLHN HHTTKSFSRTPGK		
PEP004419	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGYTFTTYYMHWVRQAP GQGLEWMGIINPRAGYTSYALKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYC TSGWDVWGQGTLVTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSS SVTVTSSTWPSQSITCNVAHPASSTKVD KKIEPRGPTIKPCPPCKCPAPNAAGGPSV FIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVN NKDLGAPIERTISKPKGSVRAPQVYVLPP PEEEMTKKQVTLTCMVTDFMPEDIYVE WTNNGKTELNYKNTEPVLDSDGSYFMY SKLRVEKKNWVERNSYSCSVVHEGLHN HHTTKSFSRTPGK		729
PEP004420	DIQMTQSPSSLSASVGDRVTITCRASQSI GRWLAWYQQKPGKAPKLLIYSASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYERFPVTFGPGTKVDIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		730

肽 ID	序列	註釋	SEQ ID NO:
PEP004421	DIQMTQSPSSLSASVGDRVTITCRASQSI GSWLAWYQQKPGKAPKLLIYSASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNSFPVTFGPGTKVDIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		731
PEP004423	DIQMTQSPSSLSASVGDRVTITCRASQSI NSWLAWYQQKPGKAPKLLIYATSTLES GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYYRFPVTFGQGTKVEIKRADAA PTVSIFPPSSEQLTSGGASVVCFLNNFYP KDINVKWKIDGSERQNGVLNSWTDQDS KDSTYSMSSTLTLTKDEYERHNSYTCEA THKTSTSPIVKSFNRNEC		732
PEP004426	DIQMTQSPSSLSASVGDRVTITCRASQSI STWLAWYQQKPGKAPKLLIYAASSLDS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYRFPVTFGQGTKVEIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		733
PEP004427	DIQMTQSPSSLSASVGDRVTITCRASQSI STWLAWYQQKPGKAPKLLIYAASSLDS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSFPVTFGQGTKVEIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		734
PEP004431	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGHTFTRYYMHWVRQAP GQGLEWMGIINPSGGYATYAQKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYC ASGLFIWGQGTLVTVSSAKTTAPSVYPL APVCGDTTGSSVTLGCLVKGYFPEPVTL TWNSGSLSSGVHTFPAVLQSDLYTLSSS VTVTSSTWPSQSITCNVAHPASSTKVDK KIEPRGPTIKPCPPCKCPAPNAAGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVSEDDP DVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNN KDLGAPIERTISKPKGSVRAPQVYVLPPP		735

肽 ID	序列	註釋	SEQ ID NO:
	EEEMTKKQVTLTCMVTDFMPEDIYVEW TNNGKTELNYKNTEPVLDSDGSYFMYS DLRVEKKNWVERNSYSCSVVHEGLHNH HTTESFSRTPGK		
PEP004433	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGYTFTDYYMHWVRQAP GQGLEWMGIINPRAGYTSYALKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYC TSGWDVWGQGTLVTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSS SVTVTSSTWPSQSITCNVAHPASSTKVD KKIEPRGPTIKPCPPCKCPAPNAAGGPSV FIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVN NKDLGAPIERTISKPKGSVRAPQVYVLPP PEEEMTKKQVTLTCMVTDFMPEDIYVE WTNNGKTELNYKNTEPVLDSDGSYFMY SDLRVEKKNWVERNSYSCSVVHEGLHN HHTTESFSRTPGK		736
PEP004435	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGYTFTRYYMHWVRQAP GQGLEWMGIINPRAGYTSYALKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYC TSGWDVWGQGTLVTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSS SVTVTSSTWPSQSITCNVAHPASSTKVD KKIEPRGPTIKPCPPCKCPAPNAAGGPSV FIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVN NKDLGAPIERTISKPKGSVRAPQVYVLPP PEEEMTKKQVTLTCMVTDFMPEDIYVE WTNNGKTELNYKNTEPVLDSDGSYFMY SDLRVEKKNWVERNSYSCSVVHEGLHN HHTTESFSRTPGK		737
PEP004436	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR		738

肽 ID	序列	註釋	SEQ ID NO:
	DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSQVQLVQSGAEVKKPG ASVKVSCKASGYTFTTYYMHWVRQAP GQGLEWMGIINPRAGYTSYALKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYC TSGWDVWGQGTLVTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSS SVTVTSSTWPSQSITCNVAHPASSTKVD KKIEPRGPTIKPCPPCKCPAPNAAGGPSV FIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVN NKDLGAPIERTISKPKGSVRAPQVYVLPP PEEEMTKKQVTLTCMVTDFMPEDIYVE WTNNGKTELNYKNTEPVLDSDGSYFMY SDLRVEKKNWVERNSYSCSVVHEGLHN HHTTESFSRTPGK		
PEP004438	QVQLVQSGAEVKKPGASVKVSCKASGD TFTRYYVHWVRQAPGQGLEWMGIINPS GGYASYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTLV TVSSAKTTAPSVYPLAPVCGDTTGSSVT LGCLVKGYFPEPVTLTWNSGSLSSGVHT FPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNAAGGPSVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPK GSVRAPQVYVLPPPEKEMTKKQVSLTCL VKDFMPEDIYVEWTNNGKTELNYKNTE PVLKSDGSYFMYSKLTVEKKNWVERNS YSCSVVHEGLHNHHTTKSFSRTPGGGGS GGGSHHHHHH		739
PEP004440	QVQLVQSGAEVKKPGASVKVSCKASGH TFTRYYMHWVRQAPGQGLEWMGIINPS GGYATYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCASGLFIWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER		740

肽 ID	序列	註釋	SEQ ID NO:
	NSYSCSVVHEGLHNHHTTKSFSRTPGGG GSGGGSHHHHHH		
PEP004442	QVQLVQSGAEVKKPGASVKVSCKASGY TFTDYYMHWVRQAPGQGLEWMGIINPR AGYTSYALKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCTSGWDVWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGGG GSGGGSHHHHHH		741
PEP004443	QVQLVQSGAEVKKPGASVKVSCKASGY TFTKNYMHWVRQAPGQGLEWLGWVSP DSGYTGYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCTTDLLSLELDDA FDIWGQGTMVTVSSAKTTAPSVYPLAPV CGDTTGSSVTLGCLVKGYFPEPVTLTWN SGSLSSGVHTFPAVLQSDLYTLSSSVTVT SSTWPSQSITCNVAHPASSTKVDKKIEPR GPTIKPCPPCKCPAPNAAGGPSVFIFPPKI KDVLMISLSPIVTCVVVDVSEDDPDVQIS WFVNNVEVHTAQTQTHREDYNSTLRVV SALPIQHQDWMSGKEFKCKVNNKDLGA PIERTISKPKGSVRAPQVYVLPPPEKEMT KKQVSLTCLVKDFMPEDIYVEWTNNGK TELNYKNTEPVLKSDGSYFMYSKLTVE KKNWVERNSYSCSVVHEGLHNHHTTKS FSRTPGGGGSGGGSHHHHHH		742
PEP004445	QVQLVQSGAEVKKPGASVKVSCKASGY TFTRYYMHWVRQAPGQGLEWMGIINPR AGYTSYALKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCTSGWDVWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER		743

肽 ID	序列	註釋	SEQ ID NO:
	NSYSCSVVHEGLHNHHTTKSFSRTPGGG GSGGGSHHHHHH		
PEP004446	QVQLVQSGAEVKKPGASVKVSCKASGY TFTTYYMHWVRQAPGQGLEWMGIINPR AGYTSYALKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCTSGWDVWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGGG GSGGGSHHHHHH		744
PEP004729	EIVLTQSPATLSLSPGERATLSCRASQSV SSYLAWYQQKPGQAPRLLIYDASNRAT GIPARFSGSGSGTDFTLTISSLEPEDFAVY YCQQSSNWPRTFGQGTKVEIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		745
PEP004810	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSQVQ LVQSGAEVKKPGASVKVSCKASGDTFT RYYVHWVRQAPGQGLEWMGIINPSGGY ASYAQKFQGRVTMTRDTSTSTVYMELS SLRSEDTAVYYCAAGLFIWGQGTLVTVS SAKTTAPSVYPLAPVCGDTTGSSVTLGC LVKGYFPEPVTLTWNSGSLSSGVHTFPA VLQSDLYTLSSSVTVTSSTWPSQSITCNV AHPASSTKVDKKIEPRGPTIKPCPPCKCP APNAAGGPSVFIFPPKIKDVLMISLSPIVT CVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWM SGKEFKCKVNNKDLGAPIERTISKPKGS VRAPQVYVLPPPEEEMTKKQVTLTCMV TDFMPEDIYVEWTNNGKTELNYKNTEP VLDSDGSYFMYSDLRVEKKNWVERNSY SCSVVHEGLHNHHTTESFSRTPGK		746
PEP004813	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR		747

肽 ID	序列	註釋	SEQ ID NO:
	DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSQVQ LVQSGAEVKKPGASVKVSCKASGYTFT RYYMHWVRQAPGQGLEWMGIINPRAG YTSYALKFQGRVTMTRDTSTSTVYMEL SSLRSEDTAVYYCTSGWDVWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTL GCLVKGYFPEPVTLTWNSGSLSSGVHTF PAVLQSDLYTLSSSVTVTSSTWPSQSITC NVAHPASSTKVDKKIEPRGPTIKPCPPCK CPAPNAAGGPSVFIFPPKIKDVLMISLSPI VTCVVVDVSEDDPDVQISWFVNNVEVH TAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPK GSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNT EPVLDSDGSYFMYSDLRVEKKNWVERN SYSCSVVHEGLHNHHTTESFSRTPGK		
PEP004818	QVQLVQSGAEVKKPGASVKVSCKASGY TFTRYYMHWVRQAPGQGLEWMGIINPR AGYTSYALKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCTSGWDVWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGK		748
PEP004822	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSQVQLVQSGAEVKKPGASVKVSCKAS GDTFTRYYVHWVRQAPGQGLEWMGIIN PSGGYASYAQKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYCAAGLFIWGQG TLVTVSSAKTTAPSVYPLAPVCGDTTGS SVTLGCLVKGYFPEPVTLTWNSGSLSSG VHTFPAVLQSDLYTLSSSVTVTSSTWPS QSITCNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKDVLM ISLSPIVTCVVVDVSEDDPDVQISWFVNN VEVHTAQTQTHREDYNSTLRVVSALPIQ HQDWMSGKEFKCKVNNKDLGAPIERTI		749

肽 ID	序列	註釋	SEQ ID NO:
	SKPKGSVRAPQVYVLPPPEEEMTKKQVT LTCMVTDFMPEDIYVEWTNNGKTELNY KNTEPVLDSDGSYFMYSDLRVEKKNWV ERNSYSCSVVHEGLHNHHTTESFSRTPG K		
PEP004825	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSQVQLVQSGAEVKKPGASVKVSCKAS GYTFTRYYMHWVRQAPGQGLEWMGII NPRAGYTSYALKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCTSGWDVWG QGTLVTVSSAKTTAPSVYPLAPVCGDTT GSSVTLGCLVKGYFPEPVTLTWNSGSLS SGVHTFPAVLQSDLYTLSSSVTVTSSTW PSQSITCNVAHPASSTKVDKKIEPRGPTI KPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFV NNVEVHTAQTQTHREDYNSTLRVVSAL PIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEEEMTKK QVTLTCMVTDFMPEDIYVEWTNNGKTE LNYKNTEPVLDSDGSYFMYSDLRVEKK NWVERNSYSCSVVHEGLHNHHTTESFS RTPGK		750
PEP004829	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSQVQLVQSGAEVKKPGASVKV SCKASGDTFTRYYVHWVRQAPGQGLE WMGIINPSGGYASYAQKFQGRVTMTRD TSTSTVYMELSSLRSEDTAVYYCAAGLF IWGQGTLVTVSSAKTTAPSVYPLAPVCG DTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSS TWPSQSITCNVAHPASSTKVDKKIEPRGP TIKPCPPCKCPAPNAAGGPSVFIFPPKIKD VLMISLSPIVTCVVVDVSEDDPDVQISWF VNNVEVHTAQTQTHREDYNSTLRVVSA LPIQHQDWMSGKEFKCKVNNKDLGAPI ERTISKPKGSVRAPQVYVLPPPEEEMTK KQVTLTCMVTDFMPEDIYVEWTNNGKT ELNYKNTEPVLDSDGSYFMYSDLRVEK KNWVERNSYSCSVVHEGLHNHHTTESF SRTPGK		751
PEP004832	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH		752

肽 ID	序列	註釋	SEQ ID NO:
	LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSQVQLVQSGAEVKKPGASVKV SCKASGYTFTRYYMHWVRQAPGQGLE WMGIINPRAGYTSYALKFQGRVTMTRD TSTSTVYMELSSLRSEDTAVYYCTSGWD VWGQGTLVTVSSAKTTAPSVYPLAPVC GDTTGSSVTLGCLVKGYFPEPVTLTWNS GSLSSGVHTFPAVLQSDLYTLSSSVTVTS STWPSQSITCNVAHPASSTKVDKKIEPRG PTIKPCPPCKCPAPNAAGGPSVFIFPPKIK DVLMISLSPIVTCVVVDVSEDDPDVQIS WFVNNVEVHTAQTQTHREDYNSTLRVV SALPIQHQDWMSGKEFKCKVNNKDLGA PIERTISKPKGSVRAPQVYVLPPPEEEMT KKQVTLTCMVTDFMPEDIYVEWTNNGK TELNYKNTEPVLDSDGSYFMYSDLRVE KKNWVERNSYSCSVVHEGLHNHHTTES FSRTPGK		
PEP004836	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGDTFTRYYVHW VRQAPGQGLEWMGIINPSGGYASYAQK FQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCAAGLFIWGQGTLVTVSSAKTTA PSVYPLAPVCGDTTGSSVTLGCLVKGYF PEPVTLTWNSGSLSSGVHTFPAVLQSDL YTLSSSVTVTSSTWPSQSITCNVAHPASS TKVDKKIEPRGPTIKPCPPCKCPAPNAAG GPSVFIFPPKIKDVLMISLSPIVTCVVVDV SEDDPDVQISWFVNNVEVHTAQTQTHR EDYNSTLRVVSALPIQHQDWMSGKEFK CKVNNKDLGAPIERTISKPKGSVRAPQV YVLPPPEEEMTKKQVTLTCMVTDFMPE DIYVEWTNNGKTELNYKNTEPVLDSDG SYFMYSDLRVEKKNWVERNSYSCSVVH EGLHNHHTTESFSRTPGK		753
PEP004839	APASSSTKKTQLQLEHLLLDLQMILNGI NNYKNPKLTRMLTAKFAMPKKATELKH LQCLEEELKPLEEVLNGAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETA TIVEFLNRWITFAQSIISTLTGGGGSGGG GSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGYTFTRYYMHW VRQAPGQGLEWMGIINPRAGYTSYALK FQGRVTMTRDTSTSTVYMELSSLRSEDT		754

肽 ID	序列	註釋	SEQ ID NO:
	AVYYCTSGWDVWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGY FPEPVTLTWNSGSLSSGVHTFPAVLQSD LYTLSSSVTVTSSTWPSQSITCNVAHPAS STKVDKKIEPRGPTIKPCPPCKCPAPNAA GGPSVFIFPPKIKDVLMISLSPIVTCVVVD VSEDDPDVQISWFVNNVEVHTAQTQTH REDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQ VYVLPPPEEEMTKKQVTLTCMVTDFMP EDIYVEWTNNGKTELNYKNTEPVLDSD GSYFMYSDLRVEKKNWVERNSYSCSVV HEGLHNHHTTESFSRTPGK		
PEP004957	APTSSSTKKTQLQLEHLLLDLQMILNGIN NYKNPKLTDMLTFEFYMPKKATELKHL QCLERELKPLEEVLNLAQSKNFHLRPRD LISNINVIVLELKGSETTFMCEYADETATI VEFLNRWITFCQSIISTLTGGGGSGGGGS GGGGSGGGGSQVQLVQSGAEVKKPGAS VKVSCKASGDTFTRYYVHWVRQAPGQ GLEWMGIINPSGGYASYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCAA GLFIWGQGTLVTVSSAKTTAPSVYPLAP VCGDTTGSSVTLGCLVKGYFPEPVTLTW NSGSLSSGVHTFPAVLQSDLYTLSSSVTV TSSTWPSQSITCNVAHPASSTKVDKKIEP RGPTIKPCPPCKCPAPNAAGGPSVFIFPP KIKDVLMISLSPIVTCVVVDVSEDDPDV QISWFVNNVEVHTAQTQTHREDYNSTL RVVSALPIQHQDWMSGKEFKCKVNNKD LGAPIERTISKPKGSVRAPQVYVLPPPEE EMTKKQVTLTCMVTDFMPEDIYVEWTN NGKTELNYKNTEPVLDSDGSYFMYSDL RVEKKNWVERNSYSCSVVHEGLHNHHT TESFSRTPGK		755
PEP004958	APTSSSTKKTQLQLEHLLLDLQMILNGIN NYKNPKLTDMLTFEFYMPKKATELKHL QCLERELKPLEEVLNLAQSKNFHLRPRD LISNINVIVLELKGSETTFMCEYADETATI VEFLNRWITFCQSIISTLTGGGGSGGGGS GGGGSGGGGSQVQLVQSGAEVKKPGAS VKVSCKASGHTFTRYYMHWVRQAPGQ GLEWMGIINPSGGYATYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCAS GLFIWGQGTLVTVSSAKTTAPSVYPLAP VCGDTTGSSVTLGCLVKGYFPEPVTLTW NSGSLSSGVHTFPAVLQSDLYTLSSSVTV TSSTWPSQSITCNVAHPASSTKVDKKIEP RGPTIKPCPPCKCPAPNAAGGPSVFIFPP KIKDVLMISLSPIVTCVVVDVSEDDPDV QISWFVNNVEVHTAQTQTHREDYNSTL		756

肽 ID	序列	註釋	SEQ ID NO:
	RVVSALPIQHQDWMSGKEFKCKVNNKD LGAPIERTISKPKGSVRAPQVYVLPPPEE EMTKKQVTLTCMVTDFMPEDIYVEWTN NGKTELNYKNTEPVLDSDGSYFMYSDL RVEKKNWVERNSYSCSVVHEGLHNHHT TESFSRTPGK		
PEP004959	APTSSSTKKTQLQLEHLLLDLQMILNGIN NYKNPKLTDMLTFEFYMPKKATELKHL QCLERELKPLEEVLNLAQSKNFHLRPRD LISNINVIVLELKGSETTFMCEYADETATI VEFLNRWITFCQSIISTLTGGGGSGGGGS GGGGSGGGGSQVQLVQSGAEVKKPGAS VKVSCKASGYTFTDYYMHWVRQAPGQ GLEWMGIINPRAGYTSYALKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCTS GWDVWGQGTLVTVSSAKTTAPSVYPLA PVCGDTTGSSVTLGCLVKGYFPEPVTLT WNSGSLSSGVHTFPAVLQSDLYTLSSSV TVTSSTWPSQSITCNVAHPASSTKVDKKI EPRGPTIKPCPPCKCPAPNAAGGPSVFIFP PKIKDVLMISLSPIVTCVVVDVSEDDPDV QISWFVNNVEVHTAQTQTHREDYNSTL RVVSALPIQHQDWMSGKEFKCKVNNKD LGAPIERTISKPKGSVRAPQVYVLPPPEE EMTKKQVTLTCMVTDFMPEDIYVEWTN NGKTELNYKNTEPVLDSDGSYFMYSDL RVEKKNWVERNSYSCSVVHEGLHNHHT TESFSRTPGK		757
PEP004960	APTSSSTKKTQLQLEHLLLDLQMILNGIN NYKNPKLTDMLTFEFYMPKKATELKHL QCLERELKPLEEVLNLAQSKNFHLRPRD LISNINVIVLELKGSETTFMCEYADETATI VEFLNRWITFCQSIISTLTGGGGSGGGGS GGGGSGGGGSQVQLVQSGAEVKKPGAS VKVSCKASGYTFTTYYMHWVRQAPGQ GLEWMGIINPRAGYTSYALKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCTS GWDVWGQGTLVTVSSAKTTAPSVYPLA PVCGDTTGSSVTLGCLVKGYFPEPVTLT WNSGSLSSGVHTFPAVLQSDLYTLSSSV TVTSSTWPSQSITCNVAHPASSTKVDKKI EPRGPTIKPCPPCKCPAPNAAGGPSVFIFP PKIKDVLMISLSPIVTCVVVDVSEDDPDV QISWFVNNVEVHTAQTQTHREDYNSTL RVVSALPIQHQDWMSGKEFKCKVNNKD LGAPIERTISKPKGSVRAPQVYVLPPPEE EMTKKQVTLTCMVTDFMPEDIYVEWTN NGKTELNYKNTEPVLDSDGSYFMYSDL RVEKKNWVERNSYSCSVVHEGLHNHHT TESFSRTPGK		758

肽 ID	序列	註釋	SEQ ID NO:
PEP004967	QVQLVESGGGVVQPGRSLRLDCKASGIT FSNSGMHWVRQAPGKGLEWVAVIWYD GSKRYYADSVKGRFTISRDNSKNTLFLQ MNSLRAEDTAVYYCATNDDYWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEEEMTKKQVTLT CMVTDFMPEDIYVEWTNNGKTELNYKN TEPVLDSDGSYFMYSDLRVEKKNWVER NSYSCSVVHEGLHNHHTTESFSRTPGGG GGSGGGGSGGGGSAPTSSSTKKTQLQLE HLLLDLQMILNGINNYKNPKLTDMLTFE FYMPKKATELKHLQCLERELKPLEEVLN LAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFCQSIIS TLT		759
PEP004973	QVQLVESGGGVVQPGRSLRLDCKASGIT FSNSGMHWVRQAPGKGLEWVAVIWYD GSKRYYADSVKGRFTISRDNSKNTLFLQ MNSLRAEDTAVYYCATNDDYWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGGG GGSGGGGSGGGGSGGGGSQVQLVQSG AEVKKPGASVKVSCKASGHTFTRYYMH WVRQAPGQGLEWMGIINPSGGYATYAQ KFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCASGLFIWGQGTLVTVSSASGG GGSGGGGSGGGGSHASDIQMTQSPSSLS ASVGDRVTITCRASQSINSWLAWYQQK PGKAPKLLIYATSTLESGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQYYRFPVT FGQGTKVEIKGGGSGGGSHHHHHH		760
PEP004974	QVQLVESGGGVVQPGRSLRLDCKASGIT FSNSGMHWVRQAPGKGLEWVAVIWYD GSKRYYADSVKGRFTISRDNSKNTLFLQ		761

肽 ID	序列	註釋	SEQ ID NO:
	MNSLRAEDTAVYYCATNDDYWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGGG GGSGGGGSGGGGSGGGGSQVQLVQSG AEVKKPGASVKVSCKASGYTFTDYYMH WVRQAPGQGLEWMGIINPRAGYTSYAL KFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCTSGWDVWGQGTLVTVSSASG GGGSGGGGSGGGGSHASDIQMTQSPSSL SASVGDRVTITCRASQSISTWLAWYQQK PGKAPKLLIYAASSLDSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYSFPVT FGQGTKVEIKGGGSGGGSHHHHHH		
PEP004978	QVQLVQSGAEVKKPGASVKVSCKASGY TFTTYYMHWVRQAPGQGLEWMGIINPS GGGTLYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTTV TVSSAKTTAPSVYPLAPVCGDTTGSSVT LGCLVKGYFPEPVTLTWNSGSLSSGVHT FPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNAAGGPSVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPK GSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNT EPVLDSDGSYFMYSDLRVEKKNWVERN SYSCSVVHEGLHNHHTTESFSRTPGGGG GSGGGGSGGGGSAPTSSSTKKTQLQLEH LLLDLQMILNGINNYKNPKLTDMLTFEF YMPKKATELKHLQCLERELKPLEEVLNL AQSKNFHLRPRDLISNINVIVLELKGSET TFMCEYADETATIVEFLNRWITFCQSIIST LT		762
PEP004981	QVQLVQSGAEVKKPGASVKVSCKASGY TFTTYYMHWVRQAPGQGLEWMGIINPS GGGTLYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTTV TVSSAKTTAPSVYPLAPVCGDTTGSSVT LGCLVKGYFPEPVTLTWNSGSLSSGVHT		763

肽 ID	序列	註釋	SEQ ID NO:
	FPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNAAGGPSVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPK GSVRAPQVYVLPPPEKEMTKKQVSLTCL VKDFMPEDIYVEWTNNGKTELNYKNTE PVLKSDGSYFMYSKLTVEKKNWVERNS YSCSVVHEGLHNHHTTKSFSRTPGGGG GSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGDTFTRYYVHW VRQAPGQGLEWMGIINPSGGYASYAQK FQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCAAGLFIWGQGTLVTVSSASGGG GSGGGGSGGGGSHASDIQMTQSPSSLSA SVGDRVTITCRASQSIGRWLAWYQQKP GKAPKLLIYSASNLETGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQYERFPVTF GPGTKVDIKGGGSGGGSHHHHHH		
PEP004982	QVQLVQSGAEVKKPGASVKVSCKASGY TFTTYYMHWVRQAPGQGLEWMGIINPS GGGTLYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTTV TVSSAKTTAPSVYPLAPVCGDTTGSSVT LGCLVKGYFPEPVTLTWNSGSLSSGVHT FPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNAAGGPSVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPK GSVRAPQVYVLPPPEKEMTKKQVSLTCL VKDFMPEDIYVEWTNNGKTELNYKNTE PVLKSDGSYFMYSKLTVEKKNWVERNS YSCSVVHEGLHNHHTTKSFSRTPGGGG GSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGDTFTRYYVHW VRQAPGQGLEWMGIINPSGGYASYAQK FQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCAAGLFIWGQGTLVTVSSASGGG GSGGGGSGGGGSHASDIQMTQSPSSLSA SVGDRVTITCRASQSIGRYLAWYQQKPG KAPKLLIYSASNLETGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYNSFPVTFG PGTKVDIKGGGSGGGSHHHHHH		764
PEP004983	QVQLVQSGAEVKKPGASVKVSCKASGY TFTTYYMHWVRQAPGQGLEWMGIINPS GGGTLYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTTV TVSSAKTTAPSVYPLAPVCGDTTGSSVT		765

肽 ID	序列	註釋	SEQ ID NO:
	LGCLVKGYFPEPVTLTWNSGSLSSGVHT FPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNAAGGPSVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPK GSVRAPQVYVLPPPEKEMTKKQVSLTCL VKDFMPEDIYVEWTNNGKTELNYKNTE PVLKSDGSYFMYSKLTVEKKNWVERNS YSCSVVHEGLHNHHTTKSFSRTPGGGG GSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGHTFTRYYMHW VRQAPGQGLEWMGIINPSGGYATYAQK FQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCASGLFIWGQGTLVTVSSASGGG GSGGGGSGGGGSHASDIQMTQSPSSLSA SVGDRVTITCRASQSINSWLAWYQQKP GKAPKLLIYATSTLESGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQYYRFPVTF GQGTKVEIKGGGSGGGSHHHHHH		
PEP004984	QVQLVQSGAEVKKPGASVKVSCKASGY TFTTYYMHWVRQAPGQGLEWMGIINPS GGGTLYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAAGLFIWGQGTTV TVSSAKTTAPSVYPLAPVCGDTTGSSVT LGCLVKGYFPEPVTLTWNSGSLSSGVHT FPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNAAGGPSVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQD WMSGKEFKCKVNNKDLGAPIERTISKPK GSVRAPQVYVLPPPEKEMTKKQVSLTCL VKDFMPEDIYVEWTNNGKTELNYKNTE PVLKSDGSYFMYSKLTVEKKNWVERNS YSCSVVHEGLHNHHTTKSFSRTPGGGG GSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGYTFTDYYMHW VRQAPGQGLEWMGIINPRAGYTSYALK FQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCTSGWDVWGQGTLVTVSSASGG GGSGGGGSGGGGSHASDIQMTQSPSSLS ASVGDRVTITCRASQSISTWLAWYQQKP GKAPKLLIYAASSLDSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQSYSFPVTF GQGTKVEIKGGGSGGGSHHHHHH		766
PEP005089	QVQLVESGGGVVQPGRSLRLDCKASGIT FSNSGMHWVRQAPGKGLEWVAVIWYD GSKRYYADSVKGRFTISRDNSKNTLFLQ MNSLRAEDTAVYYCATNDDYWGQGTL		767

肽 ID	序列	註釋	SEQ ID NO:
	VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEEEMTKKQVTLT CMVTDFMPEDIYVEWTNNGKTELNYKN TEPVLDSDGSYFMYSDLRVEKKNWVER NSYSCSVVHEGLHNHHTTESFSRTPGGG GGSGGGGSGGGGSAPASSSTKKTQLQLE HLLLDLQMILNGINNYKNPKLTRMLTA KFAMPKKATELKHLQCLEEELKPLEEVL NGAQSKNFHLRPRDLISNINVIVLELKGS ETTFMCEYADETATIVEFLNRWITFAQSI ISTLT		
PEP005090	QVQLVESGGGVVQPGRSLRLDCKASGIT FSNSGMHWVRQAPGKGLEWVAVIWYD GSKRYYADSVKGRFTISRDNSKNTLFLQ MNSLRAEDTAVYYCATNDDYWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGGG GGSGGGGSGGGGSGGGGSEVQLVESGG GLVQPGGSLRLSCAASGFNIKDTYIHWV RQAPGKGLEWVARIYPTNGYTRYADSV KGRFTISADTSKNTAYLQMNSLRAEDTA VYYCSRWGGDGFYAMDYWGQGTLVT VSSASGGGGSGGGGSGGGGSHASDIQM TQSPSSLSASVGDRVTITCRASQDVNTA VAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQ QHYTTPPTFGQGTKVEIK	AB001203_trastuzumab 對照	768
PEP005091	QVQLVESGGGVVQPGRSLRLDCKASGIT FSNSGMHWVRQAPGKGLEWVAVIWYD GSKRYYADSVKGRFTISRDNSKNTLFLQ MNSLRAEDTAVYYCATNDDYWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI		769

肽 ID	序列	註釋	SEQ ID NO:
	TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGGG GGSGGGGSGGGGSGGGGSQVQLVQSG AEVKKPGASVKVSCKASGDTFTRYYVH WVRQAPGQGLEWMGIINPSGGYASYAQ KFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCAAGLFIWGQGTLVTVSSASGG GGSGGGGSGGGGSHASDIQMTQSPSSLS ASVGDRVTITCRASQSIGRWLAWYQQK PGKAPKLLIYSASNLETGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQYNRFPVT FGPGTKVDIK		
PEP005092	QVQLVESGGGVVQPGRSLRLDCKASGIT FSNSGMHWVRQAPGKGLEWVAVIWYD GSKRYYADSVKGRFTISRDNSKNTLFLQ MNSLRAEDTAVYYCATNDDYWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEKEMTKKQVSLT CLVKDFMPEDIYVEWTNNGKTELNYKN TEPVLKSDGSYFMYSKLTVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGGG GGSGGGGSGGGGSGGGGSQVQLVQSG AEVKKPGASVKVSCKASGYTFTRYYMH WVRQAPGQGLEWMGIINPRAGYTSYAL KFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCTSGWDVWGQGTLVTVSSASG GGGSGGGGSGGGGSHASDIQMTQSPSSL SASVGDRVTITCRASQSISTWLAWYQQK PGKAPKLLIYAASSLDSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYSFPVT FGQGTKVEIK		770
PEP005469	DIQMTQSPSSLSASVGDRVTITCRASQTI SRYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPRTFGQGTKLEIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSK		771

肽 ID	序列	註釋	SEQ ID NO:
	DSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC		
PEP005470	QVQLVQSGAEVKKPGSSVKVSCKASGY TFTAYYIHWVRQAPGQGLEFMGWIHPY SGGTNYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCAIGYYYGKFDYWG QGTLVTVSSAKTTAPSVYPLAPVCGDTT GSSVTLGCLVKGYFPEPVTLTWNSGSLS SGVHTFPAVLQSDLYTLSSSVTVTSSTW PSQSITCNVAHPASSTKVDKKIEPRGPTI KPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFV NNVEVHTAQTQTHREDYNSTLRVVSAL PIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEEEMTKK QVTLTCMVTDFMPEDIYVEWTNNGKTE LNYKNTEPVLDSDGSYFMYSDLRVEKK NWVERNSYSCSVVHEGLHNHHTTESFS RTPGGGGGSGGGGSGGGGSAPTSSSTKK TQLQLEHLLLDLQMILNGINNYKNPKLT DMLTFEFYMPKKATELKHLQCLERELK PLEEVLNLAQSKNFHLRPRDLISNINVIV LELKGSETTFMCEYADETATIVEFLNRW ITFCQSIISTLT		772
PEP005471	QVQLVQSGAEVKKPGSSVKVSCKASGY TFTAYYIHWVRQAPGQGLEFMGWIHPY SGGTNYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCAIGYYYGKFDYWG QGTLVTVSSAKTTAPSVYPLAPVCGDTT GSSVTLGCLVKGYFPEPVTLTWNSGSLS SGVHTFPAVLQSDLYTLSSSVTVTSSTW PSQSITCNVAHPASSTKVDKKIEPRGPTI KPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFV NNVEVHTAQTQTHREDYNSTLRVVSAL PIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEKEMTKK QVSLTCLVKDFMPEDIYVEWTNNGKTE LNYKNTEPVLKSDGSYFMYSKLTVEKK NWVERNSYSCSVVHEGLHNHHTTKSFS RTPGGGGGSGGGGSGGGGSGGGGSQVQ LVQSGAEVKKPGASVKVSCKASGDTFT RYYVHWVRQAPGQGLEWMGIINPSGGY ASYAQKFQGRVTMTRDTSTSTVYMELS SLRSEDTAVYYCAAGLFIWGQGTLVTVS SASGGGGSGGGGSGGGGSHASDIQMTQ SPSSLSASVGDRVTITCRASQSIGRWLA WYQQKPGKAPKLLIYSASNLETGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQY NRFPVTFGPGTKVDIK		773

肽 ID	序列	註釋	SEQ ID NO:
PEP005473	DIVMTQSPLSLPVTPGEPASISCRSSQSLL HSNGYNYLDWYLQKPGQSPQLLIYLGS NRASGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCMQGTHWPPTFGQGTKVEIKR ADAAPTVSIFPPSSEQLTSGGASVVCFLN NFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSY TCEATHKTSTSPIVKSFNRNEC		774
PEP005474	QVQLVQSGAEVKKPGASVKVSCKASGY IFNGYDIHWVRQAPGQGLEWMGWMNP DNGNTGLAQKFQGRVTITADESTSTAY MELSSLRSEDTAVYYCARGMATRFPYY YYGMDVWGQGTLVTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSS SVTVTSSTWPSQSITCNVAHPASSTKVD KKIEPRGPTIKPCPPCKCPAPNAAGGPSV FIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVN NKDLGAPIERTISKPKGSVRAPQVYVLPP PEEEMTKKQVTLTCMVTDFMPEDIYVE WTNNGKTELNYKNTEPVLDSDGSYFMY SDLRVEKKNWVERNSYSCSVVHEGLHN HHTTESFSRTPGGGGGSGGGGSGGGGS APTSSSTKKTQLQLEHLLLDLQMILNGIN NYKNPKLTDMLTFEFYMPKKATELKHL QCLERELKPLEEVLNLAQSKNFHLRPRD LISNINVIVLELKGSETTFMCEYADETATI VEFLNRWITFCQSIISTLT		775
PEP005475	QVQLVQSGAEVKKPGASVKVSCKASGY IFNGYDIHWVRQAPGQGLEWMGWMNP DNGNTGLAQKFQGRVTITADESTSTAY MELSSLRSEDTAVYYCARGMATRFPYY YYGMDVWGQGTLVTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSS SVTVTSSTWPSQSITCNVAHPASSTKVD KKIEPRGPTIKPCPPCKCPAPNAAGGPSV FIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVN NKDLGAPIERTISKPKGSVRAPQVYVLPP PEKEMTKKQVSLTCLVKDFMPEDIYVE WTNNGKTELNYKNTEPVLKSDGSYFMY SKLTVEKKNWVERNSYSCSVVHEGLHN HHTTKSFSRTPGGGGGSGGGGSGGGGS GGGGSQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG		776

肽 ID	序列	註釋	SEQ ID NO:
	QGTLVTVSSASGGGGSGGGGSGGGGSH ASDIQMTQSPSSLSASVGDRVTITCRASQ SIGRWLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIK		
PEP005631	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVCTLPPSRDE LTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGGGGSGGGGSGGGGSGGGGSQ VQLVQSGAEVKKPGASVKVSCKASGDT FTRYYVHWVRQAPGQGLEWMGIINPSG GYASYAQKFQGRVTMTRDTSTSTVYME LSSLRSEDTAVYYCAAGLFIWGQGTLVT VSSASGGGGSGGGGSGGGGSHASDIQM TQSPSSLSASVGDRVTITCRASQSIGRWL AWYQQKPGKAPKLLIYSASNLETGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQ YNRFPVTFGPGTKVDIK		777
PEP005634	EVQLLESGGGLVQPGGSLRLSCAASGFS FSSYTMSWVRQAPGKGLEWVATISGGG RDIYYPDSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCVLLTGRVYFALDSW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVCTLPPSRDE LTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGGGGSGGGGSGGGGSGGGGSQ VQLVQSGAEVKKPGASVKVSCKASGYT FTRYYMHWVRQAPGQGLEWMGIINPRA GYTSYALKFQGRVTMTRDTSTSTVYME		778

肽 ID	序列	註釋	SEQ ID NO:
	LSSLRSEDTAVYYCTSGWDVWGQGTLV TVSSASGGGGSGGGGSGGGGSHASDIQ MTQSPSSLSASVGDRVTITCRASQSISTW LAWYQQKPGKAPKLLIYAASSLDSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQ QSYSFPVTFGQGTKVEIK		
PEP005789	MSTSTQVQLVESGGGVVQPGRSLRLDC KASGITFSNSGMHWVRQAPGKGLEWVA VIWYDGSKRYYADSVKGRFTISRDNSK NTLFLQMNSLRAEDTAVYYCATNDDY WGQGTLVTVSSASGGGGSGGGGSGGG GSHASEIVLTQSPATLSLSPGERATLSCR ASQSVSSYLAWYQQKPGQAPRLLIYDAS NRATGIPARFSGSGSGTDFTLTISSLEPED FAVYYCQQSSNWPRTFGQGTKVEIKEQ KLISEEDLGSGLNDIFEAQKIEWHEGKPI PNPLLGLDSTNA	納武利尤單抗-scFV	779
PEP005790	MSTSTQVQLVQSGVEVKKPGASVKVSC KASGYTFTNYYMYWVRQAPGQGLEW MGGINPSNGGTNFNEKFKNRVTLTTDSS TTTAYMELKSLQFDDTAVYYCARRDYR FDMGFDYWGQGTTVTVSSASGGGGSG GGGSGGGGSHASEIVLTQSPATLSLSPGE RATLSCRASKGVSTSGYSYLHWYQQKP GQAPRLLIYLASYLESGVPARFSGSGSGT DFTLTISSLEPEDFAVYYCQHSRDLPLTF GGGTKVEIKEQKLISEEDLGSGLNDIFEA QKIEWHEGKPIPNPLLGLDSTNA	帕博利珠單抗-scFv	780
PEP005794	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDEFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSGGGGSGGGGSGGGGSGGG GSDIQMTQSPSSLSASVGDRVTITCRASQ SIGRWLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIKEQKLIS EEDLGSGLNDIFEAQKIEWHEGKPIPNPL LGLDST	AB003178_2B07v12	781
PEP005797	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDEFTRYYVHWVRQAPGQGLEWM GIQNPSGGYASYAQKFQGRVTMTRDTS TSTVYMELSSLRSEDTAVYYCAAGLFIW GQGTLVTVSSGGGGSGGGGSGGGGSGG GGSDIQMTQSPSSLSASVGDRVTITCRAS QSIGRELAWYQQKPGKAPKLLIYDASNL ETGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQYNRFPVTFGPGTKVDIKEQKLI SEEDLGSGLNDIFEAQKIEWHEGKPIPNP LLGLDST	AB003183_2B07v14	782

肽 ID	序列	註釋	SEQ ID NO:
PEP005798	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDEFTRYYVHWVRQAPGQGLEWM GIQNPSGGYASYAQKFQGRVTMTRDTS TSTVYMELSSLRSEDTAVYYCAAGLFIW GQGTLVTVSSGGGGSGGGGSGGGGSGG GGSDIQMTQSPSSLSASVGDRVTITCRAS QSIGRWLAWYQQKPGKAPKLLIYSASN LETGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYNRFPVTFGPGTKVDIKEQKL ISEEDLGSGLNDIFEAQKIEWHEGKPIPN PLLGLDST	AB003180_2B07v13	783
PEP005801	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSGGGGSGGGGSGGGGSGGG GSDIQMTQSPSSLSASVGDRVTITCRASQ SIGRELAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIKEQKLIS EEDLGSGLNDIFEAQKIEWHEGKPIPNPL LGLDST	AB003174_2B07v11	784
PEP005803	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSGGGGSGGGGSGGGGSGGG GSDIQMTQSPSSLSASVGDRVTITCRASQ SIGRWLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIKEQKLIS EEDLGSGLNDIFEAQKIEWHEGKPIPNPL LGLDST	AB002328_2B07v4	785
PEP005817	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGETFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAAGLFIWG QGTLVTVSSGGGGSGGGGSGGGGSGGG GSDIQMTQSPSSLSASVGDRVTITCRASQ SIGRWLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRFPVTFGPGTKVDIKEQKLIS EEDLGSGLNDIFEAQKIEWHEGKPIPNPL LGLDST	AB003155_2B07v10	786
PEP005840	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGYTFTRYYMHWVRQAPGQGLEWM GIINPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCTSGWDVW GQGTLVTVSSGGGGSGGGGSGGGGSGG GGSDIQMTQSPSSLSASVGDRVTITCRAS	AB003012_7A04v7	787

肽 ID	序列	註釋	SEQ ID NO:
	QSISTWLAWYQQKPGKAPKLLIYAASSL DEGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSFPVTFGQGTKVEIKEQKL ISEEDLGSGLNDIFEAQKIEWHEGKPIPN PLLGLDST		
PEP005842	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGYTFTRYYMHWVRQAPGQGLEWM GIINPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCTSGWDVW GQGTLVTVSSGGGGSGGGGSGGGGSGG GGSDIQMTQSPSSLSASVGDRVTITCRAS QSISTWLAWYQQKPGKAPKLLIYAASSL DSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSFPVTFGQGTKVEIKEQKL ISEEDLGSGLNDIFEAQKIEWHEGKPIPN PLLGLDST	AB002365_7A04v2	788
PEP005843	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGYTFTRYYMHWVRQAPGQGLEWM GIINPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCTSGWEVW GQGTLVTVSSGGGGSGGGGSGGGGSGG GGSDIQMTQSPSSLSASVGDRVTITCRAS QSISTWLAWYQQKPGKAPKLLIYAASSL DEGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSFPVTFGQGTKVEIKEQKL ISEEDLGSGLNDIFEAQKIEWHEGKPIPN PLLGLDST	AB003007_7A04v6	789
PEP005845	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGYTFTRYYMHWVRQAPGQGLEWM GIIQPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCTSGWDVW GQGTLVTVSSGGGGSGGGGSGGGGSGG GGSDIQMTQSPSSLSASVGDRVTITCRAS QSISTWLAWYQQKPGKAPKLLIYAASSL DEGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSFPVTFGQGTKVEIKEQKL ISEEDLGSGLNDIFEAQKIEWHEGKPIPN PLLGLDST	AB003005_7A04v5	790
PEP005847	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGETFTNYYIHWVRQAPGQGLEWM GIIDPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAGGWED WGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSDIQMTQSPSSLSASVGDRVTITC RISQSISSFLAWYQQKPGKAPKLLIYSAS SLQSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSFTSPITFGQGTRLEIKEQKLI SEEDLGSGLNDIFEAQKIEWHEGKPIPNP LLGLDST	AB003209_2B05v4	791

肽 ID	序列	註釋	SEQ ID NO:
PEP005853	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGETFTNYYIHWVRQAPGQGLEWM GVINPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAGGWED WGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSDIQMTQSPSSLSASVGDRVTITC RISQSISSWLAWYQQKPGKAPKLLIYSAS SLQSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSFTSPITFGQGTRLEIKEQKLI SEEDLGSGLNDIFEAQKIEWHEGKPIPNP LLGLDST	AB003200_2B05v1	792
PEP005860	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGFTFTRYYMHWVRQAPGQGLEWM GVINPSGGYATYAQKFQGRVTMTRDTS TSTVYMELSSLRSEDTAVYYCASGWDV WGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSDIQMTQSPSSLSASVGDRVTITC RASQSISSWLAWYQQKPGKAPKLLIYAT STLESGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQQSYSSPVTFGQGTKVEIKEQ KLISEEDLGSGLNDIFEAQKIEWHEGKPI PNPLLGLDST	AB003021_2A11v7	793
PEP005863	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGGTFTNYYIHWVRQAPGQGLEWM GIIDPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAGGWED WGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSDIQMTQSPSSLSASVGDRVTITC RISQSISSWLAWYQQKPGKAPKLLIYSAS SLQSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSFTSPITFGQGTRLEIKEQKLI SEEDLGSGLNDIFEAQKIEWHEGKPIPNP LLGLDST	AB003201_2B05v2	794
PEP005867	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQGLEWM GIINPSGGYATYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCASGLFIWG QGTLVTVSSGGGGSGGGGSGGGGSGGG GSDIQMTQSPSSLSASVGDRVTITCRASQ SINSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYRFPVTFGQGTKVEIKEQKLIS EEDLGSGLNDIFEAQKIEWHEGKPIPNPL LGLDST	AB002427_2A11v5	795
PEP005868	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQGLEWM GIINPSGGYATYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCASGLFIWG QGTLVTVSSGGGGSGGGGSGGGGSGGG GSDIQMTQSPSSLSASVGDRVTITCRASQ	AB002413_2A11v3	796

肽 ID	序列	註釋	SEQ ID NO:
	SINSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYYRFPVTFGQGTKVEIKEQKLIS EEDLGSGLNDIFEAQKIEWHEGKPIPNPL LGLDST		
PEP005869	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQGLEWM GIINPSGGYATYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCASGLFIWG QGTLVTVSSGGGGSGGGGSGGGGSGGG GSDIQMTQSPSSLSASVGDRVTITCRASQ SINSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYYSFPVTFGQGTKVEIKEQKLIS EEDLGSGLNDIFEAQKIEWHEGKPIPNPL LGLDST	AB002417_2A11v4	797
PEP005880	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQGLEWM GVINPSGGYATYAQKFQGRVTMTRDTS TSTVYMELSSLRSEDTAVYYCASGWDV WGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSDIQMTQSPSSLSASVGDRVTITC RASQSINSWLAWYQQKPGKAPKLLIYA TSTLESGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQQSYSSPVTFGQGTKVEIKE QKLISEEDLGSGLNDIFEAQKIEWHEGKP IPNPLLGLDST	AB002864_2A11v6	798
PEP005887	MSTSTQVQLVQSGAEVKKPGASVKVSC KASGSTFTNYYIHWVRQAPGQGLEWM GIIDPRAGYTSYALKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAGGWED WGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSDIQMTQSPSSLSASVGDRVTITC RISQSISSFLAWYQQKPGKAPKLLIYSAS SLQSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSFTSPITFGQGTRLEIKEQKLI SEEDLGSGLNDIFEAQKIEWHEGKPIPNP LLGLDST	AB003202_2B05v3	799
PEP006177	QVQLVESGGGVVQPGRSLRLDCKASGIT FSNSGMHWVRQAPGKGLEWVAVIWYD GSKRYYADSVKGRFTISRDNSKNTLFLQ MNSLRAEDTAVYYCATNDDYWGQGTL VTVSSAKTTAPSVYPLAPVCGDTTGSSV TLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTLRVVSALPIQHQ DWMSGKEFKCKVNNKDLGAPIERTISKP KGSVRAPQVYVLPPPEEEMTKKQVTLT		800

肽 ID	序列	註釋	SEQ ID NO:
	CMVTDFMPEDIYVEWTNNGKTELNYKN TEPVLDSDGSYFMYSDLRVEKKNWVER NSYSCSVVHEGLHNHHTTESFSRTPGGG GGSGGGGSGGGGSAPTSSSTKKTQLQLE HLLLDLQMILNGINNYKNPKLTRMLTFK FYMPKKATELKHLQCLEEELKPLEEVLN LAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFCQSIIS TLT		

實例

【0088】以下實例係說明性的，且不限於本文所述之裝置、方法、系統及套組的範圍。

實例 1

一組結合人類 PD-1 及人類 IL-2 的雙重結合抗體 (DBA) 之分離

【0089】本實例描述了本揭露之感測器域 (具體地，一組結合人類 PD-1 及人類 IL-2 的 DBA) 之分離。抗 PD-1 及抗 IL-2 DBA 係分離自 Tumbler 抗體噬菌體展示文庫 (Distributed Bio, Inc.)。將抗體噬菌體展示文庫構建為併入與來自 PD-1 結合抗體的 10 個重鏈 CDR3 序列 (SEQ ID NO: 11 至 SEQ ID NO: 20) 組合的 Superhuman 2.0 抗體文庫的重鏈 CDR1、重鏈 CDR2 及輕鏈多樣性。

表 3 – PD-1 結合物之 HC-CDR3

SEQ ID NO	序列	說明
SEQ ID NO: 11	CAAGLFIW	PD-1 結合物之 HC-CDR3
SEQ ID NO: 12	CAGGWLDW	PD-1 結合物之 HC-CDR3
SEQ ID NO: 13	CARDHLGGSYQPW	PD-1 結合物之 HC-CDR3
SEQ ID NO: 14	CARDLVGVSPGINYVPRYYYY YYGMDVW	PD-1 結合物之 HC-CDR3
SEQ ID NO: 15	CARDTGLGYYYGSGDFDYW	PD-1 結合物之 HC-CDR3
SEQ ID NO: 16	CARSGYSYGYYFDYW	PD-1 結合物之 HC-CDR3
SEQ ID NO: 17	CARTGGYPAIDSW	PD-1 結合物之 HC-CDR3
SEQ ID NO: 18	CASGWDVW	PD-1 結合物之 HC-CDR3
SEQ ID NO: 19	CASSPLQWVDVW	PD-1 結合物之 HC-CDR3
SEQ ID NO: 20	CTSGMDVW	PD-1 結合物之 HC-CDR3

【0090】該文庫經歷用標準方案的四輪選擇。簡言之，將噬菌體文庫與抗原一起孵育，然後捕獲在磁珠上並在 Kingfisher 磁粉處理器上洗滌，從磁珠中沖提並藉由在大腸桿菌 (*E. coli*) 傳代來擴增。第 1 輪與 50 nM 人類 PD-1-His 融合體 (R&D Systems，產品編號8986-PD) 一起孵育，並用 TRIS NTA 生物素 (Sigma-Aldrich 產品編號75543) 及卵白素磁珠捕獲。第 2 輪與 100 nM 生物素化 IL-2 (Creative Biomart，產品編號IL2-501H，使用標準方案生物素化) 一起孵育，並捕獲在卵白素磁珠上。第 3 輪與 50 nM 食蟹獼猴 PD-1-Fc 融合體 (R&D Systems，產品編號8578-PD) 一起孵育，並捕獲在蛋白 G 磁珠上。第 4 輪與 50 nM 生物素化人類 IL-2 一起孵育，並捕獲在卵白素磁珠上。最終選擇作為單菌落接種，並挑選 380 個菌落進行桑格氏 (Sanger) 定序。選擇 151 個獨特殖株進行表現。每個殖株之 scFv 序列針對大腸桿菌 (*E. coli*) 表現進行了密碼子優化，並將相應的 DNA 序列發送至 Integrated DNA Technologies, Inc. (IDT) 以合成為具有 T7 啟動子、翻譯起始位點及 T7 終止子的 gBlock。來自編碼 scFv 的各 gBlock 的蛋白質係使用 PURExpress *活體外*蛋白合成套組 (New England Biolabs, Inc.，產品編號E6800) 來表現。PURExpress scFv 蛋白直接用於 HTRF 結合測定及基於細胞的功能測定中。測試各 scFv 與 PD-1 及人類 IL-2 之結合。其中 81 種抗體對 PD-1 和 IL-2 皆顯示出雙重結合活性，且結合曲線之螢光訊息值之總結如**表 5** 所示。為檢查 DBA 結合域阻斷 IL-2 受體結合的能力，將 V5 標記的 DBA scFvs 在 384 孔盤中連續稀釋。銪標記的卵白素、生物素標記的 IL-2 (Acro Biosystems，產品編號IL2-H82E4)、IL-2 受體 β (Fc-IL2RB) (Acro Biosystems，產品編號ILB-H5253) 及 APC 標記的抗 Fc 抗體。將盤在室溫孵育 2 小時，並在 Envision (Perkin Elmer) 上讀取 HTRF 訊息作為 IL-2:IL2RB 結合之

量度。四種 scFv (SEQ ID NO: 31 至 SEQ ID NO: 34) 結合 PD-1、結合IL-2 並阻斷 IL-2 與 IL-2RB 之結合 (**表 4**)。

表 4 – DBA 及對照

SEQ ID NO	序列	**說明**
SEQ ID NO: 31	QVQLVQSGAEVKKPGVSVKVSCKASGYTF PRSYIHWVRQAPGQGLEWMGWINPHSGDT YYAQNFQGRVTMTRDTSTSTVYMELSSLR SEDTAVYYCARDTGLGYYYGSGDFDYWG QGTLVTVSSASGGGGSGGGGSGGGGSHAS DIQMTQSPSSLSASVGDRVTITCRASQSISR YLNWYQQKPGKAPKLLIYTASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQAN RFPLTFGPGTKVDIK	能夠結合 PD-1 標記物及 IL-2 治療藥物的 DBA
SEQ ID NO: 32	QVQLVQSGAEVKKPGASVKVSCKASGYTF PRYHIHWVRQAPGQGLEWMGMINPSGGTT TYAQKFQGRVTMTRDTSTSTVYMELSSLR SEDTAVYYCARDTGLGYYYGSGDFDYWG QGTLVTVSSASGGGGSGGGGSGGGGSHAS DIQMTQSPSSLSASVGDRVTITCRASQSISS WLAWYQQKPGKAPKLLIYAASSLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQS HSFPLTFGGGTKVEIK	能夠結合 PD-1 標記物及 IL-2 治療藥物的 DBA
SEQ ID NO: 33	QVQLVQSGAEVKKPGASVKVSCKASGYTF TRYYIHWVRQAPGQGLEWMGWINAYNGD TNYAQKLQGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARDSYYYDSFDYWGQGTL VTVSSASGGGGSGGGGSGGGGSHASDIQM TQSPSSLSASVGDRVTITCRASQTITDWLA WYQQKPGKAPKLLIYGASNLQGGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQYYSS WTFGQGTKVEIK	能夠結合 PD-1 標記物及 IL-2 治療藥物的 DBA
SEQ ID NO: 34	QVQLVQSGAEVKKPGASVKVSCKASGYTF TSYYMHWVRQAPGQGLEWMGIINPSDGST TYAQSFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCASGWDVWGQGTLVTVSSASG GGGSGGGGSGGGGSHASDIVMTQSPDSLA VSLGERATINCKSSQSVFSSANNKNYLAW YQQKPGQPPKLLIYWASTRESGVPDRFSGS GSGTDFTLTISSLQAEDVAVYYCQQYFGTP VTFGGGTKVEIK	能夠結合 PD-1 標記物及 IL-2 治療藥物的 DBA

表 5

名稱	**PD1 結合**	**IL2 結合**	**IL2RB 阻斷**
無 DNA	5	6	1,490
PD1-IL2-R01-H08	576	-9	1,829
PD1-IL2-R01-H09	1,015	131	1,772

名稱	PD1 結合	IL2 結合	IL2RB 阻斷
PD1-IL2-R02-A03	1,508	635	1,714
PD1-IL2-R02-A04	909	978	1,618
PD1-IL2-R02-A05	1,557	23	1,735
PD1-IL2-R02-A06	357	515	1,772
PD1-IL2-R02-A08	995	520	1,612
PD1-IL2-R02-A09	1,421	1,470	1,495
PD1-IL2-R02-A10	500	838	1,847
PD1-IL2-R02-A11	1,625	1,559	1,783
PD1-IL2-R02-A12	1,725	130	1,586
PD1-IL2-R02-B01	746	1,077	1,516
PD1-IL2-R02-B02	1,740	1,107	1,849
PD1-IL2-R02-B04	11	2,346	1,536
PD1-IL2-R02-B05	1,665	2,489	1,613
PD1-IL2-R02-B06	1,527	32	1,605
PD1-IL2-R02-B07	1,685	628	1,814
PD1-IL2-R02-B08	1,446	92	1,680
PD1-IL2-R02-B10	211	343	1,607
PD1-IL2-R02-B11	1,426	915	1,509
PD1-IL2-R02-B12	1,264	316	1,762
PD1-IL2-R02-C01	1,463	296	1,743
PD1-IL2-R02-C02 (SEQ ID NO: 31)	1,299	298	1,069
PD1-IL2-R02-C03 (SEQ ID NO: 32)	1,383	293	1,211
PD1-IL2-R02-C04	1,622	575	1,857
PD1-IL2-R02-C06	1,376	34	1,684
PD1-IL2-R02-C07	34	87	1,607
PD1-IL2-R02-C08	1,468	619	1,671
PD1-IL2-R02-C10	174	256	1,757
PD1-IL2-R02-C12	1,367	340	1,723
PD1-IL2-R02-D01	1,421	68	1,614
PD1-IL2-R02-D02	1,473	539	1,726
PD1-IL2-R06-A10	1,269	9	1,796
PD1-IL2-R06-A11	1,376	34	1,762
PD1-IL2-R06-A12	1,305	7	1,681
PD1-IL2-R06-B01	10	2,109	1,307
PD1-IL2-R06-B02	1,666	15	1,799
PD1-IL2-R06-B03	923	4	1,661
PD1-IL2-R06-B04	1,782	28	1,666
PD1-IL2-R06-B06	1,223	17	1,648
PD1-IL2-R06-B08	1,777	1,160	1,738
PD1-IL2-R06-B10	13	31	1,847
PD1-IL2-R06-B11	1,534	24	1,699

名稱	PD1 結合	IL2 結合	IL2RB 阻斷
PD1-IL2-R06-B12	822	1,125	1,604
PD1-IL2-R06-C02	1,667	26	1,671
PD1-IL2-R06-C04	1,491	7	1,759
PD1-IL2-R06-C08	1,448	8	1,693
PD1-IL2-R06-C09	1,158	1,525	1,602
PD1-IL2-R06-C11	1,879	-2	1,785
PD1-IL2-R06-C12	1,669	1,998	1,033
PD1-IL2-R06-D02	280	432	1,677
PD1-IL2-R06-D03	9	93	1,606
PD1-IL2-R06-D05	505	-3	1,786
PD1-IL2-R06-D07	1,577	24	1,820
PD1-IL2-R06-D10	1,751	49	1,719
PD1-IL2-R06-D11	405	593	1,576
PD1-IL2-R06-D12	1,024	1,423	1,649
PD1-IL2-R06-E01	1,628	3	1,724
PD1-IL2-R06-E02	1,554	16	1,598
PD1-IL2-R06-E04 (SEQ ID NO: 33)	50	247	1,108
PD1-IL2-R06-E05	1,364	14	1,734
PD1-IL2-R06-E06	1,627	15	1,735
PD1-IL2-R06-E07	1,801	12	1,698
PD1-IL2-R06-E09	1,467	11	1,511
PD1-IL2-R06-E11	1,805	294	1,767
PD1-IL2-R06-E12	4	-7	1,735
PD1-IL2-R06-F01	196	280	1,629
PD1-IL2-R06-F03	1,377	28	1,642
PD1-IL2-R06-F04	26	779	1,726
PD1-IL2-R06-F05	1,493	18	1,625
PD1-IL2-R06-F06	1,577	46	1,595
PD1-IL2-R06-F07	1,544	335	1,682
PD1-IL2-R06-F08	1,570	9	1,780
PD1-IL2-R06-F09	30	41	1,776
PD1-IL2-R06-F10	1,745	24	1,607
PD1-IL2-R06-F11	1,586	12	1,574
PD1-IL2-R06-F12	623	8	1,645
PD1-IL2-R06-G01	130	184	1,640
PD1-IL2-R06-G02	1,754	20	1,623
PD1-IL2-R06-G04	1,348	13	1,596
PD1-IL2-R06-G05	1,382	10	1,846
PD1-IL2-R06-G06	1,383	4	1,744
PD1-IL2-R06-G08	1,708	124	1,533
PD1-IL2-R06-G09	557	756	1,527
PD1-IL2-R06-G10	1,595	35	1,703

名稱	PD1 結合	IL2 結合	IL2RB 阻斷
PD1-IL2-R06-G11	1,469	17	1,709
PD1-IL2-R06-G12	1,281	1,479	1,713
PD1-IL2-R06-H01	381	4	1,647
PD1-IL2-R06-H02	1,501	20	1,748
PD1-IL2-R06-H03	1,132	1,449	1,617
PD1-IL2-R06-H04	355	1	1,677
PD1-IL2-R06-H05	1,409	21	1,561
PD1-IL2-R06-H06	1,491	23	1,650
PD1-IL2-R06-H07	12	13	1,701
PD1-IL2-R06-H08	847	1,118	1,746
PD1-IL2-R06-H09	1,732	22	1,662
PD1-IL2-R06-H10	830	1,151	1,569
PD1-IL2-R07-A03	1,786	28	1,511
PD1-IL2-R07-A04	730	973	1,613
PD1-IL2-R07-A05	477	663	1,327
PD1-IL2-R07-A08	1,628	841	1,618
PD1-IL2-R07-A09 (SEQ ID NO: 34)	1,235	2,040	910
PD1-IL2-R07-A10	1,716	63	1,518
PD1-IL2-R07-B01	1,397	32	1,565
PD1-IL2-R07-B02	192	321	1,634
PD1-IL2-R07-B03	65	202	1,604
PD1-IL2-R07-B04	1,862	410	1,527
PD1-IL2-R07-B05	965	351	1,389
PD1-IL2-R07-B06	1,882	44	1,497
PD1-IL2-R07-B07	6	2,549	1,517
PD1-IL2-R07-B08	906	1,047	1,475
PD1-IL2-R07-B09	1,788	27	1,384
PD1-IL2-R07-B10	18	19	1,635
PD1-IL2-R07-B11	1,765	9	1,641
PD1-IL2-R07-C01	230	367	1,536
PD1-IL2-R07-C02	236	304	1,500
PD1-IL2-R07-C03	20	1,347	1,536
PD1-IL2-R07-C07	15	275	1,665
PD1-IL2-R07-C10	1,064	317	1,550
PD1-IL2-R07-C11	1,523	642	1,460
PD1-IL2-R07-C12	1,377	49	1,707
PD1-IL2-R07-D01	1,541	79	1,657
PD1-IL2-R07-D03	1,483	33	1,481
PD1-IL2-R07-D04	923	1,104	1,517
PD1-IL2-R07-D06	1,664	416	1,734
PD1-IL2-R07-D07	6	835	1,512
PD1-IL2-R07-D10	1,580	193	1,572

名稱	PD1 結合	IL2 結合	IL2RB 阻斷
PD1-IL2-R07-D11	1,401	798	1,614
PD1-IL2-R07-E02	1,473	992	1,830
PD1-IL2-R07-E03	1,459	422	1,683
PD1-IL2-R07-E05	512	913	1,513
PD1-IL2-R07-E06	1,483	1,178	1,526
PD1-IL2-R07-E07	1,181	1,060	1,524
PD1-IL2-R07-E08	1,604	472	1,717
PD1-IL2-R07-E09	1,733	23	1,569
PD1-IL2-R07-E10	1,472	251	1,545
PD1-IL2-R07-E11	1,146	56	1,777
PD1-IL2-R07-E12	1,698	106	1,764
PD1-IL2-R07-F01	3	17	1,529
PD1-IL2-R07-F02	348	752	1,537
PD1-IL2-R07-F03	1,788	520	1,750
PD1-IL2-R07-F04	1,416	145	1,767
PD1-IL2-R07-F06	1,422	438	1,579
PD1-IL2-R07-F09	1,589	17	1,456
PD1-IL2-R07-F10	24	19	1,778
PD1-IL2-R07-F12	505	196	1,553
PD1-IL2-R07-G01	4	214	1,560
PD1-IL2-R07-G02	1,610	61	1,735
PD1-IL2-R07-G04	82	147	1,600
PD1-IL2-R07-G05	981	216	1,475
PD1-IL2-R07-G06	860	512	1,655
PD1-R04-C10	1,552	4	1,550
PD1-R07-A05	653	19	1,730
PD1-R07-A10	484	25	2,290
PD1-R07-C09	1,911	20	2,080
PD1-R07-D03	1,733	22	2,208
PD1-R07-D05	1,760	16	1,578
PD1-R07-D06	1,997	22	1,749
PD1-R07-E05	633	24	2,246
PD1-R07-G12	907	11	1,577
PD1-R15-B02	1,671	28	1,797
PDL1-DB03-H02	18	11	1,725
抗 Her2 (SEQ ID NO: 28)	4	20	1,636

實例 2

雙重結合抗體 (DBA)-細胞激素蛋白複合體

【0091】本實例描述了本揭露之雙重結合抗體 (DBA)-細胞激素蛋白複合體。本揭露之各種 DBA-細胞激素蛋白複合體係經設計為包括細胞激素、連接子及一個或多個雙重結合抗體域。示例性構建體的圖示如**圖 5** 所示。

【0092】一系列 DBA-細胞激素蛋白複合體可以被設計為具有兩個標記物結合域及一個治療域。該系列中所用之 DBA 提供於**表 6** 中且序列提供於**表 8** 中，表現出對標記物及治療域的各種親和力。示例性 DBA 複合體提供於**表 6**、**表 9** 及**表 10** 中。

表 6 – 示例性 DBA 細胞激素蛋白複合體

SEQ ID NO	序列	說明
SEQ ID NO: 51	QVQLVQSGAEVKKPGASVKVSCKASGYTFST YYIHWVRQAPGQGLEWMGIINPSGGGTVYA QKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCAAGLFIWGQGTLVTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVTLTW NSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSST WPSQSITCNVAHPASSTKVDKKIEPRGPTIKPC PPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPI VTCVVVDVSEDDPDVQISWFVNNVEVHTAQ TQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYV LPPPEEEMTKKQVTLTCMVTDFMPEDIYVEW TNNGKTELNYKNTEPVLDSDGSYFMYSKLRV EKKNWVERNSYSCSVVHEGLHNHHTTKSFSR TPGK	PD1-IL2_6C12_N36T_Sym_L_Long_Pep1；對稱 DBA-細胞激素複合體 IgG 形式
SEQ ID NO: 52	APTSSSTKKTQLQLEHLLLDLQMILNGINNYK NPKLTRMLTFKFYMPKKATELKHLQCLEEEL KPLEEVLNLAQSKNFHLRPRDLISNINVIVLEL KGSETTFMCEYADETATIVEFLNRWITFCQSII STLTVPGVGVPGAGVPGVGVPGGGVPGVGV PGGGVPGAGVPGGGVPGVGVPGAGVPGVGV PGGGDIQMTQSPSSLSASVGDRVTITCRASQY ISSGLAWYQQKPGKAPKLLIYKASSLDNGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYE RLPLTFGGGTKVEIKRADAAPTVSIFPPSSEQL TSGGASVVCFLNNFYPKDINVKWKIDGSERQ NGVLNSWTDQDSKDSTYSMSSTLTLTKDEYE RHNSYTCEATHKTSTSPIVKSFNRNEC	PD1-IL2_6C12_N36T_Sym_L_Long_Pep2；對稱 DBA-細胞激素複合體 IgG 形式
SEQ ID NO: 53	APTSSSTKKTQLQLEHLLLDLQMILNGINNYK NPKLTRMLTFKFYMPKKATELKHLQCLEEEL KPLEEVLNLAQSKNFHLRPRDLISNINVIVLEL KGSETTFMCEYADETATIVEFLNRWITFCQSII	PD1-IL2_6C12_N36T_D68E_Sym_H_Short_Pep1；對稱 DBA-細

SEQ ID NO	序列	說明
	STLTGGGGSGGGGSGGGGSGGGGSQVQLVQ SGAEVKKPGASVKVSCKASGYTFSTYYIHWV RQAPGQGLEWMGIINPSGGGTVYAQKFQGR VTMTRDTSTSTVYMELSSLRSEDTAVYYCAA GLFIWGQGTLVTVSSAKTTAPSVYPLAPVCG DTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSS GVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPCKCP APNAAGGPSVFIFPPKIKDVLMISLSPIVTCVV VDVSEDDPDVQISWFVNNVEVHTAQTQTHRE DYNSTLRVVSALPIQHQDWMSGKEFKCKVN NKDLGAPIERTISKPKGSVRAPQVYVLPPPEEE MTKKQVTLTCMVTDFMPEDIYVEWTNNGKT ELNYKNTEPVLDSDGSYFMYSKLRVEKKNW VERNSYSCSVVHEGLHNHHTTKSFSRTPGK	胞激素複合體 IgG 形式
SEQ ID NO: 54	DIQMTQSPSSLSASVGDRVTITCRASQYISSGL AWYQQKPGKAPKLLIYKASSLENGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQYERLPLT FGGGTKVEIKRADAAPTVSIFPPSSEQLTSGGA SVVCFLNNFYPKDINVKWKIDGSERQNGVLN SWTDQDSKDSTYSMSSTLTLTKDEYERHNSY TCEATHKTSTSPIVKSFNRNEC	PD1-IL2_6C12_N36T_D68E_Sym_H_Short_Pep2；對稱 DBA-細胞激素複合體 IgG 形式
SEQ ID NO: 77	QVQLVQSGAEVKKPGASVKVSCKASGYTFTT YYVHWVRQAPGQGLEWMGIINPSGGSTSYA QNFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCASGWDVWGQGTTVTVSSAKTTAPSVY PLAPVCGDTTGSSVTLGCLVKGYFPEPVTLT WNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTS STWPSQSITCNVAHPASSTKVDKKIEPRGPTIK PCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVEVHT AQTQTHREDYNSTLRVVSALPIQHQDWMSG KEFKCKVNNKDLGAPIERTISKPKGSVRAPQV YVLPPPEEEMTKKQVTLTCMVTDFMPEDIYV EWTNNGKTELNYKNTEPVLDSDGSYFMYSD LRVEKKNWVERNSYSCSVVHEGLHNHHTTE SFSRTPGK	PD1-IL2_L_7A05scFv_PD1-R07-A05_Pep1；不對稱 DBA-細胞激素複合體 IgG-scFv 形式
SEQ ID NO: 78	QVQLVQSGAEVKKPGASVKVSCKASGYTFTT YYVHWVRQAPGQGLEWMGIINPSGGSTSYA QNFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCASGWDVWGQGTTVTVSSASGGGGSG GGGSGGGGSHASEIVMTQSPATLSVSPGERAT LSCRASQSVNTYLAWYQQKPGQAPRLLIYGA STRATGIPARFSGSGSGTEFTLTISSLQSEDFAV YYCQQYGSSPVTFGQGTRLEIKPRGPTIKPCPP CKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIV TCVVVDVSEDDPDVQISWFVNNVEVHTAQT QTHREDYNSTLRVVSALPIQHQDWMSGKEFK CKVNNKDLGAPIERTISKPKGSVRAPQVYVLP PPEKEMTKKQVSLTCLVKDFMPEDIYVEWTN	PD1-IL2_L_7A05scFv_PD1-R07-A05_Pep2；不對稱 DBA-細胞激素複合體 IgG-scFv 形式

SEQ ID NO	序列	說明
	NGKTELNYKNTEPVLKSDGSYFMYSKLTVEK KNWVERNSYSCSVVHEGLHNHHTTKSFSRTP GGGGSGGGSHHHHHH	
SEQ ID NO: 79	APTSSSTKKTQLQLEHLLLDLQMILNGINNYK NPKLTDMLTFKFYMPKKATELKHLQCLEEEL KPLEEVLNLAQSKNFHLRPRDLISNINVIVLEL KGSETTFMCEYADETATIVEFLNRWITFCQSII STLTGGGGSGGGGSGGGGSGGGGSEIVMTQS PATLSVSPGERATLSCRASQSVNTYLAWYQQ KPGQAPRLLIYGASTRATGIPARFSGSGSGTEF TLTISSLQSEDFAVYYCQQYGSSPVTFGQGTR LEIKRADAAPTVSIFPPSSEQLTSGGASVVCFL NNFYPKDINVKWKIDGSERQNGVLNSWTDQ DSKDSTYSMSSTLTLTKDEYERHNSYTCEAT HKTSTSPIVKSFNRNEC	PD1-IL2_L_7A05scFv_PD1-R07-A05_Pep3；不對稱 DBA-細胞激素複合體 IgG-scFv 形式

表 7 – 雙重結合抗體 (DBA)

雙重結合抗體	標記物	治療藥物	HV* SEQ ID NO:	LV** SEQ ID NO:	HV_cdr1 SEQ ID NO:	HV_cdr2 SEQ ID NO:	HV_cdr3 SEQ ID NO:	LV_cdr1 SEQ ID NO:	LV_cdr2 SEQ ID NO:	LV_cdr3 SEQ ID NO:
AB001718	PD-1	IL-2	127	135	142	148	154	157	163	168
AB001744	PD-1	IL-2	128	136	143	148	154	158	163	169
AB002022	PD-1	IL-2	129	137	144	149	154	159	164	170

*HV 係指相應抗體之重鏈可變區

**LV 係指相應抗體之輕鏈可變區

表 8 – DBA 蛋白組分之序列

SEQ ID NO:	DBA 蛋白組分	序列
SEQ ID NO: 127	AB001718_HV	QVQLVQSGAEVKKPGASVKVSCKASG DTFSTYYVHWVRQAPGQGLEWMGIINP SGGGTVYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCAAGLFIWGQGT LVTVSS
SEQ ID NO: 128	AB001744_HV	QVQLVQSGAEVKKPGASVKVSCKASG YTFSNYYIHWVRQAPGQGLEWMGIINP SGGGTVYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCAAGLFIWGQGT LVTVSS
SEQ ID NO: 129	AB002022_HV	QVQLVQSGAEVKKPGASVKVSCKASG DTFTRHYVHWVRQAPGQGLEWMGIIN PSGGYASYAQKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYCAAGLFIWGQG TLVTVSS

SEQ ID NO:	DBA 蛋白組分	序列
SEQ ID NO: 135	AB001718_LV	DIQMTQSPSSLSASVGDRVTITCRASQYI SSGLAWYQQKPGKAPKLLIYKASSLDN GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYERLPLTFGGGTKVEIK
SEQ ID NO: 136	AB001744_LV	DIQMTQSPSSLSASVGDRVTITCRASQSI GTGLAWYQQKPGKAPKLLIYKASSLDN GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYNRAPLTFGGGTKVEIK
SEQ ID NO: 137	AB002022_LV	DIQMTQSPSSLSASVGDRVTITCRASQSI GRWLAWYQQKPGKAPKLLIYSASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQYESFPVTFGPGTKVDIK
SEQ ID NO: 142	AB001718_HV_cdr1	GDTFSTYYVH
SEQ ID NO: 146	AB001843_HV_cdr1	GYTFSGYYIH
SEQ ID NO: 147	AB001866_HV_cdr1	GYTFSNYYVH
SEQ ID NO: 148	AB001718_HV_cdr2	IINPSGGGTVYAQKFQG
	AB001744_HV_cdr2	IINPSGGGTVYAQKFQG
SEQ ID NO: 149	AB002022_HV_cdr2	IINPSGGYASYAQKFQG
SEQ ID NO: 154	AB001718_HV_cdr3	AAGLFI
SEQ ID NO: 157	AB001718_LV_cdr1	RASQYISSGLA
SEQ ID NO: 158	AB001744_LV_cdr1	RASQSIGTGLA
SEQ ID NO: 159	AB002022_LV_cdr1	RASQSIGRWLA
SEQ ID NO: 160	AB001609_LV_cdr1	RASQSISNRLA
SEQ ID NO: 161	AB001638_LV_cdr1	QASQSISNYLA
SEQ ID NO: 162	AB001843_LV_cdr1	RASQSISSYLN
SEQ ID NO: 163	AB001718_LV_cdr2	KASSLDN
	AB001744_LV_cdr2	KASSLDN
SEQ ID NO: 164	AB002022_LV_cdr2	SASNLET
SEQ ID NO: 168	AB001718_LV_cdr3	QQYERLPL
SEQ ID NO: 169	AB001744_LV_cdr3	QQYNRAPL
SEQ ID NO: 170	AB002022_LV_cdr3	QQYESFPV

表 9 – 示例性 DBA-細胞激素蛋白複合體

名稱	DBA/治療藥物	DBA	類型	DBA 域	治療域	第二 Ab 域	重鏈 1 SEQ ID NO:	重鏈 2 SEQ ID NO:	重鏈 3 SEQ ID NO:
AF003229	PD-1 / IL-2	AB001718	圖 2B	2	1	N/A	80	97	114
AF003230	PD-1 / IL-2	AB001744	圖 2B	2	1	N/A	81	98	115
AF003232	PD-1 / IL-2	AB002022	圖 2B	2	1	N/A	82	99	116
AF003250	PD-1 / IL-2	AB001718	圖 2A	1	1	抗 PD-1	83	100	117

名稱	DBA/治療藥物	DBA	類型	DBA域	治療域	第二Ab域	重鏈1 SEQ ID NO:	重鏈2 SEQ ID NO:	重鏈3 SEQ ID NO:
AF003251	PD-1 / IL-2	AB001744	圖2A	1	1	抗PD-1	84	101	118
AF003253	PD-1 / IL-2	AB002022	圖2A	1	1	抗PD-1	85	102	119

表10 – 表9中之肽序列

SEQ ID NO:	DBA	序列
SEQ ID NO: 80	AF003229_Pep1	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLTF KFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ SIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKP GASVKVSCKASGDTFSTYYVHWVRQAPGQGLEWMGIINPS GGGTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVY YCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPVCGDTTGSS VTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYT LSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIVTCVVVDV SEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALP IQHQDWMSGKEFKCKVNNKDLGAPIERTISKPKGSVRAPQV YVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTE LNYKNTEPVLDSDGSYFMYSDLRVEKKNWVERNSYSCSVV HEGLHNHHTTESFSRTPGK
SEQ ID NO: 81	AF003230_Pep1	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLTF KFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ SIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKP GASVKVSCKASGYTFSNYYIHWVRQAPGQGLEWMGIINPS GGGTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVY YCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPVCGDTTGSS VTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYT LSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIVTCVVVDV SEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALP IQHQDWMSGKEFKCKVNNKDLGAPIERTISKPKGSVRAPQV YVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTE LNYKNTEPVLDSDGSYFMYSDLRVEKKNWVERNSYSCSVV HEGLHNHHTTESFSRTPGK
SEQ ID NO: 82	AF003232_Pep1	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLTF KFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ SIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKP GASVKVSCKASGDTFTRHYVHWVRQAPGQGLEWMGIINPS GGYASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVY YCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPVCGDTTGSS VTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYT LSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIVTCVVVDV SEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALP

SEQ ID NO:	DBA	序列
		IQHQDWMSGKEFKCKVNNKDLGAPIERTISKPKGSVRAPQV YVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTE LNYKNTEPVLDSDGSYFMYSDLRVEKKNWVERNSYSCSVV HEGLHNHHTTESFSRTPGK
SEQ ID NO: 83	AF003250 _Pep1	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLTF KFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ SIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKP GASVKVSCKASGDTFSTYYVHWVRQAPGQGLEWMGIINPS GGGTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVY YCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPVCGDTTGSS VTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYT LSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIVTCVVVDV SEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALP IQHQDWMSGKEFKCKVNNKDLGAPIERTISKPKGSVRAPQV YVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTE LNYKNTEPVLDSDGSYFMYSDLRVEKKNWVERNSYSCSVV HEGLHNHHTTESFSRTPGK
SEQ ID NO: 84	AF003251 _Pep1	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLTF KFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ SIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKP GASVKVSCKASGYTFSNYYIHWVRQAPGQGLEWMGIINPS GGGTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVY YCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPVCGDTTGSS VTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYT LSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIVTCVVVDV SEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALP IQHQDWMSGKEFKCKVNNKDLGAPIERTISKPKGSVRAPQV YVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTE LNYKNTEPVLDSDGSYFMYSDLRVEKKNWVERNSYSCSVV HEGLHNHHTTESFSRTPGK
SEQ ID NO: 85	AF003253 _Pep1	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLTF KFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPR DLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ SIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKP GASVKVSCKASGDTFTRHYVHWVRQAPGQGLEWMGIINPS GGYASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVY YCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPVCGDTTGSS VTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYT LSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIVTCVVVDV SEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALP IQHQDWMSGKEFKCKVNNKDLGAPIERTISKPKGSVRAPQV YVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTE LNYKNTEPVLDSDGSYFMYSDLRVEKKNWVERNSYSCSVV HEGLHNHHTTESFSRTPGK

實例 3

藉由 PD-1/IL-2 雙重結合抗體 (DBA) 細胞激素複合體減少 $CD8^+$ T 細胞 STAT5 磷酸化

【0093】本實例描述了藉由融合將 PD-1/IL-2 DBA 部分添加至 IL-2 分子中來減少 IL-2 所媒介之傳訊，如使用 CD8+ T 細胞 STAT5 磷酸化所讀出。合成**表 11** 所示的用於 PD-1/IL-2 DBA 的基因，並在 HEK293 表現為 IgG 蛋白，該 IgG 蛋白具有經由連接子融合至重鏈或輕鏈之 N 端的 IL-2 (Genscript)。儘管僅兩種抗體阻斷 IL-2 作為 scFv 與 IL-2RB 的結合，但超過 30 種抗體能夠藉由如**圖 2D** 及 **2E** 所示的形式的連接的 IL-2 域減少 IL-2 傳訊。選擇一組示例性 DBA 進行分析，並與對照抗 HER2-IL-2 免疫細胞激素進行比較 (**表 11** 及**圖 3**)。

表 11 – IgG PD-1/IL-2 DBA 蛋白複合體

名稱	重鏈序列 SEQ ID NO	輕鏈序列 SEQ ID NO
抗 HER2	(SEQ ID NO: 65) EVQLVESGGGLVQPGGSLRLSCAA SGFNIKDTYIHWVRQAPGKGLEWV ARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCS RWGGDGFYAMDYWGQGTLVTVSS AKTTAPSVYPLAPVCGDTTGSSVTL GCLVKGYFPEPVTLTWNSGSLSSG VHTFPAVLQSDLYTLSSSVTVTSST WPSQSITCNVAHPASSTKVDKKIEP RGPTIKPCPPCKCPAPNAAGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVSE DDPDVQISWFVNNVEVHTAQTQTH REDYNSTLRVVSALPIQHQDWMSG KEFKCKVNNKDLGAPIERTISKPKG SVRAPQVYVLPPPEEEMTKKQVTL TCMVTDFMPEDIYVEWTNNGKTEL NYKNTEPVLDSDGSYFMYSKLRVE KKNWVERNSYSCSVVHEGLHNHH TTKSFSRTPGK	(SEQ ID NO: 66) APTSSSTKKTQLQLEHLLLDLQ MILNGINNYKNPKLTRMLTFKF YMPKKATELKHLQCLEEELKPL EEVLNLAQSKNFHLRPRDLISNI NVIVLELKGSETTFMCEYADET ATIVEFLNRWITFCQSIISTLTVP GVGVPGAGVPGVGVPGGGVPG VGVPGGGVPGAGVPGGGVPGV GVPGAGVPGVGVPGGGDIQMT QSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSRSGTDFT LTISSLQPEDFATYYCQQHYTTP PTFGQGTKVEIKRADAAPTVSIF PPSSEQLTSGGASVVCFLNNFYP KDINVKWKIDGSERQNGVLNS WTDQDSKDSTYSMSSTLTLTKD EYERHNSYTCEATHKTSTSPIVK SFNRNEC
2-A08	(SEQ ID NO: 67)	(SEQ ID NO: 68)

名稱	重鏈序列 SEQ ID NO	輕鏈序列 SEQ ID NO
	QVQLVQSGAEVKKPGASVKVSCK VSGYTFTSYDINWVRQAPGQGLEW MGWINPNSGDTGYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYY CARDTGLGYYYGSGDFDYWGQGT LVTVSSAKTTAPSVYPLAPVCGDTT GSSVTLGCLVKGYFPEPVTLTWNS GSLSSGVHTFPAVLQSDLYTLSSSV TVTSSTWPSQSITCNVAHPASSTKV DKKIEPRGPTIKPCPPCKCPAPNAA GGPSVFIFPPKIKDVLMISLSPIVTCV VVDVSEDDPDVQISWFVNNVEVHT AQTQTHREDYNSTLRVVSALPIQH QDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEEEM TKKQVTLTCMVTDFMPEDIYVEWT NNGKTELNYKNTEPVLDSDGSYFM YSKLRVEKKNWVERNSYSCSVVHE GLHNHHTTKSFSRTPGK	APTSSSTKKTQLQLEHLLLDLQ MILNGINNYKNPKLTRMLTFKF YMPKKATELKHLQCLEEELKPL EEVLNLAQSKNFHLRPRDLISNI NVIVLELKGSETTFMCEYADET ATIVEFLNRWITFCQSIISTLTVP GVGVPGAGVPGVGVPGGGVPG VGVPGGGVPGAGVPGGGVPGV GVPGAGVPGVGVPGGGDIQMT QSPSSLSASVGDRVTITCQASQD IHNYLNWYQQKPGKAPKLLIYD VSNLETGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQAISFPLT FGGGTKVEIKRADAAPTVSIFPP SSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSW TDQDSKDSTYSMSSTLTLTKDE YERHNSYTCEATHKTSTSPIVKS FNRNEC
2-A11	(SEQ ID NO: 69) QVQLVQSGAEVKKPGASVKVSCK ASGHTFTRYYMHWVRQAPGQGLE WMGIINPSGGYATYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYY CASGWDVWGQGTLVTVSSAKTTA PSVYPLAPVCGDTTGSSVTLGCLVK GYFPEPVTLTWNSGSLSSGVHTFPA VLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKD VLMISLSPIVTCVVVDVSEDDPDVQ ISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCK VNNKDLGAPIERTISKPKGSVRAPQ VYVLPPPEEEMTKKQVTLTCMVTD FMPEDIYVEWTNNGKTELNYKNTE PVLDSDGSYFMYSKLRVEKKNWV ERNSYSCSVVHEGLHNHHTTKSFSR TPGK	(SEQ ID NO: 70) APTSSSTKKTQLQLEHLLLDLQ MILNGINNYKNPKLTRMLTFKF YMPKKATELKHLQCLEEELKPL EEVLNLAQSKNFHLRPRDLISNI NVIVLELKGSETTFMCEYADET ATIVEFLNRWITFCQSIISTLTVP GVGVPGAGVPGVGVPGGGVPG VGVPGGGVPGAGVPGGGVPGV GVPGAGVPGVGVPGGGDIQMT QSPSSLSASVGDRVTITCRASQSI NSWLAWYQQKPGKAPKLLIYA TSTLESGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQSYSFPP TFGQGTKVEIKRADAAPTVSIFP PSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSW TDQDSKDSTYSMSSTLTLTKDE YERHNSYTCEATHKTSTSPIVKS FNRNEC
2-B05	(SEQ ID NO: 71) QVQLVQSGAEVKKPGASVKVSCK ASGYTFTNYYIHWVRQAPGQGLE WMGIINPRAGYTSYALKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYY CAGGWLDWGQGTLVTVSSAKTTA PSVYPLAPVCGDTTGSSVTLGCLVK GYFPEPVTLTWNSGSLSSGVHTFPA	(SEQ ID NO: 72) APTSSSTKKTQLQLEHLLLDLQ MILNGINNYKNPKLTRMLTFKF YMPKKATELKHLQCLEEELKPL EEVLNLAQSKNFHLRPRDLISNI NVIVLELKGSETTFMCEYADET ATIVEFLNRWITFCQSIISTLTVP GVGVPGAGVPGVGVPGGGVPG

名稱	重鏈序列 SEQ ID NO	輕鏈序列 SEQ ID NO
	VLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKD VLMISLSPIVTCVVVDVSEDDPDVQ ISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCK VNNKDLGAPIERTISKPKGSVRAPQ VYVLPPPEEEMTKKQVTLTCMVTD FMPEDIYVEWTNNGKTELNYKNTE PVLDSDGSYFMYSKLRVEKKNWV ERNSYSCSVVHEGLHNHHTTKSFSR TPGK	VGVPGGGVPGAGVPGGGVPGV GVPGAGVPGVGVPGGGDIQMT QSPSSLSASVGDRVTITCRASQSI SSWLAWYQQKPGKAPKLLIYA ASSLQSGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQSFTMPI TFGQGTRLEIKRADAAPTVSIFP PSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSW TDQDSKDSTYSMSSTLTLTKDE YERHNSYTCEATHKTSTSPIVKS FNRNEC
2-B07	(SEQ ID NO: 73) QVQLVQSGAEVKKPGASVKVSCK ASGDTFTRHYVHWVRQAPGQGLE WMGIINPSGGYASYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYY CAAGLFIWGQGTLVTVSSAKTTAPS VYPLAPVCGDTTGSSVTLGCLVKG YFPEPVTLTWNSGSLSSGVHTFPAV LQSDLYTLSSSVTVTSSTWPSQSITC NVAHPASSTKVDKKIEPRGPTIKPC PPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQIS WFVNNVEVHTAQTQTHREDYNST LRVVSALPIQHQDWMSGKEFKCKV NNKDLGAPIERTISKPKGSVRAPQV YVLPPPEEEMTKKQVTLTCMVTDF MPEDIYVEWTNNGKTELNYKNTEP VLDSDGSYFMYSKLRVEKKNWVE RNSYSCSVVHEGLHNHHTTKSFSRT PGK	(SEQ ID NO: 74) APTSSSTKKTQLQLEHLLLDLQ MILNGINNYKNPKLTRMLTFKF YMPKKATELKHLQCLEEELKPL EEVLNLAQSKNFHLRPRDLISNI NVIVLELKGSETTFMCEYADET ATIVEFLNRWITFCQSIISTLTVP GVGVPGAGVPGVGVPGGGVPG VGVPGGGVPGAGVPGGGVPGV GVPGAGVPGVGVPGGGDIQMT QSPSSLSASVGDRVTITCRASQSI GRWLAWYQQKPGKAPKLLIYS ASNLETGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQANSFPV TFGPGTKVDIKRADAAPTVSIFP PSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSW TDQDSKDSTYSMSSTLTLTKDE YERHNSYTCEATHKTSTSPIVKS FNRNEC
7-A04	(SEQ ID NO: 75) QVQLVQSGAEVKKPGASVKVSCK ASGYTFTDYYMHWVRQAPGQGLE WMGIINPRAGYTSYALKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYY CTSGMDVWGQGTLVTVSSAKTTAP SVYPLAPVCGDTTGSSVTLGCLVK GYFPEPVTLTWNSGSLSSGVHTFPA VLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNAAGGPSVFIFPPKIKD VLMISLSPIVTCVVVDVSEDDPDVQ ISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCK VNNKDLGAPIERTISKPKGSVRAPQ VYVLPPPEEEMTKKQVTLTCMVTD	(SEQ ID NO: 76) APTSSSTKKTQLQLEHLLLDLQ MILNGINNYKNPKLTRMLTFKF YMPKKATELKHLQCLEEELKPL EEVLNLAQSKNFHLRPRDLISNI NVIVLELKGSETTFMCEYADET ATIVEFLNRWITFCQSIISTLTVP GVGVPGAGVPGVGVPGGGVPG VGVPGGGVPGAGVPGGGVPGV GVPGAGVPGVGVPGGGDIQMT QSPSSLSASVGDRVTITCRASQSI STWLAWYQQKPGKAPKLLIYA ASSLQSGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQSYSFPV TFGQGTKVEIKRADAAPTVSIFP PSSEQLTSGGASVVCFLNNFYPK

名稱	重鏈序列 SEQ ID NO	輕鏈序列 SEQ ID NO
	FMPEDIYVEWTNNGKTELNYKNTE PVLDSDGSYFMYSKLRVEKKNWV ERNSYSCSVVHEGLHNHHTTKSFSR TPGK	DINVKWKIDGSERQNGVLNSW TDQDSKDSTYSMSSTLTLTKDE YERHNSYTCEATHKTSTSPIVKS FNRNEC

【0094】將 PD-1/IL-2 DBA-細胞激素複合體在完全 RPMI (+10% FBS、2 mM L-麩醯胺酸、丙酮酸鈉) 中連續稀釋並添加至 96 孔盤中。向每個孔中加入 2×10^5 個人類 PBMC，並將盤在 37°C 孵育 20 分鐘。然後將等體積經預熱之固定緩衝劑 (Biolegend) 添加至各孔中，並將盤在 37°C 孵育 10 分鐘。然後將細胞於 4°C 在預冷卻之 Perm 緩衝劑 III (BD Biosciences) 固定 30 分鐘。將細胞用 FACS 洗滌緩衝劑 (PBS +2% FBS, 2 mM EDTA) 洗滌細胞，並用針對 CD3、CD4、CD8 的螢光團標記抗體 (BioLegend) 及在 FACS 洗滌緩衝劑中以 1:20 稀釋的磷酸化 STAT5 (BD Biosciences) 染色。將細胞在 4°C 孵育 1 小時，用 FACS 洗滌緩衝劑洗滌，並在 SA3800 光譜分析儀上分析。在不存在 PD-1 的情況下，與單特異性對照抗 HER2 IL-2 免疫細胞激素相比，PD-1/IL-2 DBA/細胞激素複合體在 T 細胞中誘導的 STAT5 磷酸化更少 (**圖 3**)。

實例 4

通用方法：生產複合體以驅動在人類細胞中之 PD-1 依賴性 IL-2 活性

【0095】本實例描述了 PD-1/IL-2 蛋白複合體在*活體外*及*活體內*人類細胞中之 PD-1 依賴性 IL-2 活性。PD-1/IL-2 蛋白複合體包含經由連接子連接至 IL-2 細胞激素治療域的 PD-1 感測器域 (例如，抗 PD-1 抗體或抗 PD-1 scFv)，其中 IL-2 細胞激素為治療藥物。在不存在 PD-1 的情況下，PD-1 感測器域結合 IL-2 治療域，使 IL-2 具有治療惰性。在存在 PD-1 的情況下 (例如，PD-1 在細胞諸

如免疫細胞上表現)，PD-1 感測器域結合 PD-1，從而脫離 IL-2 治療域並允許 IL-2 表現出治療活性。

【0096】 PD-1/IL-2 蛋白複合體係經重組表現或化學合成的。PD-1/IL-2 蛋白複合體係於*活體外*投予人類細胞或於*活體內*投予小鼠或有需要之人類個體。人類細胞為表現 PD-1 的細胞。向小鼠或人類個體投予係經靜脈內、肌內、皮下、皮內、腹膜內或黏膜執行。在不存在 PD-1 的情況下，IL-2 治療域仍然結合至 PD-1 感測器域，並且未觀察到治療功效 (例如，*活體外*及個體中之細胞活化未改變)。在存在 PD-1 的情況下，PD-1 感測器域結合 PD-1 且不結合 IL-2 治療域。觀察到治療功效 (例如，在*活體外*及個體中、*活體內*觀察到細胞活化)。個體患有疾病。該疾病為癌症。細胞可以內源性地或在活化後或在引入編碼 PD-1 的基因後表現 PD-1。治療效果可以為細胞生長、分化、活化或誘導 IL2 反應基因。在*活體外*，若細胞為細胞類型混合物的一部分，則可以監測混合物中反應細胞群體的任何這些變化。

實例 5

PD-1/IL-2 DBA 細胞激素複合體在淋巴球細胞株中對 STAT5 磷酸化之誘導

【0097】 本實例描述了 PD-1/IL-2 DBA-細胞激素複合體在淋巴球細胞株中對 STAT5 磷酸化之誘導。為評定 PD-1/IL-2 DBA-細胞激素複合體活性對與 PD-1 結合的依賴性，由 IL-2R+ T 細胞株 (諸如 Hut78 或 Jurkat E6.1) 生成表現 PD-1 的變異體。將 PD-1+ 及 PD-1- 變異體細胞株用滴定濃度之本揭露之 PD-1/IL-2 DBA-細胞激素複合體處理，並藉由磷酸流、TR-FRET 或用於測量 IL-2 傳訊的其他測定法評定 STAT5 磷酸化。

【0098】 HEK 293 IL-2 報導子細胞株係經工程化改造以表現 PD-1。將 PD-1+ 及 PD-1- 變異體細胞株用滴定濃度之 PD-1/IL-2 DBA-細胞激素複合體處理，並將報導子活性作為 IL-2 傳訊之測量結果來評定。PD-1/IL-2 DBA-細胞激素複合體對 PD-1+ 變異體細胞株表現出增加之效力。

實例 6

PD-1/IL-2 DBA 細胞激素複合體在初代淋巴球中對 STAT5 磷酸化及其他活化及增殖標記物之誘導

【0099】 本實例描述了 PD-1/IL-2 DBA-細胞激素複合體在初代淋巴球中對 STAT5 磷酸化及其他活化及增殖標記物之誘導。將 PBMC 用細胞增殖染料標記，並用滴定濃度之本揭露之 PD-1/IL-2 DBA-細胞激素複合體孵育 4 天。將 PBMC 用針對免疫細胞表型標記物的抗體染色，以區分 CD4+ 及 CD8+ T 細胞、Treg 細胞及自然殺手 (NK) 細胞以及細胞活化的標記物 (諸如 CD25)。藉由流式細胞分析技術檢查作為增殖的測量結果的免疫細胞亞群上之染料稀釋。

【0100】 使用負性免疫磁珠選擇 (STEMCELL) 從 PBMC 中分離總 T 細胞，並用結合在盤上的抗 CD3 及可溶性抗 CD28 刺激 72 小時以誘導 PD-1 之表現。將 PD-1+ T 細胞與滴定濃度之 PD-1/IL-2 DBA-細胞激素複合體一起孵育 20 分鐘。藉由流式細胞分析技術測量固定及透化 T 細胞中之 STAT5 磷酸化。可以在用 PD-1/IL-2 DBA-細胞激素複合體處理之前用抗 PD-1 阻斷 T 細胞上之 PD-1，以評定 PD-1/IL-2 DBA-細胞激素複合體活性對與 PD-1 之結合的依賴性。當 PD-1 被阻斷時，PD-1/IL-2 DBA-細胞激素複合體誘導極小的 STAT5 磷酸化，顯示出取決於其結合 PD-1 的能力的活性。

實例 7

非腫瘤外週組織中之*活體內* PD-1/IL-2 DBA 細胞激素複合體傳訊

【0101】 本實例描述了野生型小鼠血液中的 PD-1/IL-2 DBA-細胞激素複合體藥物動力學及非腫瘤外週組織中複合體的傳訊。在用複合體靜脈內注射 (IV) 的小鼠中測量 PD-1/IL-2 DBA-細胞激素複合體及合適的未經調節之對照 (諸如抗 PD-1、抗 HER2-IL-2 或抗 PD-1-IL-2) 的血清半衰期及外週組織活性。在治療後不同時間點收集血液、脾臟或兩者並染色以鑑定 CD8+ T 細胞及 NK 細胞。

【0102】 為檢查循環中 PD-1/IL-2 DBA-細胞激素複合體的半衰期，野生型 C57BL/6 小鼠接受單次 2.5 毫克/千克靜脈內劑量的 PD-1/IL-2 DBA-細胞激素複合體 (2B07 IL-2 mut; SEQ ID NO: 205-206)、抗 HER2/IL-2-細胞激素複合體 (始終開啓 (Always-on) IL-2 mut；SEQ ID NO: 64 及 SEQ ID NO: 207) 或抗 IL-2/IL-2-細胞激素複合體 (始終關閉 (Always-off) IL-2 mut；SEQ ID SEQ ID NO: 208 至 209)，如**表 13** 中所概述。在給藥後 30 分鐘、4 小時、24 小時、48 小時、72 小時、96 小時及 168 小時經由眶後竇對小鼠放血。將血液收集到血清分離管中，並將分離的血清冷凍於 -80°C 下冷凍，直至分析。為確定細胞激素複合體的血清中含量，將 96 孔高結合 ELISA 盤用碳酸鹽-碳酸氫鹽緩衝劑中之 1 μg/mL 兔抗 hu IL-2 捕獲抗體 (殖株 ab9618，Abcam) 塗覆，在 4°C 下過夜。將盤洗滌三次並用 SuperBlock 封閉緩衝劑 (Thermo Scientific) 封閉 1 小時。將來自不同時間點和治療組的血清樣品用 SuperBlock 稀釋，添加至盤中，並孵育 1 小時。為偵測細胞激素複合體，將盤與山羊抗小鼠 Fc-HRP (Jackson ImmunoResearch) 在 SuperBlock 中以 1:5000 一起孵育 1 小時。然後將盤洗滌並用 TMB 受質顯影。使用 EnVision 2105 酶標儀 (PerkinElmer) 測量 450 nm 處之

吸光度 (OD)。如**圖 6** 所示，在與抗 IL-2/IL-2-細胞激素複合體相似的血清濃度下偵測在所有時間點檢查的 PD-1/IL-2 DBA-細胞激素複合體。相比之下，未經調節之抗 HER2/IL-2-細胞激素複合體的血清濃度隨時間推移顯示下降幅度更大的血清濃度。

表 12 – IgG PD-1/IL-2 DBA 及對照蛋白複合體

蛋白複合體	SEQ ID NO:	序列
2B07 IL-2 mut	SEQ ID NO: 205	APASSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRML TAKFAMPKKATELKHLQCLEEELKPLEEVLNGAQSKNFHL RPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFAQSIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGA EVKKPGASVKVSCKASGDTFTRHYVHWVRQAPGQGLEW MGIINPSGGYASYAQKFQGRVTMTRDTSTSTVYMELSSLR SEDTAVYYCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPV CGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPA VLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKK IEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSP IVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDY NSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERTI SKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPED IYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK NWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
	SEQ ID NO: 206	DIQMTQSPSSLSASVGDRVTITCRASQSIGRWLAWYQQKP GKAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYESFPVTFGPGTKVDIKRADAAPTVSIFPPSSEQL TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
抗 HER2/IL-2-細胞激素複合體	SEQ ID NO: 64	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKP GKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFGQGTKVEIKRADAAPTVSIFPPSSEQ LTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 207	APASSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRML TAKFAMPKKATELKHLQCLEEELKPLEEVLNGAQSKNFHL RPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFAQSIISTLTGGGGSGGGGSGGGGSGGGGSEVQLVESGG GLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWV ARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRA EDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSAKTTAP SVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLS SGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPA SSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIK DVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQ

蛋白複合體	SEQ ID NO:	序列
		TQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKD LGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCM VTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMY SKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
始終關閉 (Always-off) IL-2 mut	SEQ ID NO: 208	APASSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRML TAKFAMPKKATELKHLQCLEEELKPLEEVLNGAQSKNFHL RPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFAQSIISTLTGGGGSGGGGSGGGGSGGGGSEVQLVESGG GLVKPGGSLRLSCAASGFTFSSYTLAWVRQAPGKGLEWV AAIDSSSYTYSPDTVRGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDSNWDALDYWGQGTLVTVSSAKTTAPSVYPL APVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKV DKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMI SLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHR EDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIE RTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFM PEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVE KKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
	SEQ ID NO: 209	DIQMTQSPSSLSASVGDRVSITCKASQNVGTNVGWYQQKP GKAPKALIYSASFRYSGVPSRFSGSGSGTDFTLTISSLQPED FATYFCQQYYTYPYTFGGGTKLEIKRADAAPTVSIFPPSSE QLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNS WTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTST SPIVKSFNRNEC

【0103】 為檢查外週組織中 PD-1/IL-2 DBA-細胞激素複合體的活性，野生型 C57BL/6 小鼠接受單次 2.5 毫克/千克靜脈內劑量的 PD-1/IL-2 DBA-細胞激素複合體 (2B07 IL-2 mut; SEQ ID NO: 205-206)、抗 HER2/IL-2-細胞激素複合體 (始終開啓 IL-2 mut；SEQ ID NO: 64 及 SEQ ID NO: 207)、抗 IL-2/IL-2-細胞激素複合體 (始終關閉 IL-2 mut；SEQ ID SEQ ID NO: 208 至 209) (如**表 12** 所示) 或 PBS。給藥前，藉由 ELISA 確認各 IL-2 細胞激素複合體內存在完整 IL-2，作為驗證其生物活性潛力的手段。治療後 5 天採集血液及脾臟，並藉由流式細胞分析技術分析，以量化每個脾臟及每微升血液中 CD8+ T 細胞及 NK 細胞的數量。PD-1/IL-2 DBA-細胞激素複合體未誘導 CD8 T 細胞或 NK 細胞之擴增，

而 HER2/IL-2-細胞激素複合體誘導外週 CD8+ T 細胞及 NK 細胞之擴增 (**圖 7A 至 7D**)。

實例 8

同基因腫瘤模型中 PD-1/IL-2 DBA 細胞激素複合體對抗腫瘤免疫之調節

【0104】本實例描述了 MC38 同基因小鼠腫瘤模型中 PD-1/IL-2 DBA-細胞激素複合體對抗腫瘤免疫之調節。評定 PD-1/IL-2 DBA-細胞激素複合體在活體內驅動抗腫瘤免疫的能力。將 500,000 個 MC38 腫瘤細胞皮下植入人類 PD-1 剔入小鼠 (GenOway) 中。每週測量兩次腫瘤，且體積按 (長度 × 寬度 × 寬度/2) 進行計算。將小鼠隨機分入治療組，並當腫瘤達到約 100 mm^3 的體積時開始治療。在腫瘤植入後第 7、10 及 13 天，將小鼠用每千克 5 毫克或 0.5 毫克的指示劑量的 PD-1/IL-2 DBA-細胞激素複合體 (2B07 IL-2 mut; SEQ ID NO: 210 至 212)、缺乏 IL-2 的 PD-1/IL-2 DBA (2B07；SEQ ID NO: 212 至 213) 或同型對照 (SEQ ID NO: 214 至 215) (如下**表 13** 中所示) 進行靜脈內治療。與缺乏 IL-2 的 PD-1/IL-2 DBA 或同型對照相比，PD-1/IL-2 DBA-細胞激素複合體顯示出增加的腫瘤生長抑制 (**圖 8**)。

表 13 – IgG PD-1/IL-2 DBA 及對照蛋白複合體

蛋白複合體	SEQ ID NO:	序列
2B07 IL-2 mut	SEQ ID NO: 210	APASSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRML TAKFAMPKKATELKHLQCLEEELKPLEEVLNGAQSKNFHL RPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFAQSIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGA EVKKPGASVKVSCKASGDTFTRYYVHWVRQAPGQGLEW MGIINPSGGYASYAQKFQGRVTMTRDTSTSTVYMELSSLR SEDTAVYYCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPV CGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPA VLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKK IEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSP IVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDY NSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERTI

蛋白複合體	SEQ ID NO:	序列
		SKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPED IYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSDLRVEKK NWVERNSYSCSVVHEGLHNHHTTESFSRTPGK
	SEQ ID NO: 211	QVQLVQSGAEVKKPGASVKVSCKASGDTFTRYYVHWVR QAPGQGLEWMGIINPSGGYASYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCAAGLFIWGQGTLVTVSSAKTTA PSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHP ASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKI KDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVSLTC LVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSYFM YSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG K
	SEQ ID NO: 212	DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLAWYQQKPG KAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQYNSFPVTFGPGTKVDIKRADAAPTVSIFPPSSEQLT SGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTD QDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIV KSFNRNEC
缺乏 IL-2 的 PD-1/IL-2 DBA	SEQ ID NO: 212	DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLAWYQQKPG KAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQYNSFPVTFGPGTKVDIKRADAAPTVSIFPPSSEQLT SGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTD QDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIV KSFNRNEC
	SEQ ID NO: 213	QVQLVQSGAEVKKPGASVKVSCKASGDTFTRYYVHWVR QAPGQGLEWMGIINPSGGYASYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCAAGLFIWGQGTLVTVSSAKTTA PSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHP ASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKI KDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFM YSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG K
同型對照	SEQ ID NO: 214	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTK KQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD

蛋白複合體	SEQ ID NO:	序列
		SDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTT KSFSRTPGK
	SEQ ID NO: 215	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKP GKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFGQGTKVEIKRADAAPTVSIFPPSSEQ LTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC

實例 9

異種移植/人類免疫細胞混合模型中 PD-1/IL-2 DBA 細胞激素複合體對抗腫瘤免疫之調節

【0105】 本實例描述了異種移植/人類免疫細胞混合模型中 PD-1/IL-2 DBA-細胞激素複合體對抗腫瘤免疫之調節。為檢查 PD-1/IL-2 DBA-細胞激素複合體在*活體內*環境下驅動抗腫瘤免疫的能力，使用混合系統。將總人類 PBMC 或人類 T 細胞及單核球來源的樹突狀細胞 (moDC) 的組合以 1:4 的比率與人類腫瘤細胞 (例如，HPAC、A375、H441) 混合，並皮下共植入 NSG 小鼠的側腹內。一天後，開始用本揭露之 PD-1/IL-2 DBA-細胞激素複合體或合適的未經調節之對照 (諸如 抗PD-1、抗 HER2-IL-2 或抗 PD-1-IL-2) 進行治療。每週測量腫瘤至少兩次，且體積按 (長度 × 寬度 × 高度/2) 進行計算。與抗 PD-1 及抗 HER2-IL-2 相比，PD-1/IL-2 DBA-細胞激素複合體表現出更高的抗腫瘤功效，且與抗 PD-1-IL-2 相比表現出降低的腫瘤外活性。

實例 10

*通用方法：*蛋白複合體之*活體外*及*活體內*表徵

【0106】 本實例描述了對 DBA-細胞激素複合體之*活體外*及*活體內*穩定性的評估。本揭露之蛋白複合體係重組表現或化學合成的。蛋白複合體包括連接至治療域的感測器域。連接子為肽連接子。感測器域能夠與治療域及標記物結

合。若不存在標記物，則感測器域結合治療域，使該治療域無法結合至其標靶且無法發揮治療活性。在存在標記物的情況下，感測器域結合標記物，使治療域自由結合至其標靶並能夠發揮治療活性。

【0107】 在*活體外*，在應激條件下 (諸如高溫、pH 變化、氧化緩衝劑或血清/血漿)，使用生物物理表徵方法來測量碎裂、展開或聚集及/或使用測試功能活性變化的方法測試蛋白複合體在基線或孵育後之穩定性及功能。在*活體內*，在哺乳動物 (諸如小鼠、大鼠或非人類靈長類動物) 中給藥後測量蛋白質之藥物動力學特性，並測量分佈、清除及降解的特性。利用這些測量結果設計或選擇 DBA-蛋白複合體的最佳治療形式。

實例 11

藉由 PD-1/IL-2 雙重結合抗體 (DBA) 細胞激素複合體的經調節之 IL-2 受體傳訊

【0108】 本實例描述了在 HEK-Blue™ IL-2 報導子細胞中藉由 PD-1/IL-2 DBA-細胞激素複合體的經 PD-1 調節之 IL-2 活性。藉由使用標準方案在哺乳動物細胞中表現以產生**圖 2E、2B 及 2H** 中所示的三種形式的 DBA-細胞激素複合體及對照抗體-細胞激素複合體。將 384 孔 ELISA 盤的孔用恆定濃度之用抗 Fc 抗體捕獲的 PD-1-Fc 或 IgG1 對照蛋白 (Jackson ImmunoResearch，產品編號 109-005-098) 塗覆。將細胞激素複合體在生長培養基中以 1:4 連續稀釋 8 個濃度點，從起始濃度 6 nM 開始，並在添加 HEK-Blue™ IL-2 報導子細胞之前短暫孵育。

【0109】 包含**圖 2E** 中所示之結構的蛋白複合體的結果如**圖 9A 至 9D** 所示。如**圖 2E** 中所示，該對稱形式包含連接至抗體可變域的一個 IL-2。包含

SEQ ID NO: 174 至 175 的 PD-1/IL-2 DBA-IL-2 複合體 AF4379 的 IL-2 活性在以 PD-1 塗覆之孔中的 EC50 為 31 pM，而在以 IgG1 塗覆之孔中為 62 pM，如**圖 9A** 所示，表現出 PD-1 依賴性。在存在 PD-1 的情況下，包含 SEQ ID NO: 64 及 176 (抗 Her2 抗體) 的抗體-細胞激素複合體 AF4377 及包含 SEQ ID NO: 177 至 178 (抗 IL-2 抗體) 的 AF4378 之 IL-2 活性不變 (分別如**圖 9B** 及**圖 9C** 所示)，而在存在 PD-1 的情況下，包含 SEQ ID NO: 179 至 180 的抗 PD-1 抗體 AF4376 之 IL-2 活性下降，如**圖 9D** 所示。蛋白複合體之序列總結見下**表 14**。

表 14 – 具有重鏈 IL-2 治療域的 IgG PD-1/IL-2 DBA 及對照蛋白複合體

蛋白複合體	SEQ ID NO:	序列
AF4379	SEQ ID NO: 174	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPVCG DTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVL QSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEP RGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIV TCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERTISK PKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIY VEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKN WVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
	SEQ ID NO: 175	DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLAWYQQKPG KAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQYNSFPVTFGPGTKVDIKRADAAPTVSIFPPSSEQLT SGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTD QDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIV KSFNRNEC
AF4377	SEQ ID NO: 64	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKP GKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFGQGTKVEIKRADAAPTVSIFPPSSEQ LTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 176	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSEVQLVESGGGL

蛋白複合體	SEQ ID NO:	序列
		VQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARI YPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDT AVYYCSRWGGDGFYAMDYWGQGTLVTVSSAKTTAPSVY PLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGV HTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTK VDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVL MISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQT HREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGA PIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTD FMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKL RVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
AF4378	SEQ ID NO: 177	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSEVQLVESGGGL VKPGGSLRLSCAASGFTFSSYTLAWVRQAPGKGLEWVAAI DSSSYTYSPDTVRGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARDSNWDALDYWGQGTLVTVSSAKTTAPSVYPLAP VCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFP AVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDK KIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHRED YNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERT ISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPE DIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEK KNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
	SEQ ID NO: 178	DIQMTQSPSSLSASVGDRVSITCKASQNVGTNVGWYQQKP GKAPKALIYSASFRYSGVPSRFSGSGSGTDFTLTISSLQPED FATYFCQQYYTYPYTFGGGTKLEIKRADAAPTVSIFPPSSE QLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNS WTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTST SPIVKSFNRNEC
AF4376	SEQ ID NO: 179	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVESGGG VVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVA VIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAE DTAVYYCATNDDYWGQGTLVTVSSAKTTAPSVYPLAPVC GDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPA VLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKK IEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSP IVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDY NSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERTI SKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPED IYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK NWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
	SEQ ID NO: 180	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQSSNWPRTFGQGTKVEIKRADAAPTVSIFPPSSEQL

蛋白複合體	SEQ ID NO:	序列
		TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC

【0110】 包含**圖 2B** 中所示之結構的蛋白複合體的結果如**圖 4A 至 4F** 所示。該形式由不對稱複合體構成，該不對稱複合體包含兩個抗體域，其中單一 IL-2 連接至其中一個域。PD-1/IL-2 DBA-IL-2 複合體 AF4386 (包含 SEQ ID NO: 212 及 181 至 182，結果如**圖 4A** 所示)、AF4387 (包含 SEQ ID NO: 183 至 185，結果如**圖 4B** 所示) 及 AF4389 (包含 SEQ ID NO: 186 至 188，結果如**圖 4C** 所示) 之 IL-2 活性為在以 PD-1 塗覆之孔中分別具有 50 pM、57 pM 及 118 pM 的 EC50，且在以 IgG1 塗覆之孔中分別具有 1.79 nM、419 pM 及 1.67 nM 的 EC50，證明了 PD-1 依賴性。抗 PD1 對照蛋白 AF4380 (包含 SEQ ID NO: 180、189 至 190，結果如**圖 4D** 所示)、抗 Her2 對照蛋白 AF4383 (包含 SEQ ID NO: 64、191 至 192，結果如**圖 4E** 所示) 及抗 IL-2 對照蛋白 AF4384 (包含 SEQ ID NO: 178、193 至 194，結果如**圖 4F** 所示) 之 IL-2 活性不變。蛋白複合體之序列總結見下**表 15**。

表 15 – 具有單一 IL-2 的 IgG PD-1/IL-2 PDA 及對照蛋白複合體

蛋白複合體	SEQ ID NO:	序列
AF4386	SEQ ID NO: 181	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCAAGLFIWGQGTLVTVSSAKTTAPSVYPLAPVCG DTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVL QSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEP RGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIV TCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERTISK PKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIY

蛋白複合體	SEQ ID NO:	序列
		VEWTNNGKTELNYKNTEPVLDSDGSYFMYSDLRVEKKN WVERNSYSCSVVHEGLHNHHTTESFSRTPGK
	SEQ ID NO: 182	QVQLVQSGAEVKKPGASVKVSCKASGDTFTRYYVHWVR QAPGQGLEWMGIINPSGGYASYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCAAGLFIWGQGTLVTVSSAKTTA PSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHP ASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKI KDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVSLTC LVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSYFM YSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG GGGSGGGSHHHHHH
	SEQ ID NO: 212	DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLAWYQQKPG KAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQYNSFPVTFGPGTKVDIKRADAAPTVSIFPPSSEQLT SGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTD QDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIV KSFNRNEC
AF4387	SEQ ID NO: 183	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGYTFTDYYMHWVRQAPGQGLEWM GIINPRAGYTSYALKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCTSGWDVWGQGTLVTVSSAKTTAPSVYPLAPVC GDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPA VLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKK IEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSP IVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDY NSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERTI SKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPED IYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSDLRVEKK NWVERNSYSCSVVHEGLHNHHTTESFSRTPGK
	SEQ ID NO: 184	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHWVR QAPGQGLEWMGIINPRAGYTSYALKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCTSGWDVWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVSLTC LVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSYFM YSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG GGGSGGGSHHHHHH
	SEQ ID NO: 185	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPG KAPKLLIYAASSLDSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSFPVTFGQGTKVEIKRADAAPTVSIFPPSSEQL

蛋白複合體	SEQ ID NO:	序列
		TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
AF4389	SEQ ID NO: 186	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGHTFTRYYMHWVRQAPGQGLEWM GIINPSGGYATYAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCASGLFIWGQGTLVTVSSAKTTAPSVYPLAPVCG DTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVL QSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEP RGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIV TCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNS TLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERTISK PKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIY VEWTNNGKTELNYKNTEPVLDSDGSYFMYSDLRVEKKN WVERNSYSCSVVHEGLHNHHTTESFSRTPGK
	SEQ ID NO: 187	QVQLVQSGAEVKKPGASVKVSCKASGHTFTRYYMHWVR QAPGQGLEWMGIINPSGGYATYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCASGLFIWGQGTLVTVSSAKTTA PSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHP ASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKI KDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVSLTC LVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSYFM YSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG GGGSGGGSHHHHHH
	SEQ ID NO: 188	DIQMTQSPSSLSASVGDRVTITCRASQSINSWLAWYQQKPG KAPKLLIYATSTLESGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQYYRFPVTFGQGTKVEIKRADAAPTVSIFPPSSEQL TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
AF4380	SEQ ID NO: 180	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQSSNWPRTFGQGTKVEIKRADAAPTVSIFPPSSEQL TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 189	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSQVQLVESGGG VVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVA VIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAE DTAVYYCATNDDYWGQGTLVTVSSAKTTAPSVYPLAPVC GDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPA

蛋白複合體	SEQ ID NO:	序列
		VLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKK IEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSP IVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDY NSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERTI SKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPED IYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSDLRVEKK NWVERNSYSCSVVHEGLHNHHTTESFSRTPGK
	SEQ ID NO: 190	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNT LFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVSLTC LVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSYFM YSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG GGGSGGGSHHHHHH
AF4383	SEQ ID NO: 64	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKP GKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFGQGTKVEIKRADAAPTVSIFPPSSEQ LTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 191	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSEVQLVESGGGL VQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARI YPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDT AVYYCSRWGGDGFYAMDYWGQGTLVTVSSAKTTAPSVY PLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGV HTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTK VDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVL MISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQT HREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGA PIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTD FMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSDL RVEKKNWVERNSYSCSVVHEGLHNHHTTESFSRTPGK
	SEQ ID NO: 192	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEKEMT KKQVSLTCLVKDFMPEDIYVEWTNNGKTELNYKNTEPVL

蛋白複合體	SEQ ID NO:	序列
		KSDGSYFMYSKLTVEKKNWVERNSYSCSVVHEGLHNHHT TKSFSRTPGGGGSGGGSHHHHHH
AF4384	SEQ ID NO: 178	DIQMTQSPSSLSASVGDRVSITCKASQNVGTNVGWYQQKP GKAPKALIYSASFRYSGVPSRFSGSGSGTDFTLTISSLQPED FATYFCQQYYTYPYTFGGGTKLEIKRADAAPTVSIFPPSSE QLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNS WTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTST SPIVKSFNRNEC
	SEQ ID NO: 193	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTDMLT FEFYMPKKATELKHLQCLERELKPLEEVLNLAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLTGGGGSGGGGSGGGGSGGGGSEVQLVESGGGL VKPGGSLRLSCAASGFTFSSYTLAWVRQAPGKGLEWVAAI DSSSYTYSPDTVRGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARDSNWDALDYWGQGTLVTVSSAKTTAPSVYPLAP VCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFP AVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDK KIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHRED YNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAPIERT ISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPE DIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSDLRVEK KNWVERNSYSCSVVHEGLHNHHTTESFSRTPGK
	SEQ ID NO: 194	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYTLAWVRQA PGKGLEWVAAIDSSSYTYSPDTVRGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARDSNWDALDYWGQGTLVTVSSAK TTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWN SGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNV AHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIF PPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEV HTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKV NNKDLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVS LTCLVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSY FMYSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSR TPGGGGSGGGSHHHHHH

【0111】包含**圖 2H** 中所示之結構的蛋白複合體的結果如**圖 5A 至 5H** 所示。如**圖 2H** 所示，這些複合體係不對稱的，且包含兩個相同的單特異性 Fab 臂，其中單一 IL-2 藉由可撓性連接子接附至一個 Fc 域且單一 scFv 藉由可撓性連接子接附至另一個 Fc 域。活性 PD-1/IL-2 DBA 複合體，包含 SEQ ID NO: 180、195、199 的 AF4403 及包含 SEQ ID NO: 180、196、199 的 AF4404，係由 Fab 臂中之抗 PD-1 域及 Fc 臂上之 PD-1/IL-2 DBA scFv 構成。對照抗體-細

胞激素複合體係由以下構成：a) 具有在 Fab 臂上之不相關抗體及 Fc 上之 DBA scFv 的抗體-細胞激素複合體 (包含 SEQ ID NO: 64、197、202 的 AF4395 及包含 SEQ ID NO: 64、198、202 的 AF4396)；b) 具有在 Fc 臂上之非 DBA scFv 的抗體-細胞激素複合體 (包含 SEQ ID NO: 180、199 至 200 的 AF4400 及包含 SEQ ID NO: 180、199、201 的 AF4401)；及 c) 具有在 Fab 及 scFv 域兩者中之非 DBA 抗體的抗體-細胞激素複合體 (包含 SEQ ID NO: 64、202 至 203 的 AF4392 及包含 SEQ ID NO: 64、202、204 的 AF4393)。如**圖 5B** 及 **5D** 所示，DBA-細胞激素複合體 AF4403 及 AF4404 之 IL-2 活性為在以 PD-1 塗覆之孔中具有分別為 31 pM 及 26 pM 的 EC50，在對照孔中具有分別為 62 pM 及 64 pM 的 EC50，證明了 IL-2 活性的 PD-1 依賴性。如上所述之對照蛋白 AF4395、AF4396、AF4400、AF4401、AF4392 及 AF4393 在以 PD-1 塗覆之孔中顯示的 EC50 皆不低於在以 IgG1 蛋白塗覆之孔中之 EC50，如**圖 5A、5C** 及 **5E 至 5H** 所示。蛋白複合體之序列總結見下**表 16**。

表 16 – 具有 C 端 scFv 及 IL-2 的 IgG PD-1 及對照蛋白複合體

蛋白複合體	SEQ ID NO:	序列
AF4403	SEQ ID NO: 180	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQSSNWPRTFGQGTKVEIKRADAAPTVSIFPPSSEQL TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 195	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNT LFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVSLTC LVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSYFM YSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG

蛋白複合體	SEQ ID NO:	序列
		GGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASV KVSCKASGDTFTRYYVHWVRQAPGQGLEWMGIINPSGGY ASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC AAGLFIWGQGTLVTVSSASGGGGSGGGGSGGGGSHASDIQ MTQSPSSLSASVGDRVTITCRASQSIGRYLAWYQQKPGKA PKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATY YCQQYNSFPVTFGPGTKVDIKGGGSGGGSHHHHHH
	SEQ ID NO: 199	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNT LFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFM YSDLRVEKKNWVERNSYSCSVVHEGLHNHHTTESFSRTPG GGGGSGGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMIL NGINNYKNPKLTDMLTFEFYMPKKATELKHLQCLERELKP LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEY ADETATIVEFLNRWITFCQSIISTLT
AF4404	SEQ ID NO: 180	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQSSNWPRTFGQGTKVEIKRADAAPTVSIFPPSSEQL TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 196	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNT LFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVSLTC LVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSYFM YSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG GGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASV KVSCKASGYTFTDYYMHWVRQAPGQGLEWMGIINPRAG YTSYALKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC TSGWDVWGQGTLVTVSSASGGGGSGGGGSGGGGSHASDI QMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGK APKLLIYAASSLDSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSFPVTFGQGTKVEIKGGGSGGGSHHHHHH
	SEQ ID NO: 199	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNT LFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG

蛋白複合體	SEQ ID NO:	序列
		SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFM YSDLRVEKKNWVERNSYSCSVVHEGLHNHHTTESFSRTPG GGGGSGGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMIL NGINNYKNPKLTDMLTFEFYMPKKATELKHLQCLERELKP LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEY ADETATIVEFLNRWITFCQSIISTLT
AF4395	SEQ ID NO: 64	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKP GKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFGQGTKVEIKRADAAPTVSIFPPSSEQ LTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 197	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEKEMT KKQVSLTCLVKDFMPEDIYVEWTNNGKTELNYKNTEPVL KSDGSYFMYSKLTVEKKNWVERNSYSCSVVHEGLHNHHT TKSFSRTPGGGGGSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGDTFTRYYVHWVRQAPGQGLEWM GIINPSGGYASYAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCAAGLFIWGQGTLVTVSSASGGGGSGGGGSGGG GSHASDIQMTQSPSSLSASVGDRVTITCRASQSIGRYLAWY QQKPGKAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQYNSFPVTFGPGTKVDIKGGGSGGGSHHH HHH
	SEQ ID NO: 202	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTK KQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD SDGSYFMYSDLRVEKKNWVERNSYSCSVVHEGLHNHHTT ESFSRTPGGGGGSGGGGSGGGGSAPTSSSTKKTQLQLEHLL LDLQMILNGINNYKNPKLTDMLTFEFYMPKKATELKHLQC

蛋白複合體	SEQ ID NO:	序列
		LERELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFCQSIISTLT
AF4396	SEQ ID NO: 64	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKP GKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFGQGTKVEIKRADAAPTVSIFPPSSEQ LTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 198	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEKEMT KKQVSLTCLVKDFMPEDIYVEWTNNGKTELNYKNTEPVL KSDGSYFMYSKLTVEKKNWVERNSYSCSVVHEGLHNHHT TKSFSRTPGGGGGSGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGYTFTDYYMHWVRQAPGQGLEWM GIINPRAGYTSYALKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCTSGWDVWGQGTLVTVSSASGGGGSGGGGSGG GGSHASDIQMTQSPSSLSASVGDRVTITCRASQSISTWLAW YQQKPGKAPKLLIYAASSLDSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQSYSFPVTFGQGTKVEIKGGGSGGGSHH HHHH
	SEQ ID NO: 202	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTK KQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD SDGSYFMYSDLRVEKKNWVERNSYSCSVVHEGLHNHHTT ESFSRTPGGGGGSGGGGSGGGGSAPTSSSTKKTQLQLEHLL LDLQMILNGINNYKNPKLTDMLTFEFYMPKKATELKHLQC LERELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFCQSIISTLT
AF4400	SEQ ID NO: 180	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQSSNWPRTFGQGTKVEIKRADAAPTVSIFPPSSEQL TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 199	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNT

蛋白複合體	SEQ ID NO:	序列
		LFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFM YSDLRVEKKNWVERNSYSCSVVHEGLHNHHTTESFSRTPG GGGGSGGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMIL NGINNYKNPKLTDMLTFEFYMPKKATELKHLQCLERELKP LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEY ADETATIVEFLNRWITFCQSIISTLT
	SEQ ID NO: 200	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNT LFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVSLTC LVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSYFM YSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG GGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLR LSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTR YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSASGGGGSGGGGSGGG GSHASDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAW YQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYTTPPTFGQGTKVEIKGGGSGGGSHH HHHH
AF4401	SEQ ID NO: 180	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQSSNWPRTFGQGTKVEIKRADAAPTVSIFPPSSEQL TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 199	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNT LFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFM YSDLRVEKKNWVERNSYSCSVVHEGLHNHHTTESFSRTPG GGGGSGGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMIL

蛋白複合體	SEQ ID NO:	序列
		NGINNYKNPKLTDMLTFEFYMPKKATELKHLQCLERELKP LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEY ADETATIVEFLNRWITFCQSIISTLT
	SEQ ID NO: 201	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNT LFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPK IKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEKEMTKKQVSLTC LVKDFMPEDIYVEWTNNGKTELNYKNTEPVLKSDGSYFM YSKLTVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG GGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVKPGGSLR LSCAASGFTFSSYTLAWVRQAPGKGLEWVAAIDSSSYTYS PDTVRGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDS NWDALDYWGQGTLVTVSSASGGGGSGGGGSGGGGSHAS DIQMTQSPSSLSASVGDRVSITCKASQNVGTNVGWYQQKP GKAPKALIYSASFRYSGVPSRFSGSGSGTDFTLTISSLQPED FATYFCQQYYTYPYTFGGGTKLEIKGGGSGGGSHHHHHH
AF4392	SEQ ID NO: 64	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKP GKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFGQGTKVEIKRADAAPTVSIFPPSSEQ LTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 202	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTK KQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD SDGSYFMYSDLRVEKKNWVERNSYSCSVVHEGLHNHHTT ESFSRTPGGGGGSGGGGSGGGGSAPTSSSTKKTQLQLEHLL LDLQMILNGINNYKNPKLTDMLTFEFYMPKKATELKHLQC LERELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFCQSIISTLT
	SEQ ID NO: 203	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF

蛋白複合體	SEQ ID NO:	序列
		KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEKEMT KKQVSLTCLVKDFMPEDIYVEWTNNGKTELNYKNTEPVL KSDGSYFMYSKLTVEKKNWVERNSYSCSVVHEGLHNHHT TKSFSRTPGGGGGSGGGGSGGGGSGGGGSEVQLVESGGGL VQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARI YPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDT AVYYCSRWGGDGFYAMDYWGQGTLVTVSSASGGGGSGG GGSGGGGSHASDIQMTQSPSSLSASVGDRVTITCRASQDV NTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGT DFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKGGG SGGGSHHHHHH
AF4393	SEQ ID NO: 64	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKP GKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFGQGTKVEIKRADAAPTVSIFPPSSEQ LTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPI VKSFNRNEC
	SEQ ID NO: 202	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTK KQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD SDGSYFMYSDLRVEKKNWVERNSYSCSVVHEGLHNHHTT ESFSRTPGGGGGSGGGGSGGGGSAPTSSSTKKTQLQLEHLL LDLQMILNGINNYKNPKLTDMLTFEFYMPKKATELKHLQC LERELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFCQSIISTLT
	SEQ ID NO: 204	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQA PGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI TCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGP SVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEF KCKVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEKEMT KKQVSLTCLVKDFMPEDIYVEWTNNGKTELNYKNTEPVL KSDGSYFMYSKLTVEKKNWVERNSYSCSVVHEGLHNHHT TKSFSRTPGGGGGSGGGGSGGGGSGGGGSEVQLVESGGGL VKPGGSLRLSCAASGFTFSSYTLAWVRQAPGKGLEWVAAI DSSSYTYSPDTVRGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARDSNWDALDYWGQGTLVTVSSASGGGGSGGGGS GGGGSHASDIQMTQSPSSLSASVGDRVSITCKASQNVGTN VGWYQQKPGKAPKALIYSASFRYSGVPSRFSGSGSGTDFT

蛋白複合體	SEQ ID NO:	序列
		LTISSLQPEDFATYFCQQYYTYPYTFGGGTKLEIKGGGSGG GSHHHHHH

實例 12

額外雙重結合抗體與 PD1 及 IL2 之結合

【0112】在先前的實例中已經觀察到雙重結合抗體 (DBA) 的有效性後，生成額外的雙重結合抗體 cFv (見下**表 17**、**表 18** 及**表 19**)。本實例描述了對 PD1 及 IL2 與這些雙重結合抗體 cFv 之結合的測量結果。各殖株的 scFv DNA 序列係作為具有 T7 啟動子、翻譯起始位點、帶有 cMyc 及 V5 標籤的 scFv 序列的編碼序列及 T7 終止子序列的 gBlock (Integrated DNA Technologies, Inc.) 合成。使用無細胞轉錄/轉譯系統 (Cosmo Bio USA, Inc.，PURExfrex2.1，產品編號 GFK-PF213，包含 DS 補充劑 (產品編號 GFK-PF005))表現來自 gBlock 片段中之各者的蛋白質。scFv 樣品經歷 ELISA 分析以偵測 PD1 及 IL2 結合。在這些實驗中，將 384 孔盤的孔用抗 V5 抗體 (Sv5-Pk1, BioRad) 以 1μg/ml 於 4 度塗覆過夜。洗滌後，將孔用 SuperBlock (ThermoFisher, 37515) 封閉，然後添加於 SuperBlock 中之飽和含量的 scFv。洗滌後，添加抗原並將盤孵育一小時。為偵測 PD1 結合，使用生物素化重組 PD1 (PD1-HisAvi, Acro Biosystems, PD1-H82E4)。為偵測 IL2 結合，將 IL2 (R&D, 202-IL) 在 SuperBlock 緩衝劑中以 2:1 之比率與生物素化抗 IL2 mAb (mab202，使用標準方法生物素化) 一起預孵育。使用卵白素 HRP 以標準方法偵測生物素化抗原。添加不同量的帶標記之測試抗原以顯示結合並估計不同 scFv 的相對親和力。**表 17A 至 17C** 示出三組 scFv 的 PD1 及 IL2 結合的 EC50 值，證明這些抗體的雙重結合能力。

【0113】資料指示除對照抗體 AB000694、AB000719、AB000880 外，**表 17A 至 17C** 中的所有抗體皆能夠有效結合 PD1 及 IL2 兩者。

表 17A：如在第一實驗中藉由 ELISA 所評定，根據本揭露之額外 DBA 與 PD1 及 IL2 之結合親和力

抗體 ID	蛋白質名稱	PD1 EC50	IL2 EC50
AB002293_2B07v2	AF003676	0.2	6
AB002353_2B07v9	AF003736	0.9	30
AB002342_2B07v5	AF003725	0.2	7
AB002328_2B07v4	AF003711	0.2	0.4
AB002326_2B07v3	AF003709	0.2	30
AB002345_2B07v6	AF003728	0.2	60
AB002348_2B07v8	AF003731	0.3	100
AB002022_2B07v1	AF002829	0.6	10
AB002347_2B07v7	AF003730	0.1	8

表 17B：如在第二實驗中藉由 ELISA 所評定，根據本揭露之額外 DBA 與 PD1 及 IL2 之結合親和力

抗體 ID	蛋白質名稱	PD1 EC50	IL2 EC50
AB000694 (抗 PD1 對照)	AF005039	0.7	-
AB000719 (抗 PD1 對照)	AF005040	0.4	-
AB000880 (抗 PD1 對照)	AF000327	4	-
AB003021_2A11v7	AF005103	0.6	40
AB002417_2A11v4	AF005148	4	50
AB002413_2A11v3	AF005147	2	2
AB002427_2A11v5	AF005149	3	0.9
AB003200_2B05v1	AF005131	0.5	弱
AB003209_2B05v4	AF005140	0.4	弱
AB003201_2B05v2	AF005132	0.5	弱
AB003202_2B05v3	AF005133	0.5	弱
AB003155_2B07v10	AF005042	0.7	0.4
AB002328_2B07v4	AF005041	2	1
AB003174_2B07v11	AF005062	0.6	7
AB003180_2B07v13	AF005068	0.6	0.8
AB003183_2B07v14	AF005071	0.3	40
AB003178_2B07v12	AF005066	1	0.3

AB003007_7A04v6	AF005087	1	10
AB002365_7A04v2	AF005095	1	8
AB003012_7A04v7	AF005092	1	7
AB003005_7A04v5	AF005085	4	3
AB002864_2A11v6	AF005116	0.4	60

表 17C：如在第三實驗中藉由 ELISA 所評定，根據本揭露之額外 DBA 與 PD1 及 IL2 之結合親和力

抗體 ID	蛋白質名稱	PD1 EC50	IL2 EC50
AB000880 (抗 PD1 對照)	AF000327	8	-
AB002360_7A04v1	AF003765	1	70
AB002365_7A04v2	AF003770	1	30
AB002370_7A04v3	AF003775	0.7	30
AB002381_7A04v4	AF003786	0.7	30
AB002410_2A11v2	AF003815	3	100
AB002413_2A11v3	AF003818	3	3
AB002417_2A11v4	AF003822	5	400
AB002427_2A11v5	AF003832	3	0.8
AB002022_2B07v1	AF002829	5	30
AB001938	AF002745	10	30

表 18：實例 12 中所述之 DBA 的 V_H 及 V_L 區之序列

ID	抗體 ID	V_H	V_L	V_H SEQ ID NO:	V_L SEQ ID NO:
AB000694_nivo	AB000694	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIK	329	330
AB000880_PD1_R04_C10	AB000880	QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYYMHWVRQAPGQGLEWMGIINPSGGGTLYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAAGLFIWGQGTTVTVSS	DIVMTQSPDSLAVSLGERATINCKASQSLLHSSSNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPITFGPGTKVDIK	331	332
AB002022_2B07v1	AB002022	QVQLVQSGAEVKKPGASVKVSCKASGDTFTRHYVHWVRQAPGQGLEWMGIINPSGGYASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAAGLFIWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSIGRWLAWYQQKPGKAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYESFPVTFGPGTKVDIK	333	334
AB002293_2B07v2	AB002293	QVQLVQSGAEVKKPGASVKVSCKASGDTFTRYYVHWVRQAPGQGLEWMGIINPSGGYASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAAGLFIWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSIGRWLAWYQQKPGKAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSFPVTFGPGTKVDIK	335	336
AB002326_2B07v3	AB002326	QVQLVQSGAEVKKPGASVKVSCKASGDTFTRYYVHWVRQAPGQGLEWMGIINPSGGYASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAAGLFIWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSIGSWLAWYQQKPGKAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSFPVTFGPGTKVDIK	337	338

ID	抗體 ID	V_H	V_L	V_H SEQ ID NO:	V_L SEQ ID NO:
AB002328_2B07v4	AB002328	QVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQ GLEWMGIINPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRWLAWYQQKPGKAPKLLIYSASNL ETGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYNRFPVTFGPGTKVDIK	339	340
AB002342_2B07v5	AB002342	QVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQ GLEWMGIINPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRWLAWYQQKPGKAPKLLIYSASNL ETGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYERFPVTFGPGTKVDIK	341	342
AB002345_2B07v6	AB002345	QVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQ GLEWMGIINPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRYLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYNSFPVTFGPGTKVDIK	343	344
AB002347_2B07v7	AB002347	QVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQ GLEWMGIINPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRYLAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYNRFPVTFGPGTKVDIK	345	346
AB002348_2B07v8	AB002348	QVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQ GLEWMGIINPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRYLAWYQQKPGKAPKLLIYYASNL ETGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYNSFPVTFGPGTKVDIK	347	348
AB002353_2B07v9	AB002353	QVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQ	DIQMTQSPSSLSASVGDRVTITCRASQS IGRWLAWYQQKPGKAPKLLIYSASNL	349	350

ID	抗體 ID	V_H	V_L	V_H SEQ ID NO:	V_L SEQ ID NO:
		GLEWMGIINPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	ETGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYESFPVTFGPGTKVDIK		
AB002360_7A04v1	AB002360	QVQLVQSGAEVKKPGASVKVSC KASGYTFTDYYMHWVRQAPGQ GLEWMGIINPRAGYTSYALKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCTSGWDVWGQGTLV TVSS	DIQMTQSPSSLSASVGDRVTITCRASQS ISTWLAWYQQKPGKAPKLLIYAASSL DSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSYSFPVTFGQGTKVEIK	351	352
AB002365_7A04v2	AB002365	QVQLVQSGAEVKKPGASVKVSC KASGYTFTRYYMHWVRQAPGQ GLEWMGIINPRAGYTSYALKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCTSGWDVWGQGTLV TVSS	DIQMTQSPSSLSASVGDRVTITCRASQS ISTWLAWYQQKPGKAPKLLIYAASSL DSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSYSFPVTFGQGTKVEIK	353	354
AB002370_7A04v3	AB002370	QVQLVQSGAEVKKPGASVKVSC KASGYTFTTYYMHWVRQAPGQ GLEWMGIINPRAGYTSYALKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCTSGWDVWGQGTLV TVSS	DIQMTQSPSSLSASVGDRVTITCRASQS ISTWLAWYQQKPGKAPKLLIYAASSL DSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSYSFPVTFGQGTKVEIK	355	356
AB002381_7A04v4	AB002381	QVQLVQSGAEVKKPGASVKVSC KASGDTFTDYYMHWVRQAPGQ GLEWMGIINPRAGYTSYALKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCTSGWDVWGQGTLV TVSS	DIQMTQSPSSLSASVGDRVTITCRASQS ISTWLAWYQQKPGKAPKLLIYAASSL DSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSYSFPVTFGQGTKVEIK	357	358
AB002410_2A11v2	AB002410	QVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQ GLEWMGIINPSGGYATYAQKFQ GRVTMTRDTSTSTVYMELSSLRS	DIQMTQSPSSLSASVGDRVTITCRASQS INSWLAWYQQKPGKAPKLLIYDTSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSFPVTFGQGTKVEIK	359	360

ID	抗體 ID	V_H	V_L	V_H SEQ ID NO:	V_L SEQ ID NO:
		EDTAVYYCASGWFVWGQGTLV TVSS			
AB002413_2A11v3	AB002413	QVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQ GLEWMGIINPSGGYATYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCASGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS INSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYYRFPVTFGQGTKVEIK	361	362
AB002417_2A11v4	AB002417	QVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQ GLEWMGIINPSGGYATYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCASGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS INSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYYSFPVTFGQGTKVEIK	363	364
AB002427_2A11v5	AB002427	QVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQ GLEWMGIINPSGGYATYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCASGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS INSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYRFPVTFGQGTKVEIK	365	366
AB002520_7A04v8	AB002520	QVQLVQSGAEVKKPGASVKVSC KASGYTFTDYYMHWVRQAPGQ GLEWMGIINPRAGYTSYALKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCTSGWDVWGQGTLV TVSS	DIQMTQSPSSLSASVGDRVTITCRASQS ISTWLAWYQQKPGKAPKLLIYAASSL DSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQSYRFPVTFGQGTKVEIK	367	368
AB002521_2A11v1	AB002521	QVQLVQSGAEVKKPGASVKVSC KASGHTFTRYYMHWVRQAPGQ GLEWMGIINPSGGYATYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCASGLDIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS INSWLAWYQQKPGKAPKLLIYATSTLE SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYRFPVTFGQGTKVEIK	369	370

ID	抗體 ID	V_H	V_L	V_H SEQ ID NO:	V_L SEQ ID NO:
AB002829_knd_A08	AB002829	QVQLVQSGAEVKKPGASVKVSCKASGYIFNGYDIHWVRQAPGQGLEWMGWMNPDNGNTGLAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGMATRFPYYYYGMDVWGQGTLVTVSS	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPPTFGQGTKVEIK	371	372
AB002864_2A11v6	AB002864	QVQLVQSGAEVKKPGASVKVSCKASGHTFTRYYMHWVRQAPGQGLEWMGVINPSGGYATYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCASGWDVWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSINSWLAWYQQKPGKAPKLLIYATSTLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSSPVTFGQGTKVEIK	373	374
AB003005_7A04v5	AB003005	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYYMHWVRQAPGQGLEWMGIIQPRAGYTSYALKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCTSGWDVWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGKAPKLLIYAASSLDEGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSFPVTFGQGTKVEIK	375	376
AB003007_7A04v6	AB003007	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYYMHWVRQAPGQGLEWMGIINPRAGYTSYALKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCTSGWEVWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGKAPKLLIYAASSLDEGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSFPVTFGQGTKVEIK	377	378
AB003012_7A04v7	AB003012	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYYMHWVRQAPGQGLEWMGIINPRAGYTSYALKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCTSGWDVWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGKAPKLLIYAASSLDEGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSFPVTFGQGTKVEIK	379	380
AB003021_2A11v7	AB003021	QVQLVQSGAEVKKPGASVKVSCKASGFTFTRYYMHWVRQAPGQ	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYATSTLE	381	382

ID	抗體 ID	V_H	V_L	V_H SEQ ID NO:	V_L SEQ ID NO:
		GLEWMGVINPSGGYATYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCASGWDVWGQGTLV TVSS	SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSSPVTFGQGTKVEIK		
AB003155_2B07v10	AB003155	QVQLVQSGAEVKKPGASVKVSC KASGETFTRYYVHWVRQAPGQ GLEWMGIINPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRWLAWYQQKPGKAPKLLIYSASNL ETGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYNRFPVTFGPGTKVDIK	383	384
AB003174_2B07v11	AB003174	QVQLVQSGAEVKKPGASVKVSC KASGDTFTRYYVHWVRQAPGQ GLEWMGIINPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRELAWYQQKPGKAPKLLIYSASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYNRFPVTFGPGTKVDIK	385	386
AB003178_2B07v12	AB003178	QVQLVQSGAEVKKPGASVKVSC KASGDEFTRYYVHWVRQAPGQ GLEWMGIINPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRWLAWYQQKPGKAPKLLIYSASNL ETGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYNRFPVTFGPGTKVDIK	387	388
AB003180_2B07v13	AB003180	QVQLVQSGAEVKKPGASVKVSC KASGDEFTRYYVHWVRQAPGQ GLEWMGIQNPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAAGLFIWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRWLAWYQQKPGKAPKLLIYSASNL ETGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYNRFPVTFGPGTKVDIK	389	390
AB003183_2B07v14	AB003183	QVQLVQSGAEVKKPGASVKVSC KASGDEFTRYYVHWVRQAPGQ GLEWMGIQNPSGGYASYAQKFQ GRVTMTRDTSTSTVYMELSSLRS	DIQMTQSPSSLSASVGDRVTITCRASQS IGRELAWYQQKPGKAPKLLIYDASNLE TGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYNRFPVTFGPGTKVDIK	391	392

ID	抗體 ID	V_H	V_L	V_H SEQ ID NO:	V_L SEQ ID NO:
		EDTAVYYCAAGLFIWGQGTLVT VSS			
AB003200_2B05v1	AB003200	QVQLVQSGAEVKKPGASVKVSC KASGETFTNYYIHWVRQAPGQG LEWMGVINPRAGYTSYALKFQG RVTMTRDTSTSTVYMELSSLRSE DTAVYYCAGGWEDWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRISQSI SSWLAWYQQKPGKAPKLLIYSASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSFTSPITFGQGTRLEIK	393	394
AB003201_2B05v2	AB003201	QVQLVQSGAEVKKPGASVKVSC KASGGTFTNYYIHWVRQAPGQG LEWMGIIDPRAGYTSYALKFQG RVTMTRDTSTSTVYMELSSLRSE DTAVYYCAGGWEDWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRISQSI SSWLAWYQQKPGKAPKLLIYSASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSFTSPITFGQGTRLEIK	395	396
AB003202_2B05v3	AB003202	QVQLVQSGAEVKKPGASVKVSC KASGSTFTNYYIHWVRQAPGQG LEWMGIIDPRAGYTSYALKFQG RVTMTRDTSTSTVYMELSSLRSE DTAVYYCAGGWEDWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRISQSI SSFLAWYQQKPGKAPKLLIYSASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSFTSPITFGQGTRLEIK	397	398
AB003209_2B05v4	AB003209	QVQLVQSGAEVKKPGASVKVSC KASGETFTNYYIHWVRQAPGQG LEWMGIIDPRAGYTSYALKFQG RVTMTRDTSTSTVYMELSSLRSE DTAVYYCAGGWEDWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRISQSI SSFLAWYQQKPGKAPKLLIYSASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSFTSPITFGQGTRLEIK	399	400
AB003232_2B05v5	AB003232	QVQLVQSGAEVKKPGASVKVSC KASGTTFTNYYIHWVRQAPGQG LEWMGVINPRAGYTSYALKFQG RVTMTRDTSTSTVYMELSSLRSE DTAVYYCTGGWLDWGQGTLVT VSS	DIQMTQSPSSLSASVGDRVTITCRASQS ISSWLAWYQQKPGKAPKLLIYSASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSVTMPVTFGQGTRLEIK	401	402

ID	抗體 ID	V_H	V_L	V_H SEQ ID NO:	V_L SEQ ID NO:
AB003422_2B05v5	AB003422	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYIHWVRQAPGQGLEWMGVINPRAGYTSYALKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAGGWLDWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQRISSWLAWYQQKPGKAPKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSFTMPVTFGQGTRLEIK	403	404
AB003465_2A11v9	AB003465	QVQLVQSGAEVKKPGASVKVSCKASGFTFTRYYMHWVRQAPGQGLEWMGVINPSGGYATYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCASGWDVWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYATSTLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSFPPTFGQGTKVEIK	405	406
AB003466_2B07v10	AB003466	QVQLVQSGAEVKKPGASVKVSCKASGETFTRYYVHWVRQAPGQGLEWMGIINPSGGYASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAAGLFIWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSIGRWLAWYQQKPGKAPKLLIYSASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSFPVTFGPGTKVDIK	407	408
AB003467_7A04v9	AB003467	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYYMHWVRQAPGQGLEWMGIINPRAGYTSYALKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCTSGWDVWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGKAPKLLIYAASSLDTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSFPVTFGQGTKVEIK	409	410
AB003470_knd_A04	AB003470	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTAYYIHWVRQAPGQGLEFMGWIHPYSGGTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAIGYYYGKFDYWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQTISRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPRTFGQGTKLEIK	411	412

表 19：實例 12 中所述之 DBA 的 V_H 及 V_L CDR 之序列

ID	抗體 ID	V_H_cdr1	V_H_cdr2	V_H_cdr3	V_L_cdr1	V_L_cdr2	V_L_cdr3	V_H_cdr1 SEQ ID NO:	V_H_cdr2 SEQ ID NO:	V_H_cdr3 SEQ ID NO:	V_L_cdr1 SEQ ID NO:	V_L_cdr2 SEQ ID NO:	V_L_cdr3 SEQ ID NO:
AB002022_2B07v1	AB002022	GDTFTRHYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRWLA	SASNLET	QQYESFPV	431	432	433	434	435	436
AB002293_2B07v2	AB002293	GDTFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRWLA	SASNLET	QQYNSFPV	437	438	439	440	441	442
AB002326_2B07v3	AB002326	GDTFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGSWLA	SASNLET	QQYNSFPV	443	444	445	446	447	448
AB002328_2B07v4	AB002328	GDTFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRWLA	SASNLET	QQYNRFPV	449	450	451	452	453	454
AB002342_2B07v5	AB002342	GDTFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRWLA	SASNLET	QQYERFPV	455	456	457	458	459	460
AB002345_2B07v6	AB002345	GDTFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRYLA	SASNLET	QQYNSFPV	461	462	463	464	465	466
AB002347_2B07v7	AB002347	GDTFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRYLA	SASNLET	QQYNRFPV	467	468	469	470	471	472
AB002348_2B07v8	AB002348	GDTFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRYLA	YASNLET	QQYNSFPV	473	474	475	476	477	478
AB002353_2B07v9	AB002353	GDTFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRWLA	SASNLET	QQYESFPV	479	480	481	482	483	484
AB002360_7A04v1	AB002360	GYTFTDYYMH	IINPRAGYTSYALKFQG	TSGWDV	RASQSISTWLA	AASSLDS	QQSYSFPV	485	486	487	488	489	490
AB002365_7A04v2	AB002365	GYTFTRYYMH	IINPRAGYTSYALKFQG	TSGWDV	RASQSISTWLA	AASSLDS	QQSYSFPV	491	492	493	494	495	496
AB002370_7A04v3	AB002370	GYTFTTYYMH	IINPRAGYTSYALKFQG	TSGWDV	RASQSISTWLA	AASSLDS	QQSYSFPV	497	498	499	500	501	502

ID	抗體 ID	V_H_cdr1	V_H_cdr2	V_H_cdr3	V_L_cdr1	V_L_cdr2	V_L_cdr3	V_H_cdr1 SEQ ID NO:	V_H_cdr2 SEQ ID NO:	V_H_cdr3 SEQ ID NO:	V_L_cdr1 SEQ ID NO:	V_L_cdr2 SEQ ID NO:	V_L_cdr3 SEQ ID NO:
AB002381_7A04v4	AB002381	GDTFTDYYMH	IINPRAGYTSYALKFQG	TSGWDV	RASQSISTWLA	AASSLDS	QQSYSFPV	503	504	505	506	507	508
AB002410_2A11v2	AB002410	GHTFTRYYMH	IINPSGGYATYAQKFQG	ASGWFV	RASQSINSWLA	DTSTLES	QQSYSFPV	509	510	511	512	513	514
AB002413_2A11v3	AB002413	GHTFTRYYMH	IINPSGGYATYAQKFQG	ASGLFI	RASQSINSWLA	ATSTLES	QQYYRFPV	515	516	517	518	519	520
AB002417_2A11v4	AB002417	GHTFTRYYMH	IINPSGGYATYAQKFQG	ASGLFI	RASQSINSWLA	ATSTLES	QQYYSFPV	521	522	523	524	525	526
AB002427_2A11v5	AB002427	GHTFTRYYMH	IINPSGGYATYAQKFQG	ASGLFI	RASQSINSWLA	ATSTLES	QQSYRFPV	527	528	529	530	531	532
AB002520_7A04v8	AB002520	GYTFTDYYMH	IINPRAGYTSYALKFQG	TSGWDV	RASQSISTWLA	AASSLDS	QQSYRFPV	533	534	535	536	537	538
AB002521_2A11v1	AB002521	GHTFTRYYMH	IINPSGGYATYAQKFQG	ASGLDI	RASQSINSWLA	ATSTLES	QQSYRFPV	539	540	541	542	543	544
AB002829_knd_A08	AB002829	GYIFNGYDIH	WMNPDNGNTGLAQKFQG	ARGMATRFPYYYYGMDV	RSSQSLLHSNGYNYLD	LGSNRAS	MQGTHWPP	545	546	547	548	549	550
AB002864_2A11v6	AB002864	GHTFTRYYMH	VINPSGGYATYAQKFQG	ASGWDV	RASQSINSWLA	ATSTLES	QQSYSSPV	551	552	553	554	555	556
AB003005_7A04v5	AB003005	GYTFTRYYMH	IIQPRAGYTSYALKFQG	TSGWDV	RASQSISTWLA	AASSLDE	QQSYSFPV	557	558	559	560	561	562
AB003007_7A04v6	AB003007	GYTFTRYYMH	IINPRAGYTSYALKFQG	TSGWEV	RASQSISTWLA	AASSLDE	QQSYSFPV	563	564	565	566	567	568
AB003012_7A04v7	AB003012	GYTFTRYYMH	IINPRAGYTSYALKFQG	TSGWDV	RASQSISTWLA	AASSLDE	QQSYSFPV	569	570	571	572	573	574

ID	抗體 ID	V_H_cdr1	V_H_cdr2	V_H_cdr3	V_L_cdr1	V_L_cdr2	V_L_cdr3	V_H_cdr1 SEQ ID NO:	V_H_cdr2 SEQ ID NO:	V_H_cdr3 SEQ ID NO:	V_L_cdr1 SEQ ID NO:	V_L_cdr2 SEQ ID NO:	V_L_cdr3 SEQ ID NO:
AB003021_2A11v7	AB003021	GFTFTRYYMH	VINPSGGYATYAQKFQG	ASGWDV	RASQSISSWLA	ATSTLES	QQSYSSPV	575	576	577	578	579	580
AB003155_2B07v10	AB003155	GETFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRWLA	SASNLET	QQYNRFPV	581	582	583	584	585	586
AB003174_2B07v11	AB003174	GDTFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRELA	SASNLET	QQYNRFPV	587	588	589	590	591	592
AB003178_2B07v12	AB003178	GDEFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRWLA	SASNLET	QQYNRFPV	593	594	595	596	597	598
AB003180_2B07v13	AB003180	GDEFTRYYVH	IQNPSGGYASYAQKFQG	AAGLFI	RASQSIGRWLA	SASNLET	QQYNRFPV	599	600	601	602	603	604
AB003183_2B07v14	AB003183	GDEFTRYYVH	IQNPSGGYASYAQKFQG	AAGLFI	RASQSIGRELA	DASNLET	QQYNRFPV	605	606	607	608	609	610
AB003200_2B05v1	AB003200	GETFTNYYIH	VINPRAGYTSYALKFQG	AGGWED	RISQSISSWLA	SASSLQS	QQSFTSPI	611	612	613	614	615	616
AB003201_2B05v2	AB003201	GGTFTNYYIH	IIDPRAGYTSYALKFQG	AGGWED	RISQSISSWLA	SASSLQS	QQSFTSPI	617	618	619	620	621	622
AB003202_2B05v3	AB003202	GSTFTNYYIH	IIDPRAGYTSYALKFQG	AGGWED	RISQSISSFLA	SASSLQS	QQSFTSPI	623	624	625	626	627	628
AB003209_2B05v4	AB003209	GETFTNYYIH	IIDPRAGYTSYALKFQG	AGGWED	RISQSISSFLA	SASSLQS	QQSFTSPI	629	630	631	632	633	634
AB003232_2B05v5	AB003232	GTTFTNYYIH	VINPRAGYTSYALKFQG	TGGWLD	RASQSISSWLA	SASSLQS	QQSVTMPV	635	636	637	638	639	640
AB003422_2B05v5	AB003422	GYTFTNYYIH	VINPRAGYTSYALKFQG	AGGWLD	RASQRISSWLA	DASSLQS	QQSFTMPV	641	642	643	644	645	646

ID	抗體 ID	V_H_cdr1	V_H_cdr2	V_H_cdr3	V_L_cdr1	V_L_cdr2	V_L_cdr3	V_H_cdr1 SEQ ID NO:	V_H_cdr2 SEQ ID NO:	V_H_cdr3 SEQ ID NO:	V_L_cdr1 SEQ ID NO:	V_L_cdr2 SEQ ID NO:	V_L_cdr3 SEQ ID NO:
AB003465_2A11v9	AB003465	GFTFTRYYMH	VINPSGGYATYAQKFQG	ASGWDV	RASQSISSWLA	ATSTLES	QQSYSFPP	647	648	649	650	651	652
AB003466_2B07v10	AB003466	GETFTRYYVH	IINPSGGYASYAQKFQG	AAGLFI	RASQSIGRWLA	SASNLET	QQYNSFPV	653	654	655	656	657	658
AB003467_7A04v9	AB003467	GYTFTRYYMH	IINPRAGYTSYALKFQG	TSGWDV	RASQSISTWLA	AASSLDT	QQSYSFPV	659	660	661	662	663	664
AB003470_knd_A04	AB003470	GYTFTAYYIH	WIHPYSGGTNYAQKFQG	AIGYYYGKFDY	RASQTISRYLN	AASSLQS	QQSYSTPR	665	666	667	668	669	670

實例 13

含有額外雙重結合抗體 (DBA) 域的 PD-1/IL-2 細胞激素複合體在*活體外*的經調節之 IL-2 受體結合

【0114】 本實例描述了包括**實例 12** 中所述之額外 DBA 結合元件的 PD-1/IL-2 DBA-細胞激素複合體的經 PD-1 調節之 IL-2 受體結合。分析抗 PD-1/IL-2 DBA-細胞激素複合體以及合適的未經調節之對照，諸如抗 PD-1、抗 Her2、抗 PDL-1 或抗 IL-2 細胞激素複合體。產生兩種形式的 DBA-細胞激素複合體及對照抗體-細胞激素複合體：(1)「對稱」免疫細胞激素 (如**圖 2E** 所示)；或 (2)「A對稱」免疫細胞激素 (如**圖 2B** 所示)，其藉由在哺乳動物細胞中表現並使用標準方法純化來產生。在存在不同量的 PD-1-Fc 或 hIgG1-Fc 的情況下，用塗覆在各孔上的恆定量之抗體-細胞激素構建體執行 ELISA 測定，用生物素化 IL-2 受體 βγ 異二聚體 Fc (IL-2RBG；Acro 貨號：ILG-H5254) 進行探測。為執行該測定，將 384 孔 ELISA 盤用在 100 mM 碳酸氫鹽溶液 (pH 9.0) 中之 1 μg/ml 抗 Fc 抗體於 4°C 塗覆過夜，並用 SuperBlock 洗滌兩次。然後將抗體-細胞激素複合體以 6nM 之恆定濃度添加至各孔中，並孵育 1 小時，並在 PBS plus 0.05% Tween 20 (PBST) 中洗滌三次。添加滴定濃度之 PD-1 Fc 或 IgG1 對照 Fc，並孵育 15 分鐘，然後添加恆定量之 10nM 生物素化 IL-2RBG。將盤額外孵育 30 分鐘，洗滌，並使用卵白素-HRP 及標準 ELISA 方案執行生物素化 IL-2RBG 偵測。

對稱設計

【0115】 包含**圖 2E** 中所示之結構的蛋白複合體的結果如**圖 9** 所示。如**圖 2E** 中所示，該對稱形式包含連接至各抗體可變域的一個 IL-2。從**圖 9** 中這些

構建體的行為可以看出，對於包含下**表 35** 中所示之肽 ID (參考肽的序列可見於表 2A 中) 的 DBA-細胞激素複合體 AF3247、AF3644、AF3651、AF3652、AF3653、AF3657、AF3930、AF3931、AF3933、AF3934 及 AF3935，添加 PD-1 Fc (但不添加陰性對照 hIgG1 Fc 蛋白) 時，IL-2RBG 結合以劑量依賴性方式增加。添加 PD-1 Fc 蛋白時，包括抗 Her2 (AF3243) 及抗IL-2 (AF3246) 的對照單特異性抗體-細胞激素複合體的 IL-2RBG 結合不變。

表 20：實施例 13 中測試的「對稱」免疫細胞激素設計及對照的多蛋白組分

蛋白複合體	肽 1	肽 2	肽 3	抗體 1
AF003232	PEP003639	PEP003648	PEP003642	AB002022_2B07v1
AF003740	PEP004243	PEP004247	PEP004159	AB002293_2B07v2
AF003747	PEP004243	PEP004247	PEP004162	AB002345_2B07v6
AF003749	PEP004243	PEP004247	PEP004163	AB002348_2B07v8
AF003753	PEP004243	PEP004247	PEP003642	AB002353_2B07v9
AF003941	PEP004251	PEP004443	PEP000169	AB001054_PDL1_DB02_D10 對照
AF003945	PEP004243	PEP004438	PEP004421	AB002326_2B07v3
AF003947	PEP004243	PEP004438	PEP004420	AB002342_2B07v5
AF003951	PEP004433	PEP004442	PEP004427	AB002360_7A04v1
AF003952	PEP004435	PEP004445	PEP004427	AB002365_7A04v2
AF003953	PEP004436	PEP004446	PEP004427	AB002370_7A04v3
AF003955	PEP004431	PEP004440	PEP004423	AB002413_2A11v3
AF003956	PEP004433	PEP004442	PEP004426	AB002520_7A04v8
AF003243	PEP003655	PEP000113		AB001203_trastuzumab 對照
AF003246	PEP003654	PEP003641		AB001923_抗 IL2 對照

不對稱設計

【0116】 包含**圖 2B** 所示之結構 (「不對稱」免疫細胞激素設計) 及下面**表 21** 所述之蛋白複合體的結果如**圖 10** 所示。該形式由包含兩個抗體域 (其中單一 IL-2 連接至其中一個域) 的不對稱複合體構成。對於包含下表 21 中所示之肽 ID (參考肽的序列可見於表 2A 中) 的 DBA-細胞激素複合體 AF3232、AF3740、AF3747、AF3749、AF3753、AF3945、AF3947、AF3951、AF3952、AF3953、

AF3955 及 AF3956，添加 PD-1 Fc 但不添加 IgG1 對照 Fc 蛋白時，IL-2RBG 結合以劑量依賴性方式增加。添加 PD-1 Fc 蛋白時，對照單特異性抗體-細胞激素複合體抗 PDL-1 (AF3941) 的 IL-2RBG 結合不變。

表 21：實施例 13 中測試的「不對稱」免疫細胞激素設計及對照的多蛋白組分

蛋白複合體	肽 1	肽 2	肽 2	抗體
AF003232	PEP003639	PEP003648	PEP003642	AB002022_2B07v1
AF003740	PEP004243	PEP004247	PEP004159	AB002293_2B07v2
AF003747	PEP004243	PEP004247	PEP004162	AB002345_2B07v6
AF003749	PEP004243	PEP004247	PEP004163	AB002348_2B07v8
AF003753	PEP004243	PEP004247	PEP003642	AB002353_2B07v9
AF003945	PEP004243	PEP004438	PEP004421	AB002326_2B07v3
AF003947	PEP004243	PEP004438	PEP004420	AB002342_2B07v5
AF003951	PEP004433	PEP004442	PEP004427	AB002360_7A04v1
AF003952	PEP004435	PEP004445	PEP004427	AB002365_7A04v2
AF003953	PEP004436	PEP004446	PEP004427	AB002370_7A04v3
AF003955	PEP004431	PEP004440	PEP004423	AB002413_2A11v3
AF003956	PEP004433	PEP004442	PEP004426	AB002520_7A04v8
AF003941	PEP004251	PEP004443	PEP000169	AB001054_PDL1_DB02_D10 對照

實例 14

兩種形式的 IL-2 與 IL-2RBG 結合對 PD-1/IL-2 細胞激素複合體的*活體外*抑制

【0117】 本實例描述了 PD-1/IL-2 DBA-細胞激素複合體中兩種形式的 IL-2 對 IL-2RBG 的結合。**圖 2H** 中所示之形式的抗體-細胞激素複合體係用野生型 (WT) IL-2 或 IL-2 3x 生成 (具有減少的與 IL-2Ralpha 之結合並具有 R38D、K43E 及 E61R 突變的 IL-2 變異體，參見例如，Vazquez-Lombardi 等人, Nat Commun., 8:15371, 2017，其藉由引用方式整體併入本文)。藉由在哺乳動物細胞中表現並使用標準方案純化以產生 DBA-細胞激素複合體及對照抗體-細胞激素複合體。為檢查 DBA 結合域阻斷 IL-2 與 IL-2RBG 結合的能力，用塗覆在各孔上的恆定量之抗體-細胞激素構建體執行 ELISA 測定，用生物素化 IL-2 受體

βγ 異二聚體 Fc (IL-2RBG；Acro 貨號：ILG-H5254) 進行探測。在這些實驗中，將 384 孔 ELISA 盤用在 100 mM 碳酸氫鹽溶液 (pH 9.0) 中之 1 μg/ml 抗 Fc 抗體 (Jackson ImmunoResearch) 於 4°C 塗覆過夜，並用 SuperBlock (ThermoFisher, 37515) 洗滌兩次。然後將抗體-細胞激素複合體以 6nM 之恆定濃度添加至各孔中，並孵育 1 小時，並在 PBS plus 0.05% Tween 20 (PBST) 中洗滌三次。添加滴定濃度之生物素化 IL-2RBG，並將盤額外孵育 45 分鐘。洗滌後，使用卵白素-HRP 及標準 ELISA 方案執行生物素化 IL-2RBG 偵測。

【0118】 下**表 22** 中所述之蛋白複合體的結果如**圖 11** 所示。如**圖 2H** 中所示，這些複合體係不對稱的，且包含兩個相同的單特異性 Fab 臂，其中單一 IL-2 (WT 或 3x) 藉由可撓性連接子接附至一個 Fc 域且單一 scFv 藉由可撓性連接子接附至另一個 Fc 域。抗體-細胞激素複合體包含 Fab 臂中之抗 PD-1 域及 Fc 臂上之 PD-1/IL-2 DBA scFv。對照抗體-細胞激素複合體包含 Fab 臂中之相同抗 PD-1 域及 Fc 臂上之抗 HER2 單特異性 scFv。在**圖 11** A 幅中，抗體-細胞激素複合體含有 Fc 域上之 WT IL-2 形式，且在 **圖 11** B 幅中，抗體-細胞激素複合體含有 Fc 上之 3x IL-2 形式。如**圖 11** A 幅所示，與抗 Her2 非 DB 非對照複合體 AF5416 相比，PD-1/IL-2 DBA 複合體 AF5418 及 AF5419 具有減少之 IL-2RBG 結合，證明 DBA 域能夠阻斷受體與 WT IL-2 之結合。如**圖 11** B 幅所示，與抗 Her2 非 DB 非對照複合體 AF4693 相比，PD-1/IL-2 DBA 複合體 AF4695 及 AF4696 具有減少之 IL-2RBG 結合，證明 DBA 域能夠阻斷受體與 IL-2 3x 之結合。

表 22：實施例 14 中測試的「Cterm」免疫細胞激素設計及對照的多蛋白組分

肽 ID	肽 1	肽 2	肽 3	抗體 1	抗體 2
AF004693	PEP004967	PEP005090	PEP004729	AB001203_trastuzumab 對照	AB000694_PD1_nivolumab 對照
AF004695	PEP004967	PEP005091	PEP004729	AB002328_2B07v4	AB000694_PD1_nivolumab 對照
AF004696	PEP004967	PEP005092	PEP004729	AB002365_7A04v2	AB000694_PD1_nivolumab 對照
AF005416	PEP006177	PEP005090	PEP004729	AB001203_trastuzumab 對照	AB000694_PD1_nivolumab 對照
AF005418	PEP006177	PEP005091	PEP004729	AB002328_2B07v4	AB000694_PD1_nivolumab 對照
AF005419	PEP006177	PEP005092	PEP004729	AB002365_7A04v2	AB000694_PD1_nivolumab 對照

實例 15

在細胞測定中藉由 PD-1/IL-2 雙重結合抗體 (DBA) 細胞激素複合體的經調節之 IL-2 受體傳訊

【0119】本實例描述了在 HEK-Blue™ IL-2 報導子細胞中藉由 PD-1/IL-2 DBA-細胞激素複合體的經 PD-1 調節之 IL-2 活性。分析抗 PD-1/IL-2 DBA-細胞激素複合體以及合適的未經調節之對照，諸如抗 Her2、抗 PDL-1 或抗 IL-2 細胞激素複合體。藉由在哺乳動物細胞中表現並使用標準方案純化以產生**圖 2B、2D、2E、2G、2H 及 2I** 所示之五種形式的 DBA-細胞激素複合體及對照抗體-細胞激素複合體，這些複合體的肽組分概述於下**表 23** 中 (其中單個組分之序列可見於表 2A 中)。在存在不同量的 PD-1-Fc 或 hIgG1-Fc 的情況下，對五種形式中之各者執行基於細胞的報導子測定。

表 23：實施例 15 中測試的免疫細胞激素設計及對照的多蛋白組分

蛋白複合體	形式 (圖)	鏈 1	鏈 2	鏈 3	抗體 1	抗體 2
AF003232	2B	PEP003639	PEP003648	PEP003642	AB002022_2B07v1	-
AF003744	2B	PEP004243	PEP004247	PEP004158	AB002328_2B07v4	-

蛋白複合體	形式 (圖)	鏈 1	鏈 2	鏈 3	抗體 1	抗體 2
AF003747	2B	PEP004243	PEP004247	PEP004162	AB002345_2B07v6	-
AF003941	2B	PEP004251	PEP004443	PEP000169	AB001054_PDL1_DB02_D10 對照	-
AF003946	2B	PEP004243	PEP004438	PEP004158	AB002328_2B07v4	-
AF003948	2B	PEP004243	PEP004438	PEP004162	AB002345_2B07v6	-
AF003952	2B	PEP004435	PEP004445	PEP004427	AB002365_7A04v2	-
AF003955	2B	PEP004431	PEP004440	PEP004423	AB002413_2A11v3	-
AF003956	2B	PEP004433	PEP004442	PEP004426	AB002520_7A04v8	-
AF003345	2D	PEP003791	PEP003786		AB002022_2B07v1	-
AF003243	2E	PEP003655	PEP000113		AB001203_trastuzumab 對照	-
AF003246	2E	PEP003654	PEP003641		AB001923_抗 IL2 對照	-
AF003247	2E	PEP003657	PEP003642		AB002022_2B07v1	-
AF003341	2E	PEP003780	PEP003782		AB002022_2B07v1	-
AF003644	2E	PEP004153	PEP004159		AB002293_2B07v2	-
AF003651	2E	PEP004153	PEP004162		AB002345_2B07v6	-
AF003657	2E	PEP004153	PEP003642		AB002353_2B07v9	-
AF003934	2E	PEP004418	PEP004427		AB002365_7A04v2	-
AF003873	2G	PEP004361	PEP003642		AB002022_2B07v1	AB000880_PD1_4C10 對照

蛋白複合體	形式 (圖)	鏈 1	鏈 2	鏈 3	抗體 1	抗體 2
AF003876	2G	PEP004363	PEP004158		AB002328_2B07v4	AB000880_PD1_4C10 對照
AF003877	2G	PEP004363	PEP004162		AB002345_2B07v6	AB000880_PD1_4C10 對照
AF003864	2H	PEP003626	PEP004356	PEP000243	AB001923_抗 IL2 對照	AB000881_PD1_對照
AF003871	2H	PEP004360	PEP000113	PEP004360	AB001203_trastuzumab 對照	AB000880_PD1_4C10 對照
AF003872	2H	PEP004359	PEP003641	PEP004359	AB001923_抗 IL2 對照	AB000880_PD1_4C10 對照
AF003913	2H	PEP003626	PEP004395	PEP000243	AB002022_2B07v1	AB000881_PD1_對照
AF003918	2H	PEP003626	PEP004398	PEP000243	AB002328_2B07v4	AB000881_PD1_對照
AF003923	2H	PEP003626	PEP004406	PEP000243	AB002360_7A04v1	AB000881_PD1_對照
AF003927	2H	PEP003626	PEP004404	PEP000243	AB002413_2A11v3	AB000881_PD1_對照
AF004502	2H	PEP005089	PEP005090	PEP004729	AB000694_PD1_nivolumab 對照	AB001203_trastuzumab 對照
AF004503	2H	PEP003628	PEP005088	PEP000113	AB001203_trastuzumab 對照	AB001203_trastuzumab 對照
AF004504	2H	PEP005089	PEP005091	PEP004729	AB002328_2B07v4	AB000694_PD1_nivolumab 對照
AF004505	2H	PEP005089	PEP005092	PEP004729	AB002365_7A04v2	AB000694_PD1_ni

蛋白複合體	形式 (圖)	鏈 1	鏈 2	鏈 3	抗體 1	抗體 2
						volumab 對照
AF004892	2H	PEP000288	PEP005631	PEP000244	AB002328_2B07v4	AB000881_PD1_對照
AF004893	2H	PEP000288	PEP005634	PEP000244	AB002365_7A04v2	AB000881_PD1_對照
AF003632	2I	PEP004130	PEP004129	PEP000244	AB000881_PD1_對照	-
AF003634	2I	PEP004134	PEP004133	PEP003782	AB002022_2B07v1	-

【0120】 在**圖 12A、12B、13A** 及 **25** 所示的實驗中，將抗體-細胞激素複合體在 384 孔經 TC 處理的盤 (Corning 3701) 中的孔中用完全 DMEM (+10% FBS、2 mM L-麩醯胺酸、丙酮酸鈉) 以及滴定濃度之 PD-1 Fc 或 IgG1 對照 Fc 稀釋至終濃度 100pM (先前顯示的濃度對於始終開啟的對照具有強報導子訊息，但對於始終關閉的對照幾乎無訊息)。孵育 15 分鐘後，將 HEK-Blue™ IL-2 報導子細胞 (12,500 個細胞) 添加至各孔中並孵育過夜。從各孔轉移 5 微升至含有 45 微升 QuantiBlue 溶液 (Invivogen 產品編號 rep-qbs) 的新盤中。30 至 60 分鐘後，使用 Perkin-Elmer Envision 確定 630 nm 處之吸光度。

【0121】 在**圖 13B、14A、14B、20** 及 **22** 中所示之替代實驗形式中，將 384 孔 ELISA 盤的孔用恆定濃度之用抗 Fc 抗體捕獲的 PD-1-Fc 或 IgG1 Fc 對照蛋白 (Jackson ImmunoResearch，產品編號 109-005-098) 塗覆。將細胞激素複合體在生長培養基中以 1:4 連續稀釋 8 個濃度點，從起始濃度 6 nM 開始，並在添加 HEK-Blue™ IL-2 報導子細胞之前短暫孵育。

【0122】包含**圖 2E** 中所示之結構的蛋白複合體的結果如**圖 12A** 及 **12B** 所示。如**圖 2E** 中所示，該對稱形式包含連接至各抗體重鏈可變域的一個 IL-2。對於 DBA-細胞激素複合體 AF3247、AF3644、AF3651、AF3657 及 AF3934，添加 PD-1 Fc 但不添加 hIgG1 Fc 蛋白時，IL-2 活性以劑量依賴性方式增加。添加 PD-1 Fc 蛋白時，對照抗 Her2 AF3243 及抗 IL-2 AF3246 單特異性抗體-細胞激素複合體之 IL-2 活性不變。**圖 12B** 中之對稱形式類似於**圖 12A** 中之 DBA-細胞激素複合體，但是 IL-2 結合至 AF3341 的重鏈可變域及 AF3345 的輕鏈可變域。添加 PD-1 Fc 但不添加 hIgG1 Fc 時，兩種對稱形式皆表現出增加之 IL-2 活性。

【0123】包含**圖 2B** 中所示之結構的蛋白複合體的結果如**圖 13A 及 13B** 所示。該形式由包含兩個抗體域 (其中單一 IL-2 連接至其中一個域) 的不對稱複合體構成。在**圖 13A** 中，對於 DBA-細胞激素複合體 AF3232、AF3744, 及 AF3747，添加 PD-1 Fc 但不添加 IgG1 對照 Fc 蛋白時，IL-2 活性以劑量依賴性方式增加。在**圖 13B** 中，顯示了不對稱構建體在其中 PD-1 Fc 或 hIgG1 Fc 被捕獲到盤上的替代測定形式中的結果。與用 hIgG1 Fc 塗覆的孔相比，DBA-細胞激素複合體 AF3946、AF3948、AF3952、AF3955 及 AF3956 在用 PD-1 塗覆的孔中表現出增加的 IL-2 活性。添加 PD-1 Fc 蛋白時，對照抗 PDL-1 單特異性抗體-細胞激素複合體 AF3941 的 IL-2 活性不變。

【0124】包含**圖 2H** 中所示之結構的蛋白複合體的結果如**圖 14A 及 14B** 所示。如**圖 2H** 中所示，這些複合體係不對稱的，且包含兩個相同的單特異性 Fab 臂，其中單一 IL-2 藉由可撓性連接子接附至一個 Fc 域且單一 scFv 藉由可撓性連接子接附至另一個 Fc 域。

【0125】在**圖 14A** 中，PD-1/IL-2 DBA 複合體由 Fab 臂中之抗 PD-1 域 (PD1-納武利尤單抗對照) 及 Fc 臂上之 PD-1/IL-2 DBA scFv 構成。對照抗體-細胞激素複合體由 Fab 臂中之相同抗 PD-1 域及 Fc 臂上之非 DBA scFv 構成。將滴定量之細胞激素複合體添加至細胞中時，與等莫耳量的對照抗 HER2 IL-2 免疫細胞激素 AF4502 及 AF4503 相比，上圖中含有細胞激素複合體 AF4504 及 AF4505 的 PD-1/IL-2 DBA 顯示出降低的報導子活化。在下圖中，將相同滴定量之細胞激素複合體添加至用 PD-1 Fc 或人類 IgG1 Fc 對照塗覆的孔中。與用人類 IgG1 Fc 塗覆的孔相比，AF4504 及 AF4505 兩者在 PD-1 中皆表現出增加的 IL-2 活性。與 hIgG1 Fc 對照相比，在用 PD1 Fc 塗覆的孔中，對照抗 HER2 IL-2 免疫細胞激素 AF4502 及 AF4503 的 IL-2 活性不變。在**圖 14B** 中，PD-1/IL-2 DBA 複合體由 Fab 臂中之不同抗 PD-1 域 (AB000881_PD1_對照) 及 Fc 臂上之 PD-1/IL-2 DBA scFv 構成。與用 hIgG1 Fc 塗覆的孔相比，含有細胞激素複合體 AF3913、AF3918、AF3923 及 AF3927 的 PD-1/IL-2 DBA 在用 PD-1 Fc 塗覆的孔中表現出增加的 IL-2 活性。在用 PD-1 塗覆的孔中，抗 IL-2 非 DBA scFv 對照抗體-細胞激素複合體 AF3864 的 IL-2 活性不變。

【0126】包含**圖 2G** 中所示之結構的蛋白複合體的結果如**圖 15** 所示。如**圖 2G** 中所示，該對稱形式包含連接至 Fab 臂中之各抗體重鏈可變域的一個 IL-2 及接附至各 Fc 域的一個 scFv。抗體-細胞激素複合體由 Fab 臂中之 PD-1/IL-2 DBA 及 Fc 域上之抗 PD-1 scFv (AB000880_PD1_4C10_對照) 構成。對照抗體-細胞激素複合體由 Fc 域中之相同抗 PD-1 域及 Fab 臂中之非 DBA 構成。AF3871 具有在 Fab 臂上之非 DBA 抗 Her2 抗體，且 AF3872 具有在 Fab 臂上之非 DBA 抗 IL-2 抗體。與用 hIgG1 塗覆的孔相比，含有複合體 AF3873、

AF3876 及 AF3877 的 PD-1/IL-2 DBA 在用 PD-1 Fc 塗覆的孔中表現出增加的 IL-2 報導子活性。在用 PD-1 Fc 塗覆的孔中，兩種對照抗體-細胞激素複合體 AF3871 及 AF3872 的 IL-2 活性不變。

【0127】 包含**圖 2I** 中所示之結構的蛋白複合體的結果如**圖 16** 所示。如**圖 2I** 中所示，這些複合體係不對稱的，且包含 Fab 臂中之 PD-1/IL-2 DBA，其中單一 IL-2 藉由可撓性連接子接附至一個 Fc 域。抗體之鉸鏈區為 IgG1 及 IgG3 之鉸鏈序列的雜合體，其中去除二硫鍵，以在 Fab 臂與 Fc 域上之 IL-2 細胞激素之間提供增加的可撓性。對照抗體-細胞激素複合體由 Fab 臂中之單特異性抗 PD-1 域及 Fc 域上之相同 IL-2 構成。對於 DBA-細胞激素複合體 AF3634，添加 PD-1 Fc 但不添加 hIgG1 Fc 蛋白時，IL-2 活性以劑量依賴性方式增加。添加 PD-1 Fc 蛋白時，對照抗 PD-1 單特異性抗體-細胞激素複合體 AF3632 的 IL-2 活性不變。

【0128】 包含**圖 2H** 中所示之結構的蛋白複合體的結果如**圖 17** 所示。如**圖 2H** 中所示且類似於**圖 14A 及 14B** 中之構建體，這些複合體係不對稱的，且包含兩個相同的單特異性 Fab 臂，其中單一 IL-2 藉由可撓性連接子接附至一個 Fc 域且單一 scFv 藉由可撓性連接子接附至另一個 Fc 域。**圖 17** 中之構建體之獨特之處在於，構建體之 Fc 部分為人類 IgG1 同型。**圖 17** 中所示之兩種構建體係由 Fab 臂中之抗 PD-1 域 (AB000881_PD1_對照) 及 Fc 臂上之 PD-1/IL-2 DBA scFv 構成。與用 mIgG2a Fc 對照塗覆的孔相比，含有細胞激素複合體 AF4892 及 AF4893 的兩種 PD-1/IL2 DBA 在用 PD-1 Fc 塗覆的孔中表現出增加的 IL-2 活性對照。

實例 16

*活體外*藉由 PD-1/IL-2 3x 雙重結合抗體 (DBA) 細胞激素複合體的經調節之 IL-2 3x 受體傳訊

【0129】本實例描述了 PD-1/IL-2 3x DBA-細胞激素複合體在 HEK-Blue™ IL-2 報導子細胞中的經 PD-1 調節之 IL-2 3x (與 IL-2Ralpha 具有減少之結合的 IL-2 變異體，Lombardi 等人，2017) 活性。分析抗 PD-1/IL-2 3x DBA-細胞激素複合體以及合適的未經調節之對照，諸如抗 Her2、抗 PD-1 或抗 IL-2 細胞激素複合體。藉由在哺乳動物細胞中表現並使用標準方案純化以產生**圖 2B 及 2H** 中所示的兩種形式的 DBA-細胞激素複合體及對照抗體-細胞激素複合體。在存在與盤結合之 PD-1-Fc 或 hIgG1-Fc 的情況下，對兩種形式中之各者執行基於細胞的報導子測定。將 384 孔 ELISA 盤 (Corning 3700) 用在 100 mM 碳酸氫鹽溶液 (pH 9.0) 中之 1 μg/ml 抗 Fc 抗體 (Jackson ImmunoResearch) 於 4°C 塗覆過夜，並用 SuperBlock (ThermoFisher) 洗滌兩次。然後 PD1-Fc 或 IgG1 對照 Fc 以 6nM 之恆定濃度添加至各孔中，並孵育 1 小時，並在 PBS plus 0.05% Tween 20 (PBST) 中洗滌三次。將抗體-細胞激素複合體用完全 DMEMDMEM (+10% FBS、2 mM L-麩醯胺酸、丙酮酸鈉) 以 1:4 連續稀釋 8 個濃度點，從起始濃度 6 nM 開始。孵育 15 分鐘後，將 HEK-Blue™ IL-2 報導子細胞 (12,500 個細胞) 添加至各孔中並孵育過夜。從各孔轉移 5 微升至含有 45 微升 QuantiBlue 溶液 (Invivogen 產品編號 rep-qbs) 的新盤中。30 至 60 分鐘後，使用 Perkin-Elmer Envision 確定 630 nm 處之吸光度。

【0130】包含**圖 2B** 中所示之結構的蛋白複合體的結果如**圖 18** 所示。該形式由包含兩個抗體域 (其中單一 IL-2 3x 連接至其中一個域) 的不對稱複合體構成。與用 hIgG1 Fc 塗覆的孔相比，DBA-細胞激素複合體 AF4385、

AF4386、AF4387、AF4388 及 AF4389 在用 PD-1 Fc 塗覆的孔中表現出增加的 IL-2 3x 活性。添加 PD-1 Fc 蛋白時，對照抗 PD-1 單特異性抗體-細胞激素複合體 AF4380 及抗 IL-2 單特異性抗體-細胞激素複合體 AF4384 之 IL-2 3x 活性不變。

【0131】包含**圖** 2H 中所示之結構的蛋白複合體的結果如**圖 19A、19B 及 19C** 所示。如**圖 2H** 中所示，這些複合體係不對稱的，且包含兩個相同的單特異性 Fab 臂，其中單一 IL-2 3x 藉由可撓性連接子接附至一個 Fc 域且單一 scFv 藉由可撓性連接子接附至另一個 Fc 域。

【0132】在**圖 19A** 中，PD-1/IL-2 DBA 複合體由 Fab 臂中之抗 PD-1 域 (AB000694_nivo) 及 Fc 臂上之 PD-1/IL-2 DBA scFv 構成。對照抗體-細胞激素複合體由 Fab 臂中之相同抗 PD-1 域及 Fc 臂上之非 DBA scFv 構成。與用 hIgG1 Fc 塗覆的孔相比，含有細胞激素複合體 AF4404、AF4405、AF4695 及 AF4696 的 PD-1/IL-2 3x DBA 在用 PD-1 Fc 塗覆的孔中表現出增加的 IL-2 3x 活性。在用 PD-1 Fc 塗覆的孔中，抗 IL-2 非 DBA scFv 對照抗體-細胞激素複合體 AF4401 及抗 Her2 非 DBA scFv 對照抗體-細胞激素複合體 AF4694 之 IL-2 3x 活性不變。在**圖 19B** 中，PD-1/IL-2 DBA 複合體由 Fab 臂中之不同抗 PD-1 域 (AB000880_PD1_R04_C10) 及 Fc 臂上之 PD-1/IL-2 DBA scFv 構成。與用 hIgG1 Fc 塗覆的孔相比，含有細胞激素複合體 AF4413、AF4414、AF4415 及 AF4416 的 PD-1/IL-2 3x DBA 在用 PD-1 Fc 塗覆的孔中表現出增加的 IL-2 3x 活性。在用 PD-1 Fc 塗覆的孔中，抗 IL-2 非 DBA scFv 對照抗體-細胞激素複合體 AF4412 之IL-2 3x 活性不變。在**圖 19C** 中，PD-1/IL-2 DBA 複合體由 Fab 臂中之抗 PD-1 域構成，其既不阻斷 PDL-1 與 PD-1 之結合，亦不阻斷納武利尤單

抗與 PD-1 之結合。與用 hIgG1 Fc 塗覆的孔相比，含有複合體 AF4771 及 AF4773 的兩種 PD-1/IL-2 DBA 在用 PD-1 Fc 塗覆的孔中表現出增加的 IL-2 3x 活性。

表 24：實施例 16 中測試的免疫細胞激素設計及對照的多蛋白組分

蛋白複合體	形式 (圖)	鏈 1	鏈 2	鏈 3	抗體 1	抗體 2
AF004385	2B	PEP004957	PEP004438	PEP004420	AB002342_2B07v5	-
AF004386	2B	PEP004957	PEP004438	PEP004162	AB002345_2B07v6	-
AF004387	2B	PEP004959	PEP004442	PEP004427	AB002360_7A04v1	-
AF004388	2B	PEP004960	PEP004446	PEP004427	AB002370_7A04v3	-
AF004389	2B	PEP004958	PEP004440	PEP004423	AB002413_2A11v3	-
AF004404	2H	PEP004967	PEP004974	PEP004729	AB002360_7A04v1	AB000694_PD1_nivolumab 對照
AF004405	2H	PEP004967	PEP004973	PEP004729	AB002413_2A11v3	AB000694_PD1_nivolumab 對照
AF004413	2H	PEP004978	PEP004981	PEP000245	AB002342_2B07v5	AB000880_PD1_4C10 對照
AF004414	2H	PEP004978	PEP004982	PEP000245	AB002345_2B07v6	AB000880_PD1_4C10 對照
AF004415	2H	PEP004978	PEP004984	PEP000245	AB002360_7A04v1	AB000880_PD1_4C10 對照
AF004416	2H	PEP004978	PEP004983	PEP000245	AB002413_2A11v3	AB000880_PD1_4C10 對照
AF004695	2H	PEP004967	PEP005091	PEP004729	AB002328_2B07v4	AB000694_PD1_nivolumab 對照
AF004696	2H	PEP004967	PEP005092	PEP004729	AB002365_7A04v2	AB000694_PD1_niv

						olumab 對照
AF004771	2H	PEP005470	PEP005471	PEP005469	AB002328_2B07v4	AB002829_knd_A04_PD1 抗體
AF004773	2H	PEP005474	PEP005475	PEP005473	AB002328_2B07v4	AB003470_knd_A08_PD1 抗體

實例 17

在細胞中藉由具有可變之連接子長度的 PD-1/IL-2 雙重結合抗體 (DBA) 細胞激素複合體的經調節之 IL-2 受體傳訊

【0133】本實例描述了在 HEK-Blue™ IL-2 報導子細胞模型中藉由具有可變之連接子長度的 PD-1/IL-2 DBA-細胞激素複合體的經 PD-1 調節之 IL-2 活性。產生**圖 2B** 中所示之形式的 DBA-細胞激素複合體，其中將 IL-2 細胞激素連接至 DBA 域的甘胺酸-絲胺酸 (GS) 連接子係於 5 個 GS 重複序列至 25 個 GS 重複序列變化。DBA-細胞激素複合體係於哺乳動物細胞中表現並使用標準方案純化。在存在與盤結合之 PD-1-Fc 或 hIgG1-Fc 的情況下執行基於細胞的報導子測定。在本實驗中，將 384 孔 ELISA 盤 (Corning 3700) 用在 100 mM 碳酸氫鹽溶液 (pH 9.0) 中之 1 μg/ml 抗 Fc 抗體 (Jackson ImmunoResearch) 於 4°C 塗覆過夜，並用 SuperBlock (ThermoFisher) 洗滌兩次。然後 PD1-Fc 或 IgG1 對照 Fc 以 6nM 之恆定濃度添加至各孔中，並孵育 1 小時，並在 PBS plus 0.05% Tween 20 (PBST) 中洗滌三次。將抗體-細胞激素複合體用完全 DMEMDMEM (+10% FBS、2 mM L-麩醯胺酸、丙酮酸鈉) 以 1:4 連續稀釋 8 個濃度點，從起始濃度 6 nM 開始。孵育 15 分鐘後，將 HEK-Blue™ IL-2 報導子細胞 (12,500 個細胞) 添加至各孔中並孵育過夜。從各孔轉移 5 微升至含有 45 微升 QuantiBlue 溶液

(Invivogen 產品編號 rep-qbs) 的新盤中。30 至 60 分鐘後，使用 Perkin-Elmer Envision 確定 630 nm 處之吸光度。

【0134】 具有可變之連接子長度的**圖 2B** 中所示之蛋白複合體的結果如**圖 20** 所示。不對稱複合體包含兩個抗體域，其中單一 IL-2 連接至其中一個域。可變之連接子長度係選自 GS5 至 GS25，以測試連接子長度對 PD-1 調節之依賴性。與用 hIgG1 Fc 塗覆的孔相比，含有 AF4262、AF4273、AF4284 及 AF4295 中之 PD-1/IL-2 DBA 域 2B07 變異體的細胞激素複合體在用 PD-1 Fc 塗覆的孔中皆表現出增加的 IL-2 活性。在含有 AF4265、AF4276、AF4287 及 AF4298 中之 PD-1/IL-2 DBA 域 7A04 變異體的細胞激素複合體中觀察到類似的結果。這些資料表明，對於在 GS5 至 GS25 變化的多個細胞激素抗體連接子長度，PD-1 調節係可能的。

實例 18

在初代人 CD8+ T 細胞中，PD-1/IL-2 DBA-細胞激素複合體對 STAT5 磷酸化之 PD-1 依賴性誘導

【0135】 本實例描述了 PD-1/IL-2 DBA-細胞激素複合體在初代人 CD8+ T 細胞中對 STAT5 磷酸化之誘導。DBA-細胞激素複合體係以如**圖 2H** 所示的形式產生。使用負性免疫磁珠選擇 (STEMCELL) 從人 PBMC 中分離 CD8+ T 細胞，並用結合在盤上的抗 CD3 及可溶性抗 CD28 刺激 72 小時以誘導 PD-1 之表現。將經刺激之 CD8+ T 細胞與抗 PD-1 阻斷抗體或同型對照抗體一起孵育 1 小時。然後將滴定濃度之 PD-1/IL-2 DBA 細胞激素複合體 (經 PD-1 調節之 IL-2) 或抗 HER2/IL-2-細胞激素複合體 (始終開啓 IL-2) 添加至 CD8+ T 細胞中，並於 37°C 孵育 20 分鐘。將 CD8+ T 細胞用 Perm 緩衝劑 III (BD Biosciences) 固

定，洗滌，並用針對 CD8、CD45RA、CD45RO 及 pSTAT5 的抗體染色。藉由流式細胞分析技術評定 CD45RA+ 及 CD45RO+ T 細胞群體內的 STAT5 磷酸化。本實驗的結果如**圖 21A 及 21B** 所示。在主要呈 PD-1 陰性的 CD8+CD45RA+ T 細胞中，與未經調節之抗 HER2/IL-2-細胞激素複合體對照相比，PD-1/IL-2 DBA 細胞激素複合體誘導 STAT5 磷酸化陽性 CD8 + T 細胞的頻率較低。在主要呈 PD-1 陽性 CD8+CD45RO+ T 細胞中，與未經調節之抗 HER2/IL-2-細胞激素複合體對照相比，PD-1/IL-2 DBA 細胞激素複合體誘導 STAT5 磷酸化陽性 CD8 + T 細胞的頻率相當。此外，在用顯示出對 PD-1 結合的活性依賴性的 PD-1/IL-2 DBA 細胞激素複合體處理後，用抗 PD-1 阻斷抗體預處理的 CD8+CD45RO+ T 細胞具有較低頻率的 STAT5 磷酸化陽性細胞。綜上所述，這些資料表明，PD-1/IL-2 DBA 細胞激素複合體在 PD-1 陰性細胞上顯示出降低的活性。在 PD-1 陽性細胞上，PD-1/IL-2 DBA 細胞激素複合體活性因 PD-1 阻斷而減弱。

實例 19

在混合淋巴球反應中，PD-1/IL-2 DBA-細胞激素複合體對人類 T 細胞活化的調節

【0136】 本實例描述了在混合淋巴球反應 (MLR) 模型中 PD-1/IL-2 DBA-細胞激素複合體對人類 CD4+ T 細胞活化的調節。在該模型中，評定了 T 細胞對外來抗原呈遞細胞的活化及我們的免疫細胞激素構建體調節該活化的能力。使用負性免疫磁珠選擇 (STEMCELL) 從人類 PBMC 中分離 CD4+CD25- T 細胞，並按照製造方案用 CellTrace Violet 增殖染料 (ThermoFisher) 標記進行標記。為產生單核球來源的樹突狀細胞 (MDDC)，使用負性免疫磁珠選擇

(STEMCELL) 從不同供體的 PBMC 中分離單核球，並存在 GM-CSF (100ng/mL) 及 IL-4 (50ng/mL) 的情況下培養。3 天後更換培養基，並於第 7 天收集 MDDC。將 10,000 個 MDDC 添加到 96 孔圓底盤的各中，然後添加 50,000 個經增殖染料標記的 CD4+ T 細胞。生成各免疫細胞激素複合體的稀釋系列，並將其添加至細胞培養物中。於 37°C 培養 5 天後，將細胞用活/死活力染料 (ThermoFisher) 染色，然後於 4°C 下在固定/透化緩衝劑 (BD Biosciences) 中孵育 20 分鐘。然後將細胞用針對 CD4 及顆粒酶 B 的螢光團偶合抗體 (BD Bioscience) 染色，並藉由流式細胞分析技術評定增殖 CD4+ T 細胞中表現顆粒酶 B 的頻率。本實驗的結果如**圖 22A** 及**圖 22B** 所示。儘管 HER2-IL2 誘導極小的 T 細胞特異性活化 (如所預期的，因為 T 細胞不攜帶 HER2 分子)，但未經調節及經調節之 PD1-IL2 構建體能夠刺激 T 細胞活化，如劑量依賴性顆粒酶 B 表現所示。這些資料證明經調節之 PD1-IL2 複合體具有 PD-1 結合依賴性活性 (經由其活化 T 細胞的能力)。此外，在經調節及未經調節之 PD1-IL2 複合體之間觀察到的顆粒酶 B 誘導程度相當，表明在適當允許的條件下，向 IL2 中添加調節部分不減弱 IL2 的活性。

實例 20

同基因腫瘤模型中 PD-1/IL-2 DBA-細胞激素複合體對抗腫瘤免疫之調節

【0137】 本實例描述了 MC38 同基因小鼠腫瘤模型中 PD-1/IL-2 DBA-細胞激素複合體對抗腫瘤免疫之調節。評定 PD-1/IL-2 DBA-細胞激素複合體在活體內驅動抗腫瘤免疫的能力。將 500,000 個 MC38 腫瘤細胞皮下植入人類 PD-1 剔入小鼠 (GenOway) 中。每週測量兩次腫瘤，且體積按 (長度 × 寬度 × 寬度/2) 進行計算。將小鼠隨機分入治療組，並當腫瘤達到約 100 mm^3 的體積時開始治

療。在腫瘤植入後第 7、10 及 13 天，將小鼠用 0.5 毫克/千克體重的 PD-1/IL-2 DBA-細胞激素複合體、未經調節之抗 PD1-IL2、抗 HER2-IL2、抗 PD-1 或抗 HER2 進行靜脈內治療。本實驗的結果如**圖 23A** 及 **23B** 所示。與未經調節之 PD1-IL2 相比，PD-1/IL-2 DBA-細胞激素複合體顯示出可比較之腫瘤生長抑制，且與抗 PD1 及抗 HER 抗體相比，表現出優異的腫瘤生長抑制。

實例 21

PD1-IL2 增強 T 細胞雙特異性接合物活性 (預見性)

【0138】 可生成其中經 PD1 調節之 IL2 用於增強 T 細胞雙特異性抗體 (TCB) 活性的經 PD1 調節之免疫細胞激素。在本實例中，可生成其中 PD1-IL2 DBA scFv 融合至一條重鏈之 C 端且 IL-2 變異體融合至 TCB 之相對重鏈之 C 端的 PD1-IL2 TCB。PD1-IL2 TCB 之 N 端可變區可針對 CD3 及腫瘤相關抗原 (諸如 PSMA、HER2、CD20) 或針對 CD3 及不相關抗原。為評定 PD1-IL2 TCB 活性，從新鮮 PBMC 中分離人類 T 細胞，並與表現不同含量的腫瘤相關抗原的腫瘤細胞株共培養。將滴定濃度之裸 TCB 或 PD1-IL2 TCB 添加至 T 細胞:腫瘤細胞共培養物中。在不同時間點評定腫瘤毒殺以及 T 細胞活化及細胞激素產生。

實例 22

靶向 T 細胞相關抗原經 PD-1 調節之 IL-2 活性 (預見性)

【0139】 可生成其中經 PD1 調節之 IL2 使用任意 T 細胞標記物靶向 T 細胞的經 PD1 調節之免疫細胞激素。例如，PD1-IL2 DBA scFv 可融合至針對表現 T 細胞所表現之標記物的抗體 (包括但不限於 CD28、CD28H、OX40、GITR、CD137、CD27、HVEM、CTLA-4、PD-1、TIM-3、BTLA、VISTA、

LAG-3、TIGIT、CD244、ICOS、CD40L、CD4、CD8、KLRG1、FasL 及 CD7)之一條重鏈之 C 端且 IL-2 變異體可融合至相對重鏈之 C 端。可在各種條件下活化 T 細胞，以誘導給定 T 細胞標記物之表現。然後可以添加針對目標標記物或不相關標記物的滴定濃度之含有 PD1-IL2 DBA 的免疫細胞激素。然後可以將 STAT5 磷酸化作為靶向 IL-2 活性之測量結果來評定。在一些實驗中，在用含有 PD1-IL2 DBA 之免疫細胞激素處理之前，可以添加針對目標標記物的阻斷抗體以顯示特異性。

【0140】 儘管本揭露之較佳實施例已展示及描述於本文中，對熟習此項技術者顯而易見的是，該等實施例僅係藉由此類實施例提供。熟習此項技術者將構想出諸多變化、改變及取代，此並不背離本揭露。應理解，本文所描述之本揭露實施例的各種替代形式可用於實踐本揭露。下列申請專利範圍意欲界定本揭露之範圍，且意欲由此涵蓋該等申請專利範圍及其等效形式之範圍內的方法及結構。

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【發明申請專利範圍】

【請求項1】

一種複合體，其包含：

(a) 包含 IL-2 肽的治療域 (therapeutic domain)；

(b) 連接子；及

(c) 包含抗體的感測器域 (sensor domain)，其中該感測器域經組態為以相互排斥方式結合 PD-1 及 IL-2，

其中該治療域藉由該連接子與該感測器域連接。

【請求項2】

如請求項 1 之複合體，其中該感測器域經組態為：(i) 在不存在 PD-1 的情況下結合 IL-2；以及 (ii) 在存在 PD-1 的情況下不結合 IL-2。

【請求項3】

如請求項 1 或 2 之複合體，其中該抗體為抗體片段或抗體衍生物。

【請求項4】

如請求項 1 至 3 中任一項之複合體，其中該感測器域包含經組態以結合 PD-1 及 IL-2 的單一雙重結合抗體 (DBA)。

【請求項5】

如請求項 1 至 4 中任一項之複合體，其中該 DBA 包含與 SEQ ID NO: 11 至 20、154 至 156、168 至 173、114 至 119、415、421、433、439、445、451、457、463、469、475、481、487、493、499、505、511、517、523、529、535、541、547、553、559、565、571、577、583、589、595、601、607、613、619、625、631、637、643、649、655、661 或 667 中之任一者具有至少 80 % 同一性的重鏈 CDR3。

【請求項6】

如請求項 1 至 4 中任一項之複合體，其中該 DBA 包含：含有與表 3、表 7、表 8 或表 19 中列舉的序列中之任一者具有至少 80% 同一性的序列之重鏈 CDR1、CDR2 或 CDR3。

【請求項7】

如請求項 1 至 4 中任一項之複合體，其中該 DBA 包含：含有與表 18 中列舉的序列中之任一者具有至少 80% 同一性的序列之 V_H 或 V_L。

【請求項8】

如請求項 1 至 7 中任一項之複合體，其中該複合體包含 Fc 域。

【請求項9】

如請求項 8 之複合體，其中該 Fc 域係同二聚體的 (homodimeric)。

【請求項10】

如請求項 8 之複合體，其中該 Fc 域係異二聚體的 (heterodimeric)。

【請求項11】

如請求項 10 之複合體，其中該 Fc 域包含：(a) 包含杵突變 (knob mutation) 的第一多肽及 (b) 包含臼突變 (hole mutation) 的第二多肽。

【請求項12】

如請求項 11 之複合體，其中該杵突變包含或該臼突變包含下列相對於 IgG 的殘基對中之任一對之突變：366 與 407、405 與 394、或 407 與 366。

【請求項13】

如請求項 12 之複合體，其中該杵突變包含精胺酸殘基、苯丙胺酸殘基、酪胺酸殘基或色胺酸殘基，且該臼突變包含丙胺酸殘基、絲胺酸殘基、蘇胺酸殘基或纈胺酸殘基。

【請求項14】

如請求項 1 至 12 中任一項之複合體，其中該複合體包含含有全長 DBA 的感測器域，其中該 IL-2 肽與該全長 DBA 之重鏈之 N 端連接，或其中該 IL-2 肽與該全長 DBA 之輕鏈之 N 端連接。

【請求項15】

如請求項 1 至 12 中任一項之複合體，其中該複合體包含含有全長 DBA 的感測器域，其中該 IL-2 肽與該全長 DBA 之重鏈之 C 端連接。

【請求項16】

如請求項 1 至 9 或 13 中任一項之複合體，其中該複合體包含：

(a) 根據 N-[IL-2]-[連接子]-[V_H]-[C_H]-[鉸鏈 (hinge)]-Fc-C 的第一多肽；及

根據 N-[V_L]-[C_L]-C 的第二多肽，或

(b) 根據 N-[V_H]-[C_H]-[鉸鏈]-Fc-C 的第一多肽；及

根據 N-[IL-2]-[連接子]-[V_L]-[C_L]-C 的第二多肽，

其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示該 DBA 之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，V_L 表示該 DBA 之輕鏈可變域，[鉸鏈] 表示免疫球蛋白之鉸鏈區，Fc 表示免疫球蛋白之 Fc 區，且 CL 表示免疫球蛋白之輕鏈恆定域。

【請求項17】

如請求項 16 之複合體，其中該複合體包含 AF003345、AF003243、AF003246、AF003247、AF003341、AF003644、AF003651、AF003657 或 AF003934 中之任一者。

【請求項18】

如請求項 1 至 8、10 至 12 或 13 中任一項之複合體，其中該複合體

包含：

(a) 根據 N-[IL-2]-[連接子]-[V_H]-[C_H]-[鉸鏈]-Fc[杵]-C 的第一多肽；

根據 N-[V_L]-[C_L]-C 的第二多肽；及

根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[臼]-C 的第三多肽，或

(b) 根據 N-[IL-2]-[連接子]-[V_H]-[C_H]-[鉸鏈]-Fc[臼]-C 的第一多肽；

根據 N-[V_L]-[C_L]-C 的第二多肽；及

根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[杵]-C 的第三多肽，

其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示該 DBA 之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，V_L 表示該 DBA 之輕鏈可變域，[鉸鏈] 表示免疫球蛋白之鉸鏈區，Fc[杵] 表示包含杵突變的免疫球蛋白之 Fc，Fc[臼] 表示包含臼突變的免疫球蛋白之 Fc 區，且 C_L 表示免疫球蛋白之輕鏈恆定域。

【請求項19】

如請求項 18 之複合體，其中該杵突變或該臼突變包含下列相對於 IgG 的殘基對中之任一對之突變：366 與 407、405 與 394、或 407 與 366。

【請求項20】

如請求項 18 至 19 中任一項之複合體，其中該複合體包含 AF003229、AF003230、AF003232、AF003740、AF003747、AF003749、AF003753、AF003945、AF003947、AF003951、AF003952、AF003953、AF003955、AF003956 或 AF003941 中之任一者。如請求項 1 至 9 或 15 中任一項之複合體，其中該複合體包含：

(a) 根據 N-[IL-2]-[連接子]-[V_H]-[C_H]-[鉸鏈]-Fc-[scFv]-C 的第一

多肽；及

(b) 根據 N-[V_L]-[C_L]-C 的第二多肽，或

其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示抗 PD-1 單選擇性 (monoselective) 抗體之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，V_L 表示抗 PD-1 單選擇性抗體之輕鏈可變域，[鉸鏈] 表示免疫球蛋白之鉸鏈區，Fc 表示免疫球蛋白之 Fc 區，C_L 表示免疫球蛋白之輕鏈恆定域，且 [scFv] 表示包含該 DBA 之 V_H 域及 V_L 域的 scFv。

【請求項21】

如請求項 20 之複合體，其中該 scFv 係根據 N-[V_H]-[連接子 2]-[V_L]-C 定向。

【請求項22】

如請求項 20 或 21 之複合體，其中包含該 DBA 之 V_H 域及 V_L 域的該 scFv 包含：

(a) V_H 域，其包含與 AB002022_2B07v1、AB002328_2B07v4、AB002360_7A04v1 、 AB002413_2A11v3 、 AB002342_2B07v5 、AB002345_2B07v6 或 AB002365_7A04v2 中之任一者之 V_H 域具有至少 80% 同一性的序列；或

(b) V_L 域，其包含與 AB002022_2B07v1、AB002328_2B07v4、AB002360_7A04v1 、 AB002413_2A11v3 、 AB002342_2B07v5 、AB002345_2B07v6 或 AB002365_7A04v2 中之任一者之 V_L 域具有至少 80% 同一性的序列。

【請求項23】

如請求項 20 或 21 之複合體，其中包含該 DBA 之 V_H 域及 V_L 域的

該 scFv 包含：

(a) AB002022_2B07v1、AB002328_2B07v4、AB002360_7A04v1、AB002413_2A11v3 、 AB002342_2B07v5 、 AB002345_2B07v6 或 AB002365_7A04v2 中之任一者之重鏈 CDR；或

(b) AB002022_2B07v1、AB002328_2B07v4、AB002360_7A04v1、AB002413_2A11v3 、 AB002342_2B07v5 、 AB002345_2B07v6 或 AB002365_7A04v2 中之任一者之輕鏈 CDR。

【請求項24】

如請求項 20 至 22 中任一項之複合體，其中該複合體包含 AF003864、AF003871、AF003872、AF003913、AF003918、AF003923、AF003927、AF004502、AF004503、AF004504、AF004505、AF004892 或 AF004893 中之任一者。

【請求項25】

如請求項 1 至 8、10 至 12 或 15 中任一項之複合體，其中該複合體包含：

(a) 根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[杵]-[連接子]-[IL-2]-C 的第一多肽；

根據 N-[V_L]-[C_L]-C 的第二多肽；及

根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[臼]-[連接子]-[scFv]-C 的第三多肽，或

(b) 根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[臼]-[連接子]-[IL-2]-C 的第一多肽；

根據 N-[V_L]-[C_L]-C 的第二多肽；及

根據 N-[V_H]-[C_H]-[鉸鏈]-Fc[杵]-[連接子]-[scFv]-C 的第三多肽；

其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示該 DBA 之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，VL 表示該 DBA 之輕鏈可變域，[鉸鏈] 表示免疫球蛋白之鉸鏈區，Fc[杵] 表示包含杵突變的免疫球蛋白之 Fc，Fc[臼] 表示包含臼突變的免疫球蛋白之 Fc 區，C_L 表示免疫球蛋白之輕鏈恆定域，且 [scFv] 表示該 DBA 之 scFv。

【請求項26】

如請求項 25 之複合體，其中該複合體包含 AF004693、AF004695、AF004696、AF005416、AF005418 或 AF005419 中之任一者。

【請求項27】

如請求項 1 至 8、10 至 12 或 15 中任一項之複合體，其中該複合體包含：

(a) 根據 N-[V_H]-[C_H]-[het-鉸鏈]-Fc[杵]-[連接子]-[IL-2]-C 的第一多肽；

根據 N-[V_L]-[C_L]-C 的第二多肽；及

根據 N-[V_H]-[C_H]-[het-鉸鏈]-Fc[臼]-C 的第三多肽，或

(b) 根據 N-[V_H]-[C_H]-[het-鉸鏈]-Fc[臼]-[連接子]-[IL-2]-C 的第一多肽；

根據 N-[V_L]-[C_L]-C 的第二多肽；及

根據 N-[V_H]-[C_H]-[het-鉸鏈]-Fc[杵]-C 的第三多肽，

其中 N- 表示肽 N 端，C- 表示肽 C 端，[連接子] 表示該連接子，V_H 指示該 DBA 之重鏈可變域，C_H 指示免疫球蛋白之重鏈恆定域，V_L 表示該 DBA 之輕鏈可變域，[het-鉸鏈] 表示與該 Fc 區異源的鉸鏈區，Fc[杵] 表示包含杵突變的免疫球蛋白之 Fc，Fc[臼] 表示包含

臼突變的免疫球蛋白之 Fc 區，且 C_L 表示免疫球蛋白之輕鏈恆定域。

【請求項28】

如請求項 27 之複合體，其中與該 Fc 區異源的該鉸鏈區為：(a) 衍生自 IgG3 抗體的鉸鏈區，或 (b) 基於 G4S 的連接子。

【請求項29】

如請求項 27 或 28 之複合體，其中該複合體包含 AF003632 或 AF003634。

【請求項30】

如請求項 1 至 29 中任一項之複合體，其中該 IL-2 肽包含野生型人類 IL-2 肽。

【請求項31】

如請求項 30 之複合體，其中該 IL-2 肽包含與人類 IL-2 具有至少約 80%、至少約 81%、至少約 82%、至少約 83%、至少約 84%、至少約 85%、至少約 86%、至少約 87%、至少約 88%、至少約 89%、至少約 90%、至少約 91%、至少約 92%、至少約 93%、至少約 94%、至少約 95%、至少約 96%、至少約 97%、至少約 98%、至少約 99% 或實質上 100% 序列同一性的序列。

【請求項32】

如請求項 31 之複合體，其中該複合體包含 AF003232、AF003243、AF003246、AF003247、AF003341、AF003345、AF003632、AF003634、AF003644、AF003651、AF003652、AF003653、AF003657、AF003740、AF003744、AF003747、AF003749、AF003753、AF003864、AF003873、AF003876、AF003877、AF003913、AF003918、AF003923、AF003927、AF003930、AF003931、AF003933、AF003934、AF003935、AF003941、

AF003945、AF003946、AF003947、AF003948、AF003951、AF003952、AF003953、AF003955、AF003956、AF004262、AF004265、AF004273、AF004276、AF004284、AF004287、AF004295、AF004298、AF004385、AF004386、AF004387、AF004388、AF004389、AF004404、AF004405、AF004413、AF004414、AF004415、AF004416、AF004504、AF004505、AF004693、AF004695、AF004696、AF004771、AF004773、AF004892 或 AF004893 中之任一者。

【請求項33】

一種增強 T 細胞對異源性細胞反應性之方法，其包含向有需要之個體投予如請求項 1 至 32 中任一項之複合體。

【請求項34】

如請求項 33 之方法，其中該等異源性細胞為癌細胞。

【請求項35】

一種治療有需要之個體之方法，其包含向該有需要之個體投予如請求項 1 至 32 中任一項之複合體。

【請求項36】

如請求項 35 之方法，其中該投予包含靜脈內、肌內或皮下投予。

【請求項37】

如請求項 35 至 36 中任一項之方法，其中該有需要之個體患有癌症。

【請求項38】

如請求項 35 至 37 中任一項之方法，其中該治療域治療該有需要之個體。

【請求項39】

如請求項 35 至 38 中任一項之方法，其中該有需要之個體為哺乳動

物。

【請求項40】

如請求項 39 之方法，其中該有需要之個體為人類。

【請求項41】

一種組成物，其包含編碼如請求項 1 至 32 中任一項之複合體的重組核酸。

【請求項42】

一種醫藥組成物，其包含如請求項 1 至 32 中任一項之複合體及醫藥上可接受之賦形劑。

【發明圖式】

圖 1A

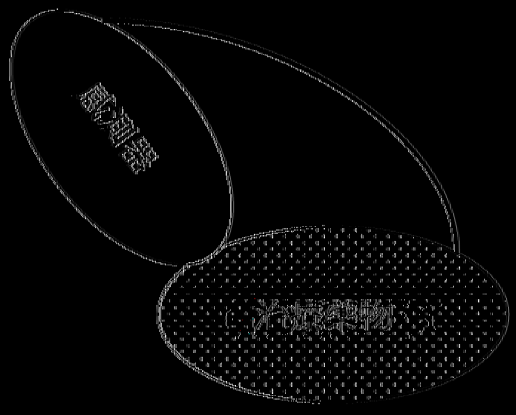


圖 1B

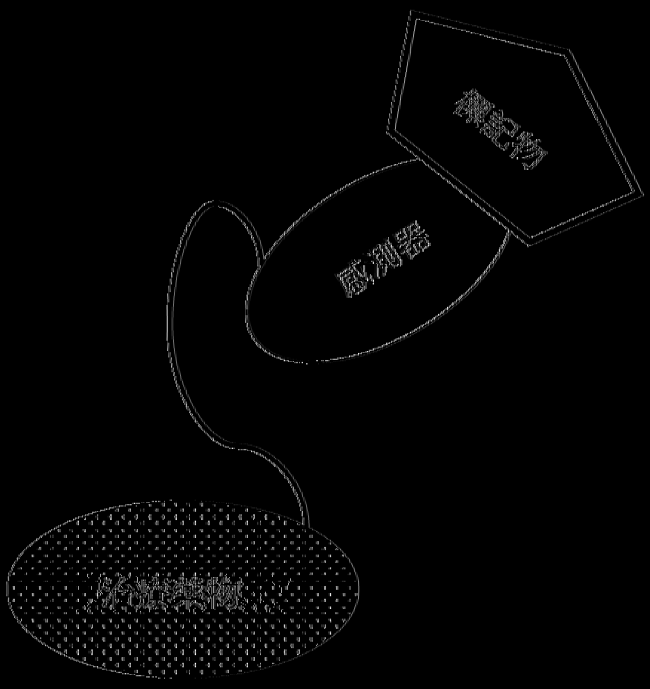


圖 1

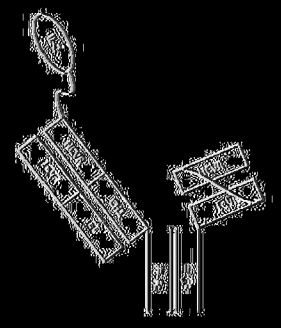


圖 2A

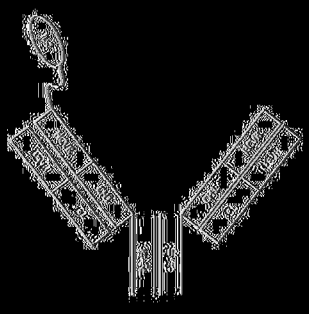


圖 2B

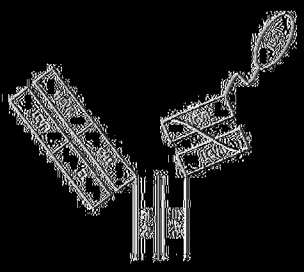


圖 2C

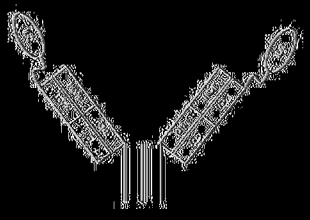


圖 2D

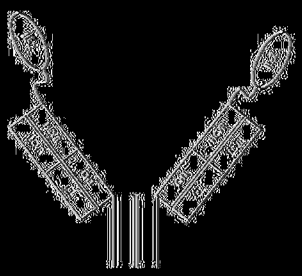


圖 2E

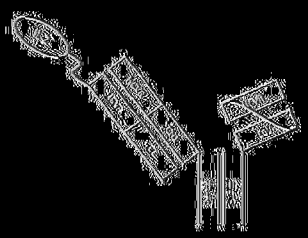


圖 2F

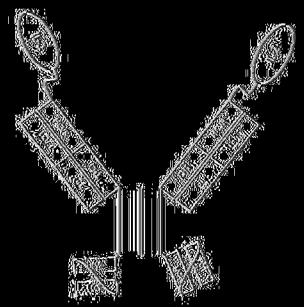


圖 2G

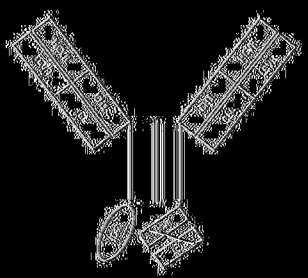


圖 2H

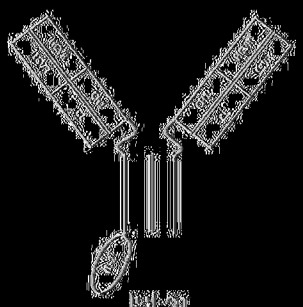


圖 2I

圖 2

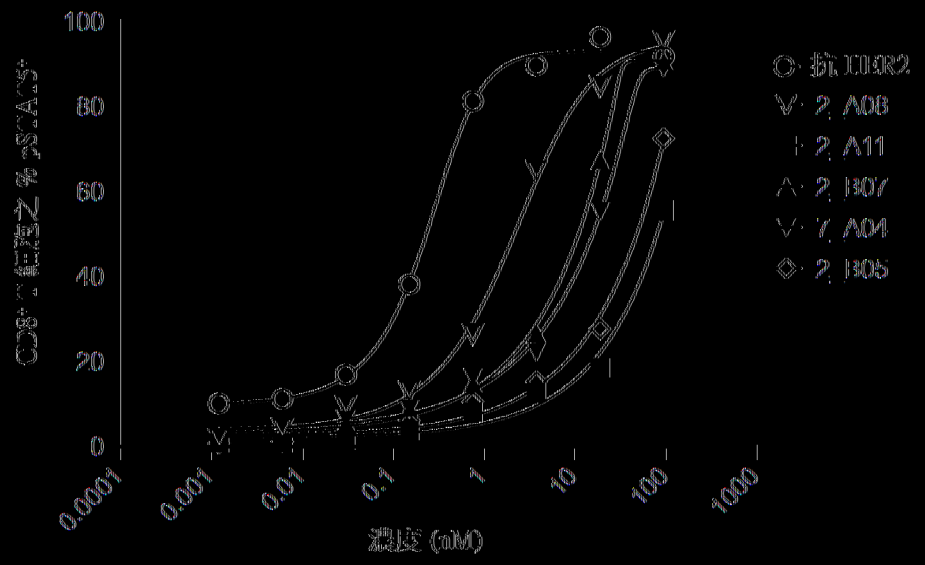

100
80
60
40
20
0
0.0001
0.001
0.01
0.1
1
10
100
1000
濃度 (nM)
抗IL6R2
2, A08
2, A11
2, B07
7, A04
2, B05

圖 3

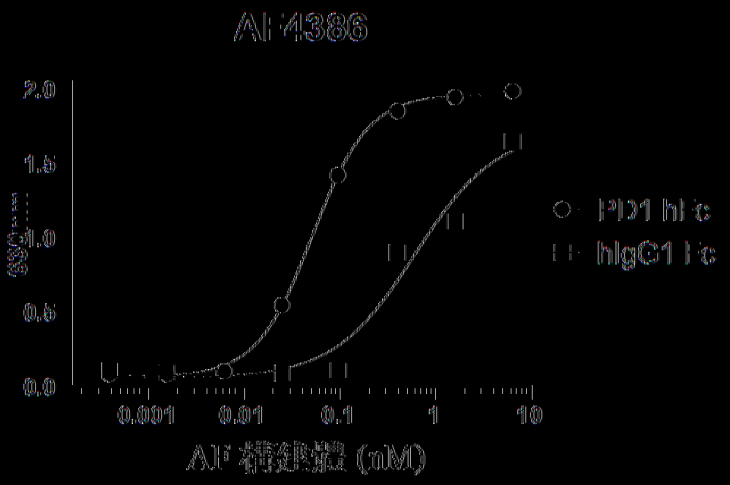

AF4386
2.0
1.5
1.0
0.5
0.0
0.001
0.01
0.1
1
10
AF 濃度 (nM)
PD1 hFc
hIgG1 Fc

圖 4A

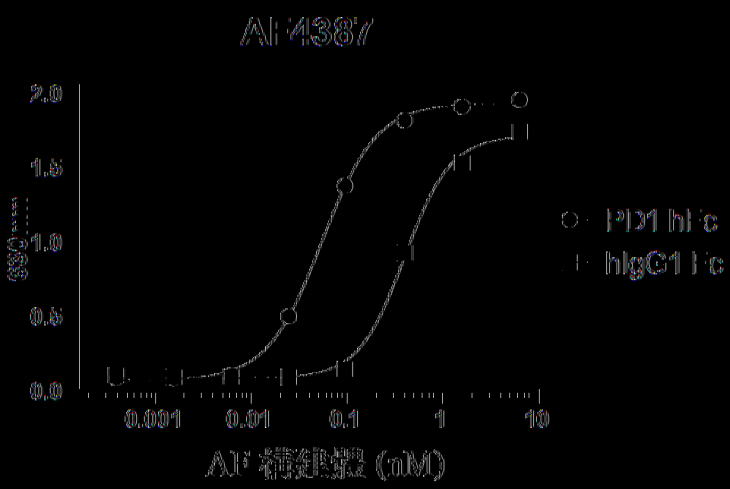

AF4387
2.0
1.5
1.0
0.5
0.0
0.001
0.01
0.1
1
10
AF 濃度 (nM)
PD1 hFc
hIgG1 Fc

圖 4B

AF4389

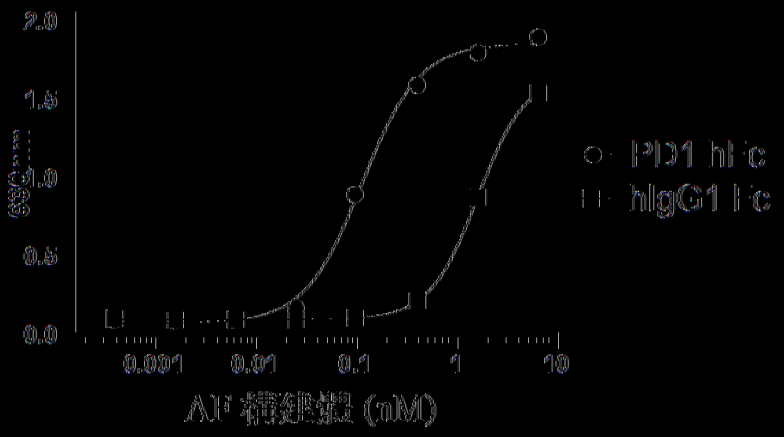


圖 4C

AF4380

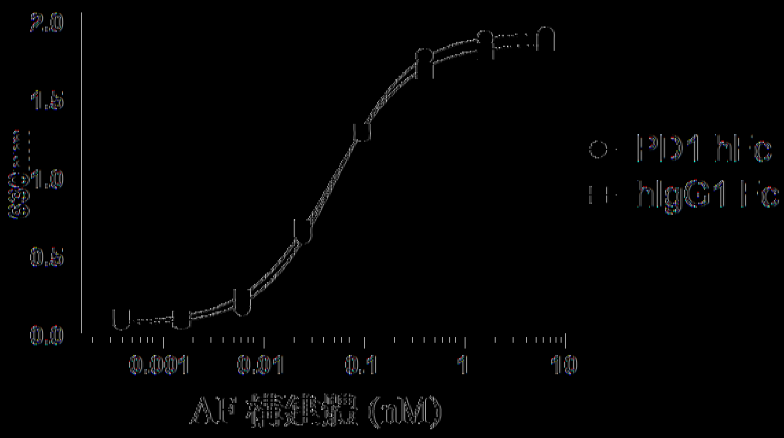


圖 4D

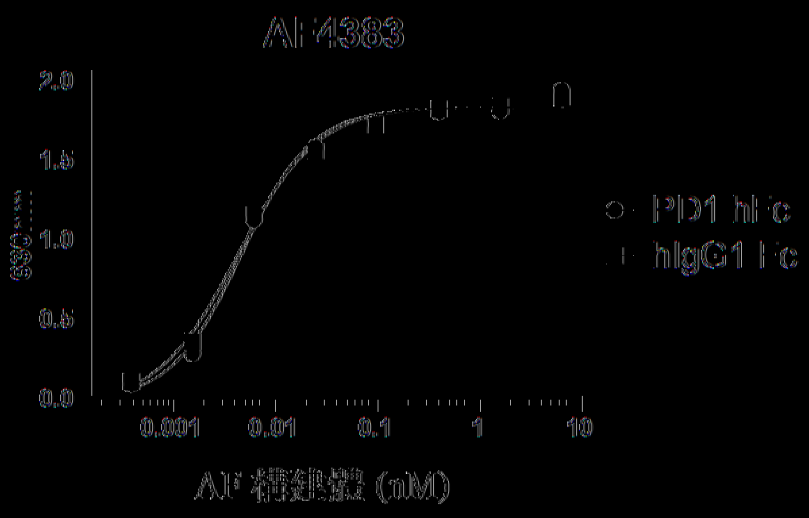

AF4383
2.0
1.5
1.0
0.5
0.0
0.001
0.01
0.1
1
10
PD1 hFc
hIgG1 Fc
AF 稀釋濃 (nM)

圖 4E

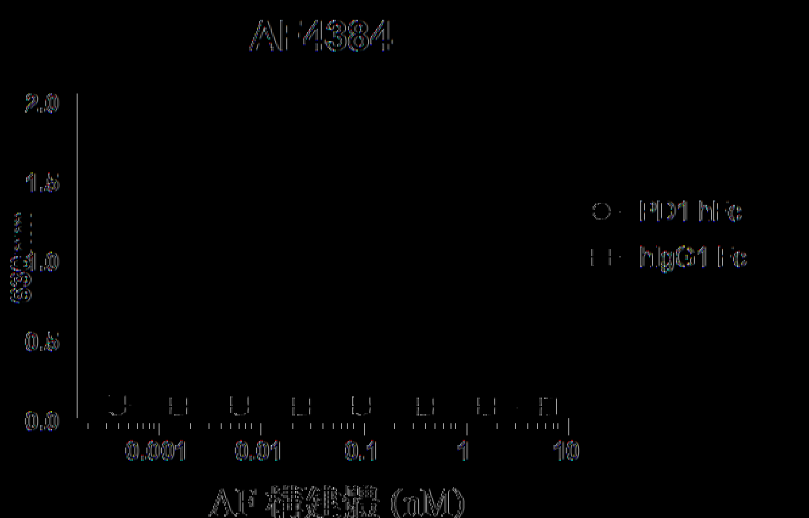
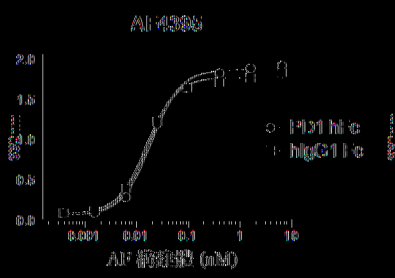

AF4384
2.0
1.5
1.0
0.5
0.0
0.001
0.01
0.1
1
10
PD1 hFc
hIgG1 Fc
AF 稀釋濃 (nM)

圖 4F

Fab: Her2 PD1

scFv

PD1/Il2 DBA 2B07 雙功能



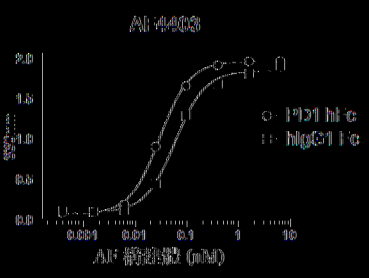
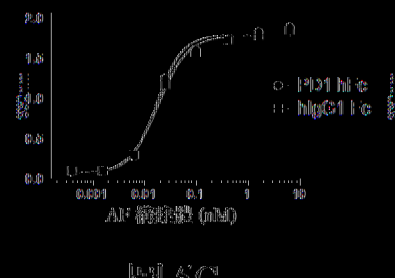


圖 5A 圖 5B

PD1/Il2 DBA 7A01 雙功能



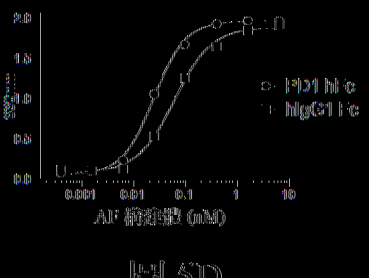
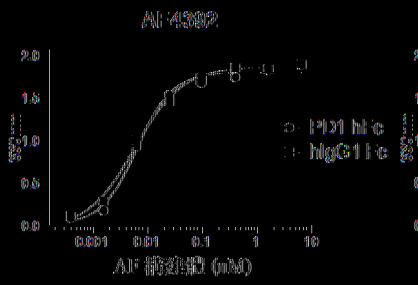


圖 5C 圖 5D

Fab: Her2 PD1

scFv

Her2



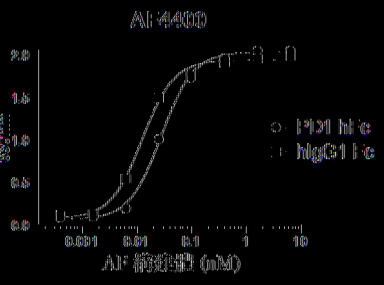
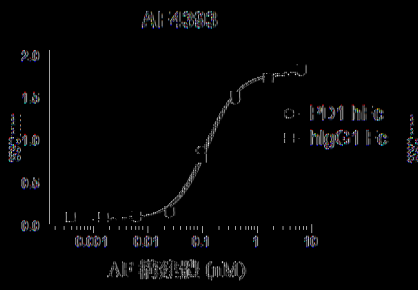


圖 5E 圖 5F

IL-2



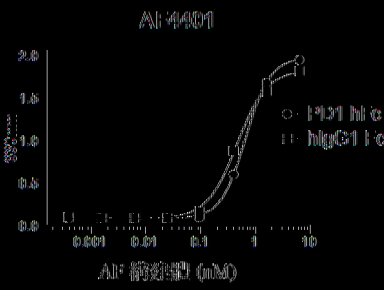


圖 5G 圖 5H

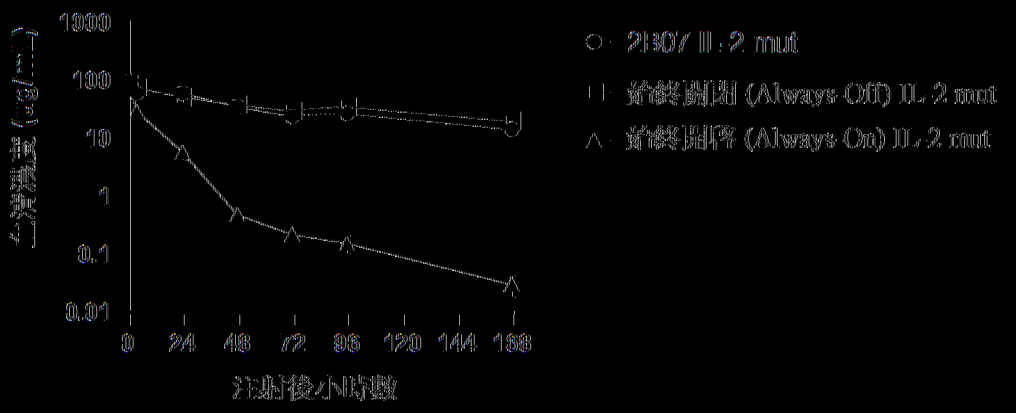

1000
100
10
1
0.1
0.01
0
24
48
72
96
120
144
168
注射後小時數
○ 2B7 II-2 mut
□ 常態關閉 (Always Off) IL-2 mut
△ 常態開啓 (Always On) IL-2 mut

圖 6

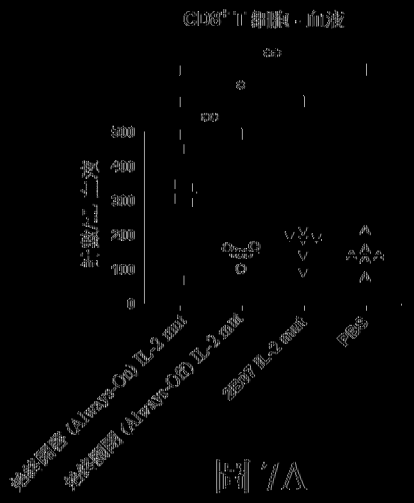


圖 7A

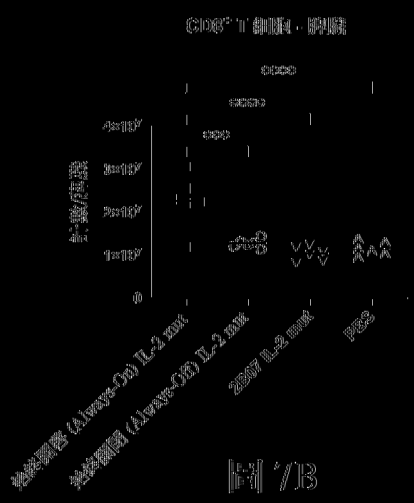


圖 7B

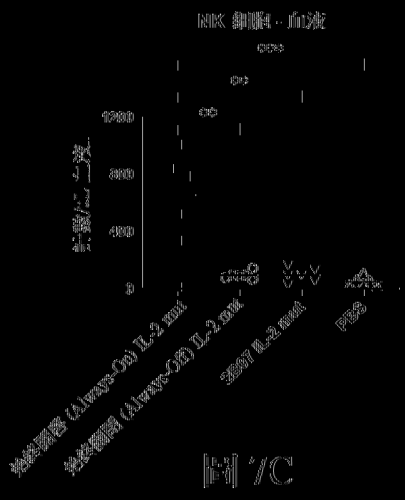


圖 7C

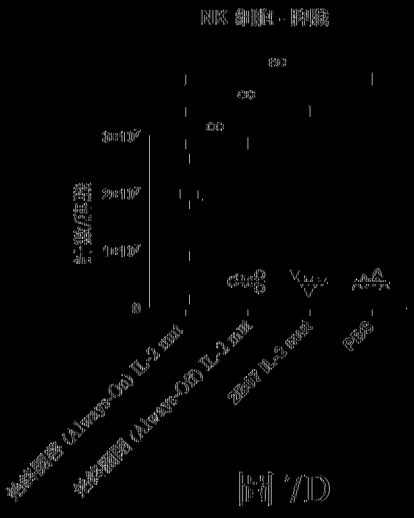


圖 7D

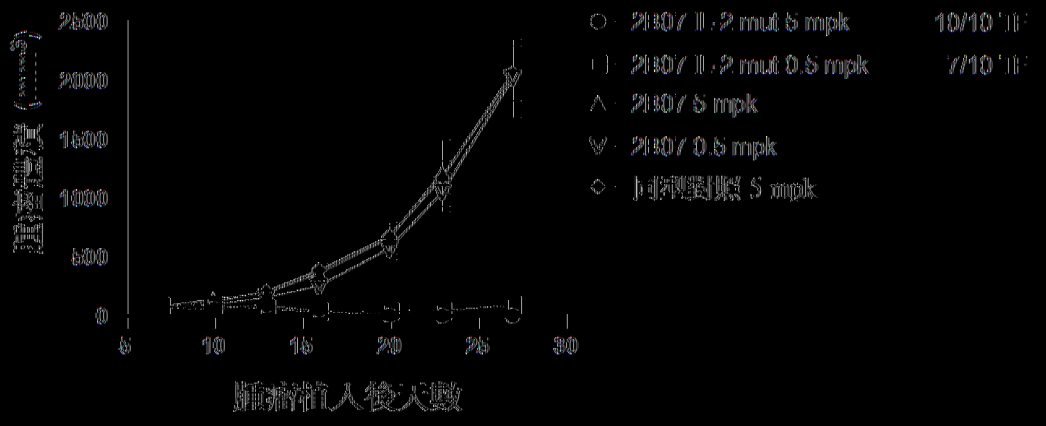

腫瘍体積 (mm3)
25000
20000
15000
10000
5000
0
5
10
15
20
25
30
腫瘍植え込み後日数
○ 2B07 II-2 mut 5 mpk 10/10 匹
□ 2B07 II-2 mut 0.5 mpk 7/10 匹
△ 2B07 5 mpk
▽ 2B07 0.5 mpk
◇ 対照製剤 5 mpk

図 8

圖 6

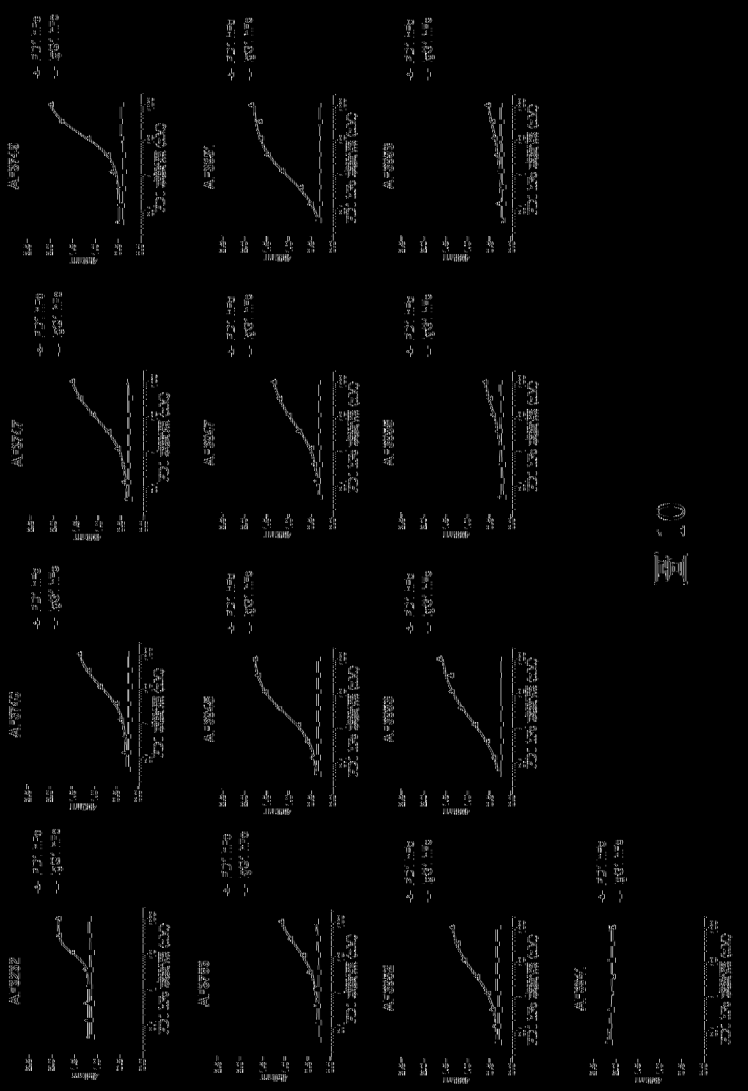


圖 3

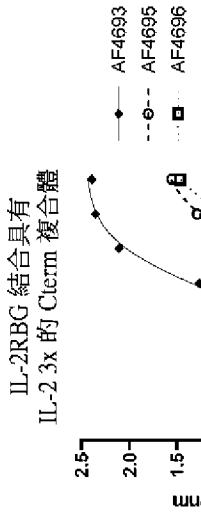


圖 11B

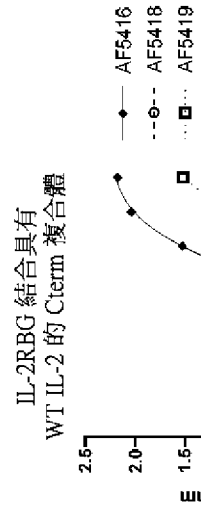


圖 11A

圖 11

圖 2A

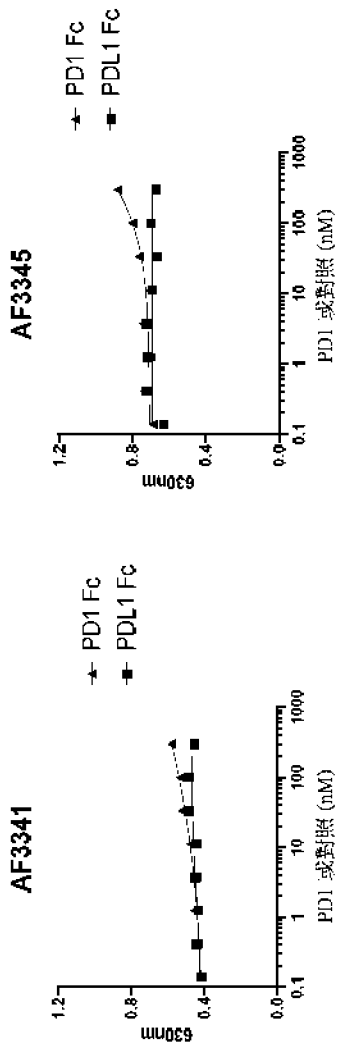

AF3345
PD1 Fc
PDL1 Fc
630nm
1.2
0.8
0.4
0.0
0.1
1
10
100
1000
PD1 或對照 (nM)
AF3341
PD1 Fc
PDL1 Fc
630nm
1.2
0.8
0.4
0.0
0.1
1
10
100
1000
PD1 或對照 (nM)

圖 12B

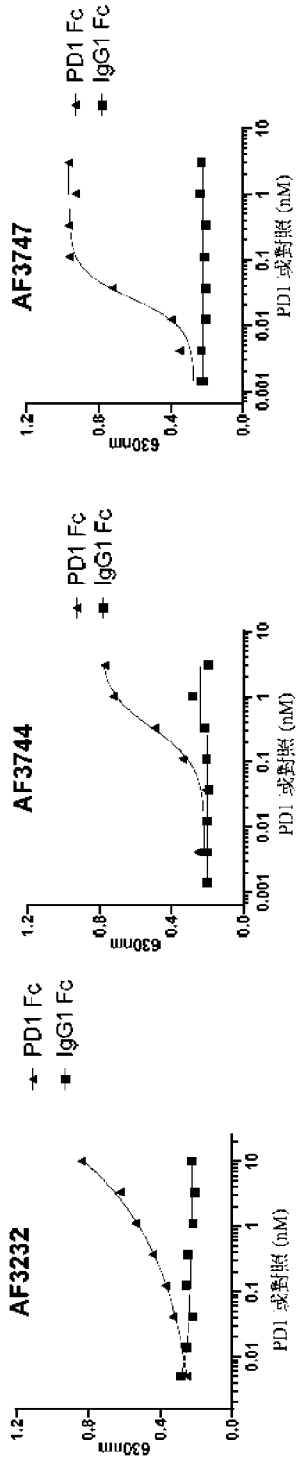

AF3232
AF3744
AF3747
PD1 Fc
IgG1 Fc
630nm
PD1 或對照 (nM)
0.0
0.4
0.8
1.2
0.001
0.01
0.1
1
10

圖 13A

AP波形
AP振幅(mV)
AP振幅(mV)
AP波形
AP波形
AP振幅(mV)
AP振幅(mV)
AP波形
AP波形
AP振幅(mV)
AP振幅(mV)
AP波形
AP波形
AP振幅(mV)
AP振幅(mV)
AP波形

圖 13B

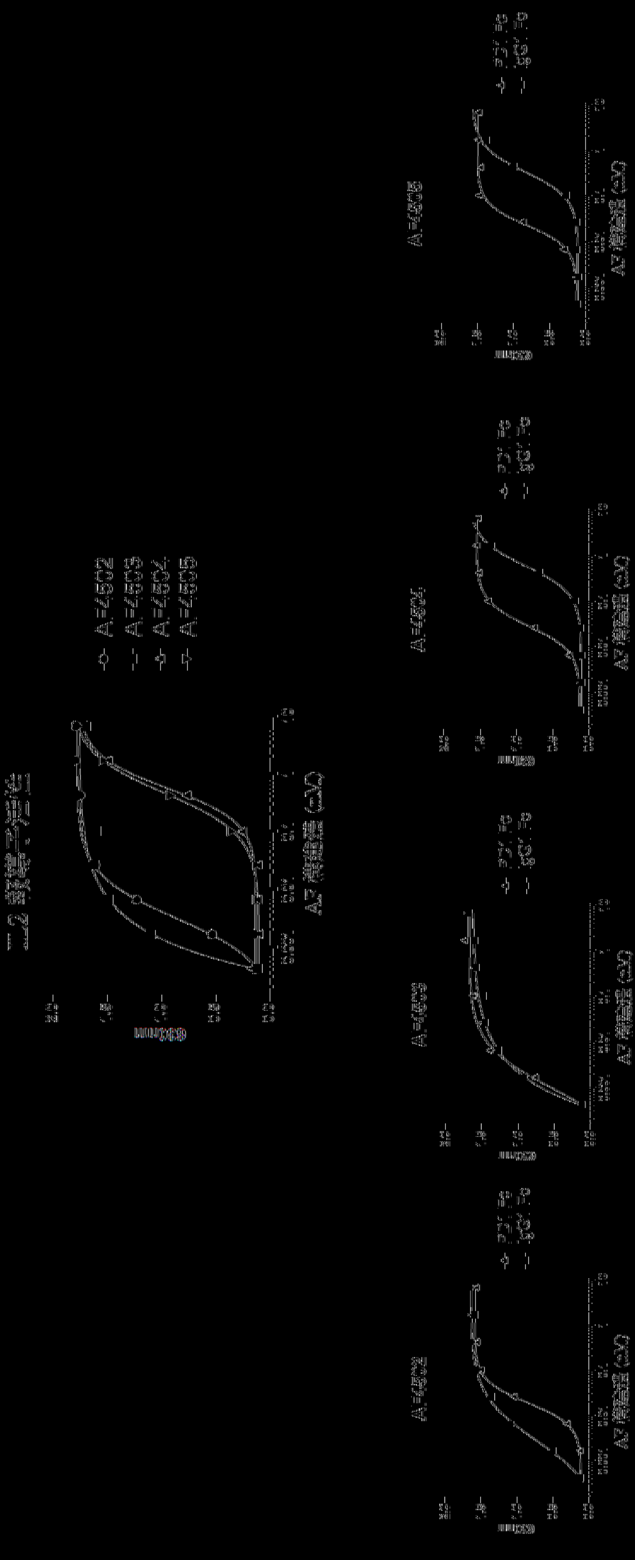


圖 4A

AT3G23
AT3G16
AT3G64
AT3G27
AT 基因編號 (TAIR)
mRNA
D1
D2
D3
D4
D5
D6
D7
D8
D9
D10
D11
D12
D13
D14
D15
D16

圖 1-4B

A-WFT
AP 振幅 (dB)
時間 (ms)
A-WFT
AP 振幅 (dB)
時間 (ms)
A-WFT
AP 振幅 (dB)
時間 (ms)
A-WFT
AP 振幅 (dB)
時間 (ms)
A-WFT
AP 振幅 (dB)
時間 (ms)

圖 15

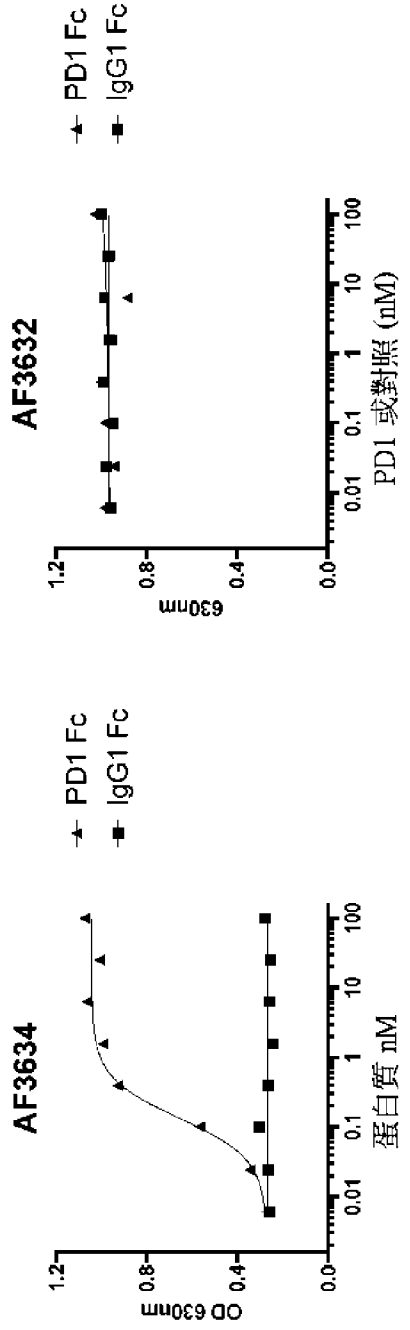

AF3634
PD1 Fc
IgG1 Fc
OD 630nm
1.2
0.8
0.4
0.0
0.01
0.1
1
10
100
蛋白質 nM
AF3632
PD1 Fc
IgG1 Fc
630nm
1.2
0.8
0.4
0.0
0.01
0.1
1
10
100
PD1 或對照 (nM)

圖 16

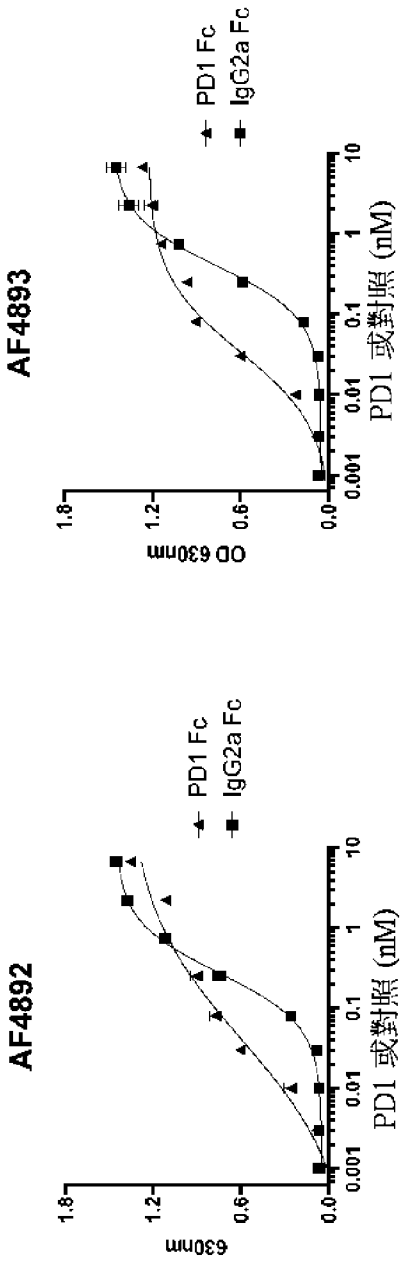

AF4892
AF4893
PD1 Fc
IgG2a Fc
630nm
OD 630nm
PD1 或對照 (nM)
0.0
0.6
1.2
1.8
0.001
0.01
0.1
1
10

圖 17

A2488
A2487
A2486
A2485
A2484
A2483
A2482
A2481
A2480
A2479
A2478
A2477
A2476
A2475
A2474
A2473
A2472
A2471
A2470
A2469
A2468
A2467
A2466
A2465
A2464
A2463
A2462
A2461
A2460
A2459
A2458
A2457
A2456
A2455
A2454
A2453
A2452
A2451
A2450
A2449
A2448
A2447
A2446
A2445
A2444
A2443
A2442
A2441
A2440
A2439
A2438
A2437
A2436
A2435
A2434
A2433
A2432
A2431
A2430
A2429
A2428
A2427
A2426
A2425
A2424
A2423
A2422
A2421
A2420
A2419
A2418
A2417
A2416
A2415
A2414
A2413
A2412
A2411
A2410
A2409
A2408
A2407
A2406
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圖 1GB

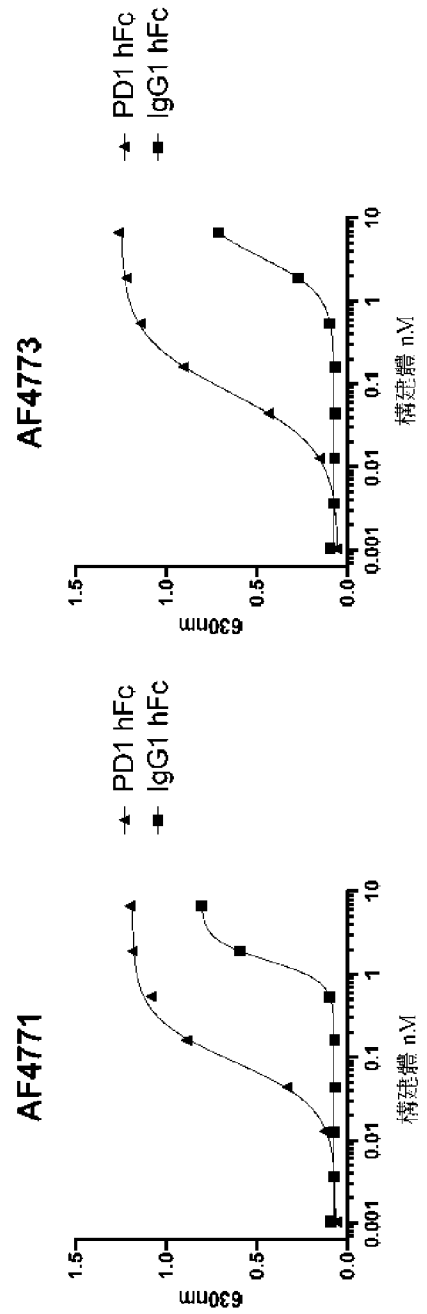

AF4773
PD1 hFc
IgG1 hFc
630nm
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AF4771
PD1 hFc
IgG1 hFc
630nm
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構建體 nM

圖 19C

圖 20

A-3824.CX510
A-3818.CX510
A-3814.CX510
A-3824.CX51A
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A-3814.CX51A

圖 2A

CO2 T 關閉之 % 初始 I_ISC3
CV45-A
-V
CV45-NO
-V
A-4505-EE2-2
A-4504-2307-2
A-4505-7A04-2
A-4505-EE2-2
A-4504-2307-2
A-4505-7A04-2
無線感測裝置
無 P.C. 預置
無線感測裝置
無 P.C. 預置

第 2 圖

相對 CO+ 脫附之 dQ/dT
溫度 (°C)
A-Co/Al2O3-T-2
A-Co/Al2O3-T-1
A-Co/Al2O3-M-2
A-Co/Al2O3-M-1
A-Al2O3-T-2
相對 CO+ 脫附之 dQ/dT
溫度 (°C)
A-Co/Al2O3-T-2
A-Co/Al2O3-T-1
A-Co/Al2O3-M-2
A-Co/Al2O3-M-1
A-Al2O3-T-2

圖 2A

相對 CO4T 細胞之 % CCR5
偏壓因子 (CV)
A-002725 IIE=2
A-004886 237-2
A-004884 IIE=2-2
A-004886 230T-2
A-004886 7AW-2

相對 CO4T 細胞之 % CCR5
偏壓因子 (CV)
A-002725 IIE=2
A-004886 237-2
A-004884 IIE=2-2
A-004886 230T-2
A-004886 7AW-2

圖 22B

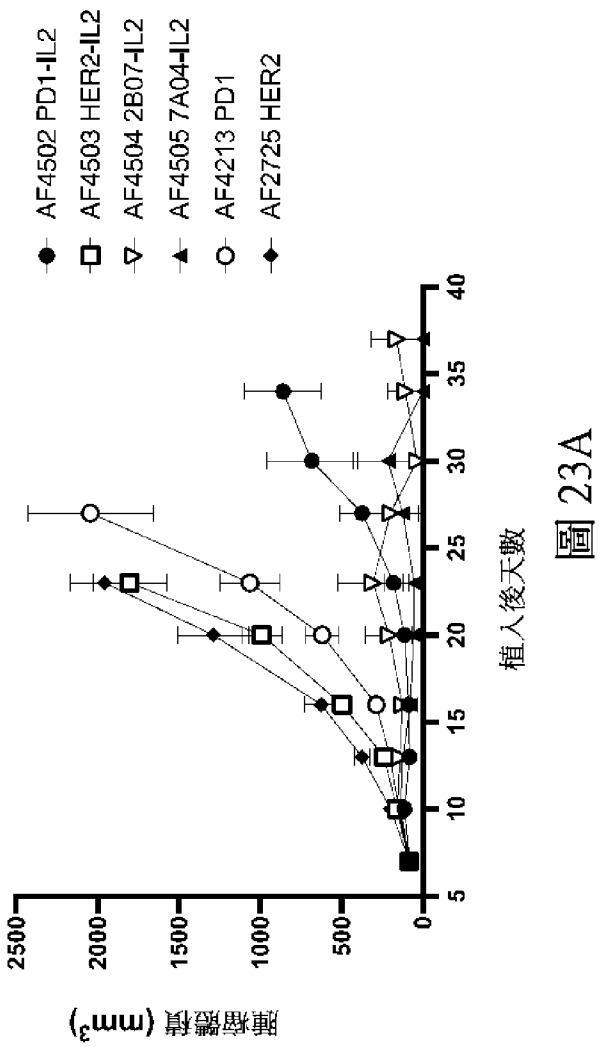

AF4502 PD1-IL2
AF4503 HER2-IL2
AF4504 2B07-IL2
AF4505 7A04-IL2
AF4213 PD1
AF2725 HER2
腫瘤體積 (mm³)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
植入後天數

圖 23A

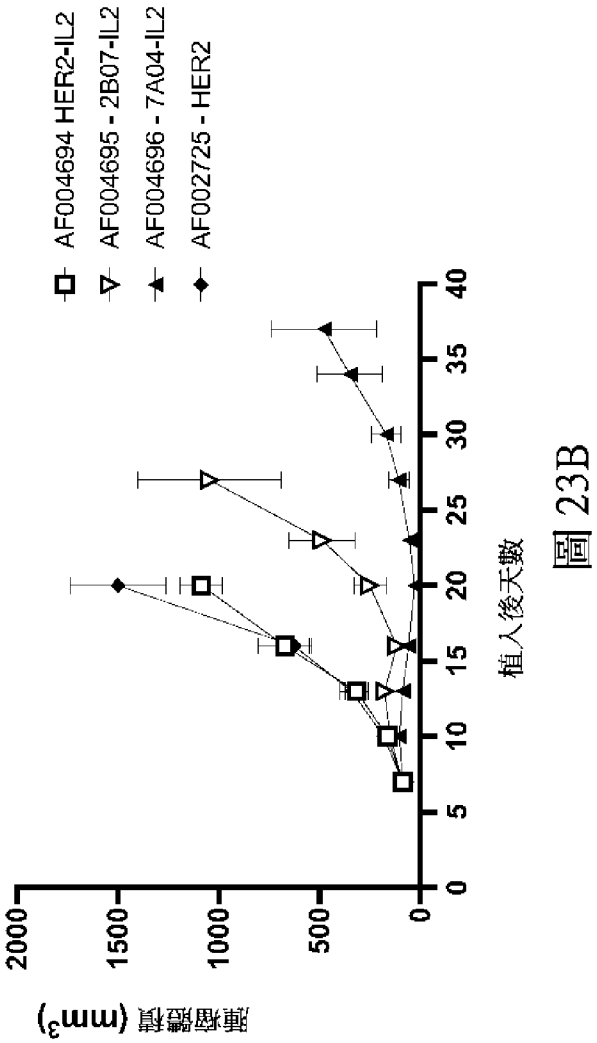

AF004694 HER2-IL2
AF004695 - 2B07-IL2
AF004696 - 7A04-IL2
AF002725 - HER2
腫瘤體積 (mm3)
2000
1500
1000
500
0
0
5
10
15
20
25
30
35
40
植入後天數

圖 23B