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(56)參考文獻：

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(54)名稱

一種標靶ＣＤ４０的抗原結合蛋白及其製備和應用

(57)摘要

本發明揭示了一種標靶 CD40 的抗原結合蛋白及其製備和應用。所述標靶 CD40 的抗原結合蛋白具有與 CD40 的高親和力和對訊息途徑的促效活性強的特性，尤其是交聯後促效活性增強，使得本發明所述的標靶 CD40 的抗原結合蛋白具有更大的治療範圍，有望為多種腫瘤的治療帶來新的機遇。

指定代表圖：

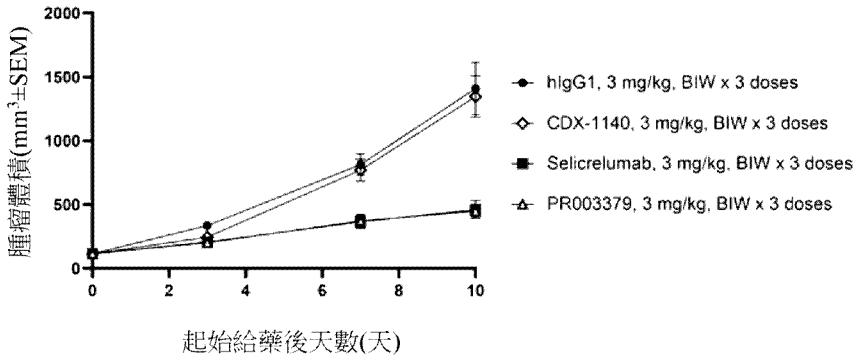
腫瘤體積(mm³±SEM)
2000
1500
1000
500
0
0
2
4
6
8
10
起始給藥後天數(天)
hIgG1, 3 mg/kg, BIW x 3 doses
CDX-1140, 3 mg/kg, BIW x 3 doses
Selicrelumab, 3 mg/kg, BIW x 3 doses
PR003379, 3 mg/kg, BIW x 3 doses

圖 8A

公告本

I856595

【發明摘要】

【中文發明名稱】　一種標靶CD40的抗原結合蛋白及其製備和應用

【中文】

本發明揭示了一種標靶CD40的抗原結合蛋白及其製備和應用。所述標靶CD40的抗原結合蛋白具有與CD40的高親和力和對訊息途徑的促效活性強的特性，尤其是交聯後促效活性增強，使得本發明所述的標靶CD40的抗原結合蛋白具有更大的治療範圍，有望為多種腫瘤的治療帶來新的機遇。

【指定代表圖】　圖8A

【代表圖之符號簡單說明】

無

【特徵化學式】

無

【發明說明書】

【中文發明名稱】　一種標靶CD40的抗原結合蛋白及其製備和應用

【技術領域】

【0001】　本申請主張申請日為2022/4/2的中國專利申請202210351188 9的優先權。本申請引用上述中國專利申請的全文。

【0002】　本發明涉及生物製藥領域，尤其涉及一種標靶CD40的抗原結合蛋白及其製備和應用。

【先前技術】

【0003】　CD40是一種醣基化的I型跨膜蛋白，屬腫瘤壞死因子受體超家族(TNFRSF)成員，又稱為腫瘤壞死因子受體超家族成員5(TNFRSF5)。CD40表現在一系列抗原呈現細胞(APC)表面，包括單核細胞、樹突狀細胞(DC)、B細胞和巨噬細胞。其配體CD40L，主要表現在淋巴細胞表面，包括T細胞、B細胞、自然殺手細胞(NK)，通常以三聚體以及多聚體形式存在。CD40和CD40L是一對共刺激分子，CD40下游訊息途徑的活化，需要三聚體以及多聚體形式的CD40L對CD40形成交聯。它們在細胞表面相互作用，引起CD40重新分佈到膜脂筏，並發生構象變化，CD40透過胞內端結構域在細胞質中募集TNFR相關因子(TRAF)促進細胞內訊息傳導，從而活化不同的訊息途徑，例如經典和非經典核因子κB途徑、p38絲裂原活化

蛋白激酶、磷脂醯肌醇-3激酶(PI3K)和磷脂酶Cγ途徑等，並透過這些訊息途徑標靶的基因，進一步調控細胞凋亡、細胞週期進程、細胞激素生產以及細胞表面免疫調節器的表現。由此，活化CD40可以增加抗原呈現、促進細胞激素分泌、活化淋巴細胞，同時刺激活化人先天性免疫系統和獲得性免疫系統，產生協同效應，抵抗癌症的發生和發展。

【0004】 CD40在腫瘤細胞中也有廣泛表現，其在幾乎所有的B細胞惡性腫瘤以及廣泛的固態腫瘤中表現，包括黑色素瘤、肺癌、乳腺癌、結腸癌、前列腺癌、胰腺癌、腎癌、卵巢癌和頭頸部癌等。表現在腫瘤細胞表面的CD40能媒介的腫瘤細胞死亡。在沒有免疫輔助細胞的情況下，透過CD40L交聯表現在多種腫瘤細胞表面的CD40將媒介直接的細胞毒作用。在體外，透過CD40L交聯CD40被證明能誘導腫瘤細胞凋亡，抑制固態腫瘤細胞和B惡性腫瘤細胞的生長。在體內，活化CD40也媒介腫瘤抑制作用。證據表明，在免疫缺陷型小鼠中，透過CD40L干預腫瘤細胞表面的CD40，即使沒有淋巴細胞活化，也會抑制乳腺癌細胞移植瘤或者B淋巴細胞移植瘤的生長。

【0005】 因此，CD40媒介的腫瘤細胞死亡的機制可以是雙重的，即刺激免疫系統對腫瘤細胞的毒殺和直接的腫瘤細胞毒作用，可以協同抗腫瘤。促效型的抗CD40抗體，類似CD40L，可以交聯和

活化免疫細胞及腫瘤細胞表面的CD40，起到顯著的抗腫瘤效果。這種抗腫瘤效果已經在臨床前動物模型和臨床腫瘤患者的試驗中得到證明，並且可以與化療藥物聯用，比如吉西他濱和紫杉醇，也可以與免疫調節類藥物聯用，比如PD-1抗體和CTLA-4抗體，產生協同的抗腫瘤效果。

【0006】 目前，處於臨床試驗階段的CD40抗體藥物已有20餘項，但最早產品僅處於臨床二期，尚未有任何上市產品。因此，開發其它CD40抗體將為多種腫瘤和免疫系統相關疾病的治療提供可能，具有很高的市場價值。

【0007】 在抗腫瘤方面，CD40抗體在臨床上面臨的最主要問題包括，偏低的客觀緩解率、顯著的毒副作用和較低的耐受劑量等。導致這些結果的可能原因是促效劑活性偏弱，比如Celldex公司的產品CDX-1140。在其一期臨床試驗中，單藥治療的42位患者中，沒有出現完全或者部分緩解；在聯合rhFLT3L的治療中，20位患者中，也僅1例患者出現部分緩解。該產品體外對DC細胞的活化較弱，且在交聯的情況下，促效劑活性得不到加強。羅氏公司的CD40抗體Selicrelumab，臨床試驗中，用藥劑量超過0.2 mg/kg的情況下，即在部分受試患者體內引起顯著的細胞激素釋放症候群和肝臟毒性等毒副作用；Apexigen公司的CD40抗體APX005M，臨床試驗中，用藥劑量超過0.3 mg/kg的情況下，即在部分受試患者體內引起顯

著的嗜中性顆粒細胞減少症，以及進一步的敗血症和敗血性休克。另外，人鼠嵌合序列的CD40單抗ChiLob7/4，由於在一期臨床實驗中遭遇人抗嵌合抗體效應(Human Anti-Chimeric Antibody，HACA)而失敗。綜上所言，目前臨床上的CD40抗體面臨著有效性和安全性之間治療範圍過小的問題和挑戰。

【發明內容】

【0008】 針對現有技術中CD40抗體存在的有效性和安全性之間治療範圍小的技術缺陷，本發明提供了一種標靶CD40的抗原結合蛋白及其製備和應用。所述標靶CD40的抗原結合蛋白具有與CD40的高親和力和對訊息途徑的促效活性強的特性，尤其是交聯後促效活性增強，使得本發明所述的標靶CD40的抗原結合蛋白具有更大的治療範圍，安全性好，有望為多種腫瘤的治療帶來新的機遇。

【0009】 為解決上述技術問題，本發明提供的一個技術方案為：一種標靶CD40的抗原結合蛋白，所述抗原結合蛋白包含輕鏈可變區和重鏈可變區，所述輕鏈可變區(VL)包含LCDR1、LCDR2和LCDR3，所述重鏈可變區(VH)包含HCDR1、HCDR2和HCDR3；其中：

【0010】 所述LCDR1包括如SEQ ID NO: 33所示的胺基酸序列或在SEQ ID NO: 33上具有3、2或1個胺基酸突變的變異體1，所述LCDR2包括如SEQ ID NO: 41所示的胺基酸序列或在SEQ ID

NO: 41上具有3、2或1個胺基酸突變的變異體2，所述LCDR3包括如SEQ ID NO: 49所示的胺基酸序列或在SEQ ID NO: 49上具有3、2或1個胺基酸突變的變異體3；所述HCDR1包括如SEQ ID NO: 7所示的胺基酸序列或在SEQ ID NO: 7上具有3、2或1個胺基酸突變的變異體4，所述HCDR2包括如SEQ ID NO: 15所示的胺基酸序列或在SEQ ID NO: 15上具有3、2或1個胺基酸突變的變異體5，所述HCDR3包括如SEQ ID NO: 23所示的胺基酸序列或在SEQ ID NO: 23上具有3、2或1個胺基酸突變的變異體6。

【0011】 較佳地，所述變異體3包括在SEQ ID NO: 49所示胺基酸序列上具有PTM位址突變的胺基酸序列，優選包括在SEQ ID NO: 49所示胺基酸序列的第4位和/或第5位上發生胺基酸突變的胺基酸序列，所述胺基酸突變優選為胺基酸替代，更優選為胺基酸的守恆替代。

【0012】 在本發明一些技術方案中，所述變異體3為如SEQ ID NO: 50-73任一項所示的胺基酸序列。

【0013】 在本發明一些技術方案中，所述LCDR1包括如SEQ ID NO: 33所示的胺基酸序列，所述LCDR2包括如SEQ ID NO: 41所示的胺基酸序列，所述LCDR3包括如SEQ ID NO: 49-73任一項所示的胺基酸序列；所述HCDR1包括如SEQ ID NO: 7所示的胺基酸序列，所述HCDR2包括如SEQ ID NO: 15所示的胺基酸序列，

所述HCDR3包括如SEQ ID NO: 23所示的胺基酸序列，具體CDR組合見下表1-1。

表1-1：具體CDR組合

	SEQ ID NO:					
抗體編號	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
PR003379	33	41	49	7	15	23
PR006239	33	41	49	7	15	23
PR006492	33	41	50	7	15	23
PR006493	33	41	51	7	15	23
PR006494	33	41	52	7	15	23
PR006495	33	41	53	7	15	23
PR006496	33	41	54	7	15	23
PR006497	33	41	55	7	15	23
PR006498	33	41	56	7	15	23
PR006499	33	41	57	7	15	23
PR006500	33	41	58	7	15	23
PR006501	33	41	59	7	15	23
PR006502	33	41	60	7	15	23
PR006503	33	41	61	7	15	23
PR006504	33	41	62	7	15	23
PR006505	33	41	63	7	15	23
PR006506	33	41	64	7	15	23
PR006507	33	41	65	7	15	23
PR006509	33	41	66	7	15	23
PR006510	33	41	67	7	15	23
PR006511	33	41	68	7	15	23
PR006512	33	41	69	7	15	23
PR006513	33	41	70	7	15	23
PR006514	33	41	71	7	15	23
PR006515	33	41	72	7	15	23
PR006516	33	41	73	7	15	23

【0014】 較佳地，所述輕鏈可變區包括如SEQ ID NO: 85所示的胺基酸序列或與SEQ ID NO: 85有至少85%、90%、92%、94%、95%、96%、97%、98%或99%相同性的胺基酸序列，所述重鏈可變區包括如SEQ ID NO: 81所示的胺基酸序列或與SEQ ID NO: 81有至少85%、90%、92%、94%、95%、96%、97%、98%或99%相同性的胺基酸序列。更佳地，所述輕鏈可變區包括如SEQ ID NO: 85-109任一項所示的胺基酸序列，所述重鏈可變區包括如SEQ ID NO: 81 所示的胺基酸序列，具體輕鏈可變區和重鏈可變區組合如下表1-2所示。

表1-2：具體輕鏈可變區和重鏈可變區組合

	SEQ ID NO:	
抗體編號	輕鏈可變區	重鏈可變區
PR003379	85	81
PR006239	85	81
PR006492	86	81
PR006493	87	81
PR006494	88	81
PR006495	89	81
PR006496	90	81
PR006497	91	81
PR006498	92	81
PR006499	93	81
PR006500	94	81
PR006501	95	81
PR006502	96	81
PR006503	97	81
PR006504	98	81
PR006505	99	81

PR006506	100	81
PR006507	101	81
PR006509	102	81
PR006510	103	81
PR006511	104	81
PR006512	105	81
PR006513	106	81
PR006514	107	81
PR006515	108	81
PR006516	109	81

【0015】 較佳地，所述標靶CD40的抗原結合蛋白滿足以下三項中至少一項：

(1)所述標靶CD40的抗原結合蛋白為全長抗體、Fab、Fab’、$F(ab')_2$或Fv，所述Fv優選為scFv；

(2)所述標靶CD40的抗原結合蛋白為單特異性抗體、雙特異性抗體或多特異性抗體；

(3)所述標靶CD40的抗原結合蛋白為單株抗體或多株抗體。

【0016】 較佳地，所述標靶CD40的抗原結合蛋白為全長抗體，所述全長抗體包含輕鏈和重鏈；所述輕鏈包括輕鏈恆定區(CL)，所述輕鏈恆定區優選為人源抗體輕鏈恆定區；所述重鏈包括重鏈恆定區(CH)，所述重鏈恆定區優選為人源抗體重鏈恆定區，更優選為hIgG1、hIgG2、hIgG3或hIgG4亞型的重鏈恆定區，進一步優選為hIgG1亞型的重鏈恆定區。

【0017】 在本發明一些技術方案中，所述標靶CD40的抗原結合蛋白為全長抗體，所述全長抗體包含輕鏈和重鏈，所述重鏈包括如SEQ ID NO: 114或115所示的胺基酸序列，所述輕鏈包括如SEQ ID NO: 119-143任一項所示的胺基酸序列。較佳地，所述重鏈包括如SEQ ID NO: 114所示的胺基酸序列，所述輕鏈包括如SEQ ID NO: 119所示的胺基酸序列；或，所述重鏈包括如SEQ ID NO: 115所示的胺基酸序列，所述輕鏈包括如SEQ ID NO: 119-143任一項所示的胺基酸序列，具體輕鏈和重鏈組合見下表1-3。

表1-3：具體輕鏈和重鏈組合

	SEQ ID NO:	
抗體編號	輕鏈	重鏈
PR003379	119	114
PR006239	119	115
PR006492	120	115
PR006493	121	115
PR006494	122	115
PR006495	123	115
PR006496	124	115
PR006497	125	115
PR006498	126	115
PR006499	127	115
PR006500	128	115
PR006501	129	115
PR006502	130	115
PR006503	131	115
PR006504	132	115
PR006505	133	115
PR006506	134	115
PR006507	135	115

PR006509	136	115
PR006510	137	115
PR006511	138	115
PR006512	139	115
PR006513	140	115
PR006514	141	115
PR006515	142	115
PR006516	143	115

【0018】 本發明中，所述變異體1、變異體2、變異體3、變異體4、變異體5和變異體6中的數字僅用以區分不同變異體，並不表示實際含義。

【0019】 本發明中，所述PTM位址為蛋白質或多肽胺基酸鏈在細胞中轉譯合成後有時會引入化學修飾的位址，稱為轉譯後修飾(PTM)位址。

【0020】 本發明中CDR的胺基酸序列按照Chothia定義規則確定。

【0021】 為解決上述技術問題，本發明提供的另一個技術方案為：一種嵌合抗原受體(CAR)，其包含如本發明所述的標靶CD40的抗原結合蛋白。

【0022】 為解決上述技術問題，本發明提供的另一個技術方案為：一種分離的核酸，其編碼如本發明所述的標靶CD40的抗原結合蛋白或如本發明所述的嵌合抗原受體。

【0023】 為解決上述技術問題，本發明提供的另一個技術方案為：一種重組表現載體，其包含如本發明所述的分離的核酸。較佳地，所述重組表現載體包含真核細胞表現載體和/或原核細胞表現載體。

【0024】 為解決上述技術問題，本發明提供的另一個技術方案為：一種轉形株，其包含如本發明所述的分離的核酸或如本發明所述的重組表現載體。較佳地，所述轉形株的宿主細胞為原核細胞和/或真核細胞，所述原核細胞優選為*E. coli* 細胞如TG1、BL21，所述真核細胞優選HEK293細胞或CHO細胞。

【0025】 為解決上述技術問題，本發明提供的另一個技術方案為：一種如本發明所述的標靶CD40的抗原結合蛋白的製備方法，其包括以下步驟：培養如本發明所述的轉形株，從培養物中獲得所述標靶CD40的抗原結合蛋白。

【0026】 為解決上述技術問題，本發明提供的另一個技術方案為：一種抗體藥物偶聯物(Antibody-drug conjugate, ADC)，其包含如本發明所述的標靶CD40的抗原結合蛋白和細胞毒性劑或標籤。較佳地，所述細胞毒性劑為MMAF或MMAE，所述標籤為螢光劑。

【0027】 為解決上述技術問題，本發明提供的另一個技術方案為：一種基因修飾的細胞，其表現如本發明所述的嵌合抗原受體。

較佳地，所述基因修飾的細胞為真核細胞，優選分離的人細胞，更優選免疫細胞如T細胞，或NK細胞。

【0028】 為解決上述技術問題，本發明提供的另一個技術方案為：一種藥物組成物，其包含如本發明所述的標靶CD40的抗原結合蛋白、如本發明所述的分離的核酸、如本發明所述的重組表現載體、如本發明所述的基因修飾的細胞和/或如本發明所述的抗體藥物偶聯物，以及藥學上可接受的載劑和/或藥學上可接受的佐劑。較佳地，所述藥物組成物還包括其他抗腫瘤抗體作為活性成分。

【0029】 為解決上述技術問題，本發明提供的另一個技術方案為：一種檢測試劑，其包含如本發明所述的標靶CD40的抗原結合蛋白和/或如本發明所述的抗體藥物偶聯物。較佳地，所述檢測試劑為液體劑型、氣體劑型、固體劑型和半固體劑型。更佳地，所述檢測試劑還包括二抗、CD40或其衍生物，所述二抗例如抗人IgG的抗體偶聯辣根過氧化物酶和抗人IgG的抗體偶聯生物素蛋白。

【0030】 為解決上述技術問題，本發明提供的另一個技術方案為：一種套裝藥盒，其包含藥盒A，所述藥盒A含有如本發明所述的標靶CD40的抗原結合蛋白、如本發明所述的藥物組成物、如本發明所述的檢測試劑、如本發明所述的基因修飾的細胞和如本發明所述的抗體藥物偶聯物中的一種或多種。

【0031】 較佳地，所述套裝藥盒還包括藥盒B，所述藥盒B含有其他抗腫瘤抗體或者包含所述其他抗腫瘤抗體的藥物組成物，和/或由激素製劑、標靶小分子製劑、蛋白酶體抑制劑、成像劑、診斷劑、化療劑、溶瘤藥物、細胞毒性劑、細胞激素、共刺激分子的活化劑、抑制性分子的抑制劑以及疫苗組成的群組中的一種或多種。

【0032】 為解決上述技術問題，本發明提供的另一個技術方案為：如本發明所述的標靶CD40的抗原結合蛋白、如本發明所述的藥物組成物、如本發明所述的檢測試劑、如本發明所述的套裝藥盒、如本發明所述的基因修飾的細胞和如本發明所述的抗體藥物偶聯物中的一種或多種在製備診斷、預防和/或治療腫瘤等疾病的藥物中的用途。較佳地，所述腫瘤包括固態腫瘤和血液瘤。更佳地，所述腫瘤包括B系NHL、慢性淋巴細胞性白血病(CLL)、多毛細胞白血病(HCL)、霍奇金病、多發性骨髓瘤、膀胱癌、腎癌、卵巢癌、子宮頸癌、乳腺癌、肺癌、鼻咽癌、惡性黑色素瘤、胰腺癌和結腸癌。

【0033】 為解決上述技術問題，本發明提供的另一個技術方案為：一種檢測樣品中CD40的方法，其包括使用如本發明所述的標靶CD40的抗原結合蛋白、如本發明所述的檢測試劑和如本發明所述的抗體藥物偶聯物中的一種或多種與所述樣品接觸的步驟。所述樣品例如血液樣本(例如全血樣本和血清樣本)和包含CD40的試劑。較佳

地，所述方法為非診斷和/或治療目的，例如科學研究中檢測CD40標準品的濃度、其他試劑是否被CD40污染等。

【0034】 為解決上述技術問題，本發明提供的另一個技術方案為：一種診斷、治療和/或預防腫瘤的方法，所述方法包括向有需要的患者施用治療有效量的如本發明所述的標靶CD40的抗原結合蛋白、如本發明所述的分離的核酸、如本發明所述的重組表現載體、如本發明所述的藥物組成物、如本發明所述的檢測試劑、如本發明所述的基因修飾的細胞和如本發明所述的抗體藥物偶聯物中的一種或多種，或者使用如本發明所述的套裝藥盒診斷或治療有需要的患者。較佳地，所述腫瘤包括固態腫瘤和血液瘤。更佳地，所述腫瘤包括B系NHL、慢性淋巴細胞性白血病(CLL)、多毛細胞白血病(HCL)、霍奇金病、多發性骨髓瘤、膀胱癌、腎癌、卵巢癌、子宮頸癌、乳腺癌、肺癌、鼻咽癌、惡性黑色素瘤、胰腺癌和結腸癌。

【0035】 為解決上述技術問題，本發明提供的另一個技術方案為：如本發明所述的標靶CD40的抗原結合蛋白、如本發明所述的分離的核酸、如本發明所述的重組表現載體、如本發明所述的藥物組成物、如本發明所述的檢測試劑、如本發明所述的套裝藥盒、如本發明所述的基因修飾的細胞和/或如本發明所述的抗體藥物偶聯物的一種或多種在製備診斷、預防或治療腫瘤的藥物中的用途。較佳地，所述腫瘤包括固態腫瘤和血液瘤。更佳地，所述腫瘤包括B系

NHL、慢性淋巴細胞性白血病(CLL)、多毛細胞白血病(HCL)、霍奇金病、多發性骨髓瘤、膀胱癌、腎癌、卵巢癌、子宮頸癌、乳腺癌、肺癌、鼻咽癌、惡性黑色素瘤、胰腺癌和結腸癌。

【0036】 本發明中，“具有3、2或1個胺基酸突變”是指包括在原胺基酸序列的基礎上發生胺基酸的插入、缺失或替換。示例性的解釋是對CDR的突變可以包含3個、2個或1個胺基酸的突變，這些CDR之間可以任選地選擇相同或不同數目的胺基酸殘基進行突變，例如可以是對CDR1進行1個胺基酸的突變，對CDR2和CDR3不進行胺基酸突變。

【0037】 本發明中，“PTM位址突變”是指相較於原胺基酸序列而言，變異體的序列存在PTM位址上胺基酸的突變。根據抗體序列和PTM序列模式的不同，有不同的突變設計方法。一種方法是將“熱點”胺基酸(如NS模式中的N或S)替換成物理化學性質相似的胺基酸(如把N突變為Q)。如果PTM序列模式來源於體細胞高頻突變，而並不存在於胚系基因序列中，那麼另一種方法可以是把該序列模式替換成對應的胚系基因序列。

【0038】 本發明中，所述的VH、VL或所述的全長抗體均可包含在所限定的序列的基礎上進行突變的情形。所述突變為所限定的胺基酸序列上發生了一個或多個胺基酸殘基的缺失、取代或添加，且所述突變的胺基酸序列與所限定的胺基酸序列具有至少85%序列相

同性，並保持或改善了包含該突變的胺基酸序列的抗原結合蛋白的結合活性；所述至少85%序列相同性優選為至少90%序列相同性；更優選為至少95%序列相同性；最優選為至少99%序列相同性。

【0039】 本發明中，“包括”、“包含”和“為”在某些具體的實施例中表示一樣的意思。

【0040】 在符合本領域常識的基礎上，上述各優選條件，可任意組合，即得本發明各較佳實例。

【0041】 本發明所用試劑和原料均市售可得。

【0042】 本發明的積極進步效果在於：

【0043】 所述標靶CD40的抗原結合蛋白具有與CD40的高親和力和對訊息途徑的促效活性強的特性，尤其是交聯後促效活性增強，使得本發明所述的標靶CD40的抗原結合蛋白具有更大的治療範圍，為在臨床試驗中，在安全耐受的劑量條件下，顯著提高患者響應率提供良好基礎。

【圖式簡單說明】

【0044】 圖1A、圖1B、圖1C和圖1D分別展示部分CD40抗體結合高表現人CD40的CHO-K1細胞的位準。

【0045】 圖2A、圖2B、圖2C、圖2D和圖2E分別展示部分CD40抗體結合高表現人CD40的Raji細胞的位準。

【0046】 圖3A、圖3B、圖3C和圖3D分別展示部分CD40抗體結合高表現食蟹猴CD40的CHO-K1細胞的位準。

【0047】 圖4A、圖4B、圖4C和圖4D分別展示待測CD40抗體PR003379和三個對照抗體在有或者沒有CHO-K1/hCD32B細胞媒介交聯的條件下對HEK293-hCD40-NFkB螢光報導基因細胞的活化作用的位準。

【0048】 圖5A為CD40抗體PR003379的變異體分子在有CHO-K1/hCD32B細胞媒介交聯的條件下對HEK293-hCD40-NFkB細胞的活化的螢光強度增強倍數，圖5 B為CD40抗體PR003379的變異體分子在沒有CHO-K1/hCD32B細胞媒介交聯的條件下對HEK293-hCD40-NFkB細胞的活化的螢光強度增強倍數。

【0049】 圖6A、圖6B、圖6C和圖6D分別展示待測CD40抗體PR003379和三個對照抗體在有或者沒有CHO-K1/hCD32B細胞媒介交聯的條件下對人DC細胞的活化作用(IL12p40釋放位準)。

【0050】 圖7顯示了CD40抗體抑制CD40和CD40L的結合位準。

【0051】 圖8A為CD40抗體在MC38-hPD-L1/CD40人源化小鼠模型中的抗腫瘤效果的腫瘤體積變化，圖8B為CD40抗體在MC38-hPD-L1/CD40人源化小鼠模型中的抗腫瘤效果的小鼠體重變化。

【實施方式】

具體實施方式

【0052】 以下由特定的具體實施例說明本申請發明的實施方式，熟悉此技術的人士可由本說明書所揭示的內容容易地瞭解本申請發明的其他優點及效果。

【0053】 在本申請中，術語“結合蛋白”或者“抗原結合蛋白”通常是指包含結合抗原的部分的蛋白質，以及任選地允許結合抗原的部分採用促進抗原結合蛋白與抗原結合的構象的支架或骨架部分。可典型地包含抗體輕鏈可變區(VL)、抗體重鏈可變區(VH)或上述兩者。VH和VL區可進一步被區分為稱為互補決定區(CDR)的高度變異區，它們散佈在稱為框架區(FR)的更守恆的區域中。每個VH和VL可由三個CDR和四個FR區構成，它們從氨基端至羧基端可按以下順序排列：FR-1、CDR1、FR-2、CDR2、FR-3、CDR3和FR-4。重鏈和輕鏈的可變區含有與抗原相互作用的結合結構域。VH的三個CDR分別表示為HCDR1、HCDR2和HCDR3，也可表示為VH CDR1、VH CDR2和VH CDR3；VL的三個CDR分別表示為LCDR1、LCDR2和LCDR3，也可表示為VL CDR1、VL CDR2和VL CDR3。抗原結合蛋白的實例包括但不限於抗體、抗原結合片段(Fab，Fab’，$F(ab)_2$，Fv片段，$F(ab')_2$，scFv，di-scFv和/或dAb)、免疫綴合物、多特異性抗體(例如雙特異性抗體)、抗體片段、抗體衍

生物、抗體類似物或融合蛋白等，只要它們顯示出所需的抗原結合活性即可。

【0054】 在本申請中，所述CDR的胺基酸序列均是按照Chothia定義規則所示出的。但是，本領域人員公知，在本領域中可以透過多種方法來定義抗體的CDR，例如基於序列可變性的Kabat定義規則(參見，Kabat等人，免疫學的蛋白質序列，第五版，美國國立衛生研究院，貝塞斯達，馬裡蘭州(1991))和基於結構環區域位置的Chothia定義規則(參見JMol Biol 273:927-48,1997)。在本發明的技術方案中，還可以使用包含了Kabat定義和Chothia定義的Combined定義規則來確定可變結構域序列中的胺基酸殘基。其中Combined定義規則即是將Kabat定義和Chothia定義的範圍相結合，基於此取了一個更大的範圍，詳見下表1-4。本領域技術人員應當理解的是，除非另有規定，否則術語給定抗體或其區(例如可變區)的“CDR”及“互補決定區”應瞭解為涵蓋如透過本發明描述的上述已知方案中的任何一種界定的互補決定區。雖然本發明中請求保護的範圍是基於Chothia定義規則所示出的序列，但是根據其他CDR的定義規則所對應的胺基酸序列也應當落在本發明的保護範圍中。

表1-4：本申請抗體CDR定義方法

	Kabat	Chothia	Combined
LCDR1	L24--L34	L24--L34	L24-L34
LCDR2	L50--L56	L50--L56	L50-L56
LCDR3	L89--L97	L89--L97	L89-L97
HCDR1	H31--H35	H26--H32	H26-H35
HCDR2	H50--H65	H52--H56	H50-H65
HCDR3	H95--H102	H95--H102	H95-H102

【0055】 其中，Laa-Lbb可以指從抗體輕鏈的N端開始，第aa位(Chothia編碼規則)至第bb位(Chothia編碼規則)的胺基酸序列；Haa-Hbb可以指從抗體重鏈的N端開始，第aa位(Chothia編碼規則)至第bb位(Chothia編碼規則)的胺基酸序列。例如，L24-L34可以指從抗體輕鏈N端開始，按照Chothia編碼規則的從第24位至第34位的胺基酸序列；H26-H32可以指從抗體重鏈N端開始，按照Chothia編碼規則的從第26位至第32位的胺基酸序列。本領域技術人員應當知曉的是，在用Chothia編碼CDR時，有些位置會有插入位址的情況(可參見http://bioinf.org.uk/abs/)。

【0056】 在本申請中，術語“單株抗體”通常是指從一群基本上同質的抗體獲得的抗體，即集群中的個別抗體是相同的，除了可能存在的少量的自然突變。單株抗體通常針對單個抗原位址具有高度特異性。而且，與常規多株抗體製劑(通常具有針對不同決定位的不同抗體)不同，各單株抗體是針對抗原上的單個決定位。除了它們的

特異性之外，單株抗體的優點在於它們可以透過融合瘤培養合成，不受其他免疫球蛋白污染。修飾語“單株”表示從基本上同質的抗體群體獲得的抗體的特徵，並且不被解釋為需要透過任何特定方法產生抗體。例如，根據本發明使用的單株抗體可以在融合瘤細胞中製備，或者可以透過重組DNA方法製備。

【0057】 在本申請中，術語“全人源抗體”通常是指將人類編碼抗體的基因全部轉移至基因工程改造的抗體基因缺失動物中，使動物表現的抗體。抗體所有部分(包括抗體的可變區和恆定區)均由人類來源的基因所編碼。全人源抗體可以大大減少異源抗體對人體造成的免疫副反應。本領域獲得全人源抗體的方法可以有噬菌體展示技術、基因轉殖小鼠技術等。

【0058】 在本申請中，術語“特異性結合”、“標靶”通常是指抗體透過其抗原結合域與表位結合，並且該結合需要抗原結合域和表位之間的一些互補性。根據該定義，當抗體相比於其將結合隨機的，不相關的表位而言更容易透過其抗原結合域與表位結合時，抗體被稱為“特異性結合”該抗原。“表位”是指抗原上與抗原結合蛋白(如抗體)結合的特定的原子基團(例如，醣側鏈、磷醯基、磺醯基)或胺基酸。

【0059】 在本申請中，術語“Fab”通常指常規抗體(例如IgG)中與抗原結合的部分，包括抗體的重鏈可變區VH、輕鏈可變區VL和

重鏈恆定區結構域CH1以及輕鏈恆定區CL。在常規抗體中，VH的C端與CH1的N端聯結形成重鏈Fd片段，VL的C端與CL的N端聯結形成輕鏈，CH1的C端又進一步與重鏈的樞紐區和其他恆定區結構域聯結形成重鏈。在一些實施例中，“Fab”也指Fab的變異體結構。例如，在某些實施例中，VH的C端與CL的N端聯結形成一個多肽鏈，VL的C端與CH1的N端聯結形成另一個多肽鏈，形成Fab (cross VH/VL)的結構；在某些實施例中，Fab的CH1不與樞紐區聯結，而是CL的C端與重鏈的樞紐區聯結，形成Fab (cross Fd/LC)的結構。

【0060】 在本申請中，術語“VH”通常指抗體的重鏈可變區VH結構域，即可以是人或者其他動物的常規抗體(H2L2結構)的重鏈可變區VH，也可以是駱駝科等動物的重鏈抗體(HCAb結構)的重鏈可變區VHH，還可以是利用Harbour HCAb基因轉殖小鼠產生的全人源重鏈抗體(HCAb結構)的重鏈可變區VH。

【0061】 在本申請中，術語“CD40”通常是指腫瘤壞死因子受體超家族成員5蛋白、其功能變異體和/或其功能片段，也稱為TNFRSF5。CD40序列是本領域已知的。例如，示例性的人CD40蛋白的胺基酸序列可在UniProt登錄號P25942下找到；示例性的食蟹猴CD40蛋白序列可在Uniprot登錄號G7PG38下找到；示例性的小鼠CD40蛋白序列可在Uniprot登錄號P27512下找到。CD40L是CD40的天然三聚體配體分子。

實施例

【0062】 下面透過實施例的方式進一步說明本發明，但並不因此將本發明限制在所述的實施例範圍之中。實施例不包括對傳統方法的詳細描述，如那些用於建構載體和質體的方法，將編碼蛋白的基因插入到這樣的載體和質體的方法或將質體引入宿主細胞的方法。這樣的方法對於本領域中具有普通技術的人員是眾所周知的，並且在許多出版物中都有所描述。下列實施例中未註明具體條件的實驗方法，按照常規方法和條件，或按照商品說明書選擇。

實施例1 CD40抗體的製備

【0063】 基因轉殖技術的進步使得可以培育出基因工程化小鼠，其攜帶人免疫球蛋白免疫庫並使其內源的鼠的免疫庫缺失。這種基因轉殖小鼠產生的抗體具有全人源的序列，因而無需再進一步做人源化改造，大大提高了治療性抗體開發的效率。Harbour H2L2小鼠(Harbour Antibodies BV)是一種攜帶人免疫球蛋白免疫庫的基因轉殖小鼠，其產生的抗體具有完整的人的抗體可變結構域和大鼠恆定結構域。

【0064】 用可溶的重組人CD40胞外段融合蛋白(Acrobiosystems, #CD0-H5253)對Harbour H2L2小鼠進行多輪免疫。抗原蛋白與免疫佐劑混合成免疫原試劑，然後透過皮下經腹股溝注射或透過腹腔注射。在每一輪免疫中，每隻小鼠接受的總注

射劑量是100 μL。在首輪免疫中，每隻小鼠接受用50 μg抗原蛋白與完全弗氏佐劑(Sigma，#F5881)以體積比1:1混合配製的免疫原試劑的免疫。在隨後的每輪增強免疫中，每隻小鼠接受用25 μg抗原蛋白與Sigma Adjuvant System佐劑(Sigma，#S6322)混合配製的免疫原試劑的免疫。每輪增強免疫的間隔時間至少為兩周，通常不超過五輪增強免疫。免疫時間為第0、14、28、42、56、70天；並且在第49、77天，檢測小鼠血清抗體效價。在進行細胞融合前3天，以每隻小鼠25 μg抗原蛋白的劑量進行最後一次增強免疫。

【0065】 當檢測小鼠血清中CD40特異的抗體效價達到一定的位準後，將小鼠的脾細胞取出並與骨髓瘤細胞株融合得到融合瘤細胞；對融合瘤細胞經過多輪篩選和選殖之後，分離出表現CD40單株抗體分子的融合瘤。分離的融合瘤表現具有完整的人可變結構域和大鼠恆定結構域的重鏈和輕鏈的抗體分子。對上述單株抗體進行進一步的鑒定，根據其對人CD40的結合能力、食蟹猴CD40的結合能力、活化CD40下游訊息途徑的能力等參數，選出若干個融合瘤選殖進行定序。在篩選過程中，使用了如表1-5所列陽性對照抗體(相應序列編號見表4)。利用常規的融合瘤定序手段獲得編碼抗體分子可變結構域的核苷酸序列以及對應的胺基酸序列。在本實施例中，從免疫的Harbour H2L2小鼠得到的CD40單株抗體分子可變結構域

的序列是人源抗體序列。抗體可變結構域的CDR序列可以透過Kabat或者Chothia或者其他CDR定義規則(表1-5)進行分析。

表1-5：CD40陽性對照抗體

抗體編號	抗體名稱
PR001028	Selicrelumab
PR001303	APX005
PR001304	APX005M
PR001306	CDX-1140

【0066】 在得到編碼抗體分子的輕、重鏈可變結構域序列以後，可以採用常規的重組DNA技術，將輕、重鏈可變結構域序列和相應的人的抗體輕、重鏈恆定結構域序列進行融合表現，得到重組抗體分子。在本實施例中，抗體重鏈可變結構域序列(VH)透過基因合成並選殖到編碼人IgG2抗體重鏈恆定結構域序列的哺乳動物細胞表現質體載體中，以編碼產生IgG2抗體的全長重鏈。抗體輕鏈可變結構域序列(VL)透過基因合成並選殖到編碼人抗體Igκ輕鏈恆定結構域序列的哺乳動物細胞表現質體載體中，以編碼產生抗體的全長輕鏈。在本實施例中，得到全人源的抗CD40重組IgG2抗體。

【0067】 PR006239是透過基因合成，將編碼PR003379的重鏈可變區(VH)的核酸連接到編碼含有L234A, L235A, G237A突變的IgG1亞型的抗體重鏈恆定結構域序列的核酸上，並選殖到哺乳動物細胞表現質體中，編碼產生IgG1(L234A, L235A, G237A)全長

重鏈。編碼抗體輕鏈可變結構域序列(VL)的核酸透過基因合成並選殖到編碼人抗體Igκ輕鏈恆定結構域序列的哺乳動物細胞表現質體載體中，以編碼產生抗體的全長輕鏈。將兩個質體共轉到哺乳動物細胞中，表現生產以及純化後，即得到全人源的抗CD40重組IgG1(L234A, L235A, G237A)抗體PR006239。具體的抗體表現和純化方法參見實施例2。

實施例2 抗體的瞬時轉染表現和純化

【0068】 本實施例介紹了利用哺乳動物宿主細胞(例如，人胚腎細胞HEK293或中國倉鼠卵巢細胞CHO及其衍生細胞)、瞬時轉染表現和親和捕獲分離等技術來製備抗體的一般方法。本方法適用於含有Fc區的目標抗體；目標抗體可以由一條或多條蛋白質多肽鏈組成；可以來源於一個或多個表現質體。

【0069】 將抗體多肽鏈的胺基酸序列透過密碼子優化方法轉換成核苷酸序列；合成編碼的核苷酸序列並選殖到與宿主細胞兼容的表現載體上。將編碼抗體多肽鏈的質體按照特定比例同時轉染哺乳動物宿主細胞，利用常規的重組蛋白表現和純化技術，可以得到具有正確折疊和多肽鏈組裝的重組抗體。具體地，將FreeStyle™ 293-F細胞(Thermo, #R79007)在FreeStyle™ F17 Expression Medium培養基(Thermo, #A1383504)中擴培。瞬時轉染開始之前，調節細胞濃度至6–8×10^5細胞/ml，於37℃ 8% CO_2震盪培養箱

中培養24小時，細胞濃度在1.2×10^{6}細胞/ml。準備30 ml培養的細胞。將編碼抗體多肽鏈的質體(pTT5，NRC)按照一定比例混合共計30 μg質體(質體與細胞的比例為1 μg：1 ml)溶解於1.5 ml Opti-MEM減血清培養基(Thermo,#31985088)，並用0.22 μm濾膜過濾除菌。再取1.5 ml Opti-MEM溶入1 mg/ml PEI(Polysciences, #23966-2)120 μl，靜置5分鐘。把PEI緩慢加入質體中，室溫培育10分鐘，邊搖晃培養瓶邊緩慢滴入質體PEI混合溶液，於37℃ 8% CO_2震盪培養箱中培養5天。5天後觀測細胞存活率。收集培養物，以3300g轉速離心10分鐘後取上清液；然後將上清液高速離心去除雜質。用PBS pH7.4緩衝液平衡含有MabSelect™(GE Healthcare, #71-5020-91)的重力管柱(Bio-Rad, #7311550)，2-5倍管柱體積沖洗。將上清液樣品通過管柱；用5-10倍管柱體積的PBS緩衝液沖洗管柱，再用pH3.5的0.1M甘胺酸洗提目標蛋白，隨後用pH 8.0的Tris-HCl調節至中性，最後用超濾管(Millipore, #UFC901024)濃縮換液至PBS緩衝液或者含有其他成分的緩衝液，得到純化的重組抗體溶液。最後用NanoDrop (Thermo, NanoDrop™ One)測定濃度，分裝、存儲備用。

實施例3 抗體的序列分析和優化

【0070】 抗體的重鏈可變結構域序列來源於染色體上重鏈基因群的胚系基因V、D、J基因片段的基因重排和體細胞高頻突變等事

件；輕鏈可變結構域序列來源於輕鏈基因群的胚系基因V、J基因片段的基因重排和體細胞高頻突變等事件。基因重排和體細胞高頻突變是增加抗體多樣性的主要因素。來源於相同胚系V基因片段的抗體也可能產生不同的序列，但總體上相似性較高。利用一些算法，例 如IMGT/DomainGapAlign (http://imgt.org/3Dstructure-DB/cgi/DomainGapAlign.cgi) 或 者NCBI/IgBLAST (https://www.ncbi.nlm.nih.gov/igblast/) 可以從抗體的可變結構域序列推測出其發生基因重排時可能的胚系基因片段。將實施例1得到的CD40抗體序列進行分析，其重鏈可變結構域(VH)和輕鏈可變結構域(VL)的胚系基因V基因片段列於表2。

【0071】 蛋白質或多肽胺基酸鏈在細胞中轉譯合成後有時會引入化學修飾，稱為轉譯後修飾(PTM)。如果在抗體的可變結構域尤其是抗原結合區域(如CDR)中存在PTM，那麼這些PTM的存在有可能會對抗原的結合有較大的影響，也可能對抗體的物理化學性質帶來變化。例如，醣基化、脫醯胺、異構化、氧化等都可能增加抗體分子的不穩定性或異質性，從而增加抗體開發的難度和風險。因而避免一些潛在的PTM對於治療性抗體的開發是非常重要的。隨著經驗的積累，人們發現一些PTM是和胺基酸序列的組成尤其是相鄰胺基酸組成的“模式”是高度相關的，這樣使得可以從蛋白質的一級胺基

酸序列預測出潛在的PTM。表2列出了實施例1的抗體的可變結構域VH和VL的預測的PTM(NS可能是脫醯胺位址)。

【0072】 可以透過胺基酸突變來破壞PTM的胺基酸序列模式，從而降低或者去除特定PTM的形成。根據抗體序列和PTM序列模式的不同，有不同的突變設計方法。一種方法是將“熱點”胺基酸(如NS模式中的N或S)替換成物理化學性質相似的胺基酸(如把N突變為Q)。如果PTM序列模式來源於體細胞高頻突變，而並不存在於胚系基因序列中，那麼另一種方法可以是把該序列模式替換成對應的胚系基因序列。實際操作中，對同一個PTM序列模式可能採用多種突變設計方法。

【0073】 表3列出了對抗體PR003379進行胺基酸突變得到的新的抗體分子。

【0074】 表4列出了本發明申請中CD40抗體的序列和根據Chothia定義規則定義的CDR的胺基酸序列。這些CD40抗體包括陽性對照抗體、本發明的CD40抗體PR003379及其突變體分子。

表2：CD40抗體的胚系基因分析和PTM位址分析

選殖號	VH胚系V基因	VL胚系V基因	VH PTM	VL PTM	重組抗體	重組抗體亞型
18C4A12-1B1	IGHV1-2	IGKV1-9		NS (LCDR3)	**PR003379**	人IgG2

表3：CD40抗體的PR003379的突變位址設計

變異體編號	可變區突變	重組抗體亞型	Fc 突變
PR006239	無	人 IgG1	L234A, L235A, G237A
PR006492	L:N92E	人 IgG1	L234A, L235A, G237A
PR006493	L:N92L	人 IgG1	L234A, L235A, G237A
PR006494	L:N92T	人 IgG1	L234A, L235A, G237A
PR006495	L:N92A	人 IgG1	L234A, L235A, G237A
PR006496	L:N92F	人 IgG1	L234A, L235A, G237A
PR006497	L:N92Y	人 IgG1	L234A, L235A, G237A
PR006498	L:N92I	人 IgG1	L234A, L235A, G237A
PR006499	L:N92W	人 IgG1	L234A, L235A, G237A
PR006500	L:N92M	人 IgG1	L234A, L235A, G237A
PR006501	L:N92Q	人 IgG1	L234A, L235A, G237A
PR006502	L:N92D	人 IgG1	L234A, L235A, G237A
PR006503	L:N92G	人 IgG1	L234A, L235A, G237A
PR006504	L:N92V	人 IgG1	L234A, L235A, G237A
PR006505	L:S93I	人 IgG1	L234A, L235A, G237A
PR006506	L:S93F	人 IgG1	L234A, L235A, G237A
PR006507	L:S93E	人 IgG1	L234A, L235A, G237A
PR006509	L:S93L	人 IgG1	L234A, L235A, G237A
PR006510	L:S93R	人 IgG1	L234A, L235A, G237A
PR006511	L:S93N	人 IgG1	L234A, L235A, G237A
PR006512	L:S93T	人 IgG1	L234A, L235A, G237A
PR006513	L:S93Q	人 IgG1	L234A, L235A, G237A
PR006514	L:S93V	人 IgG1	L234A, L235A, G237A
PR006515	L:S93M	人 IgG1	L234A, L235A, G237A
PR006516	L:S93H	人 IgG1	L234A, L235A, G237A

表4：本發明申請中CD40抗體的序列和CDR序列(Chothia)的序列編號表

抗體編號	輕鏈	重鏈	VL	VH	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
PR001028 (Selicrelumab)	116	110	82	78	30	38	46	4	12	20
PR001303 (APX005)	117	111	83	79	31	39	47	5	13	21
PR001304 (APX005M)	117	112	83	79	31	39	47	5	13	21
PR001306 (CDX-1140)	118	113	84	80	32	40	48	6	14	22
PR003379	119	114	85	81	33	41	49	7	15	23
PR006239	119	115	85	81	33	41	49	7	15	23
PR006492	120	115	86	81	33	41	50	7	15	23
PR006493	121	115	87	81	33	41	51	7	15	23
PR006494	122	115	88	81	33	41	52	7	15	23
PR006495	123	115	89	81	33	41	53	7	15	23
PR006496	124	115	90	81	33	41	54	7	15	23
PR006497	125	115	91	81	33	41	55	7	15	23
PR006498	126	115	92	81	33	41	56	7	15	23
PR006499	127	115	93	81	33	41	57	7	15	23
PR006500	128	115	94	81	33	41	58	7	15	23
PR006501	129	115	95	81	33	41	59	7	15	23
PR006502	130	115	96	81	33	41	60	7	15	23
PR006503	131	115	97	81	33	41	61	7	15	23
PR006504	132	115	98	81	33	41	62	7	15	23
PR006505	133	115	99	81	33	41	63	7	15	23
PR006506	134	115	100	81	33	41	64	7	15	23
PR006507	135	115	101	81	33	41	65	7	15	23
PR006509	136	115	102	81	33	41	66	7	15	23
PR006510	137	115	103	81	33	41	67	7	15	23
PR006511	138	115	104	81	33	41	68	7	15	23
PR006512	139	115	105	81	33	41	69	7	15	23
PR006513	140	115	106	81	33	41	70	7	15	23
PR006514	141	115	107	81	33	41	71	7	15	23
PR006515	142	115	108	81	33	41	72	7	15	23
PR006516	143	115	109	81	33	41	73	7	15	23

實施例4 結合表現CD40的細胞

【0075】 本實施例是為了研究標靶CD40的抗體結合表現有CD40的細胞的結合活性。

【0076】 利用流式細胞術FACS檢測CD40抗體與高表現人CD40的CHO-K1/hCD40(北京康源博創建構)和高表現食蟹猴CD40的CHO-K1/cyCD40(北京康源博創建構)以及高表現人CD40的淋巴瘤細胞Raji(ATCC, # CCL-86)等細胞的結合能力。具體地，消化細胞並用完全培養基(CHO-K1細胞用F-12K；Raji細胞用RPMI-1640）重新懸浮；將細胞密度調整為1×10^6細胞/mL。以100 μL細胞/孔接種於96孔V底盤(Corning, #3894)，隨後加入100 μL/孔，2倍於終濃度的待測抗原結合蛋白，混合均勻。其中抗原結合蛋白最高終濃度為300 nM，共8個濃度，5倍濃度梯度稀釋，並以hIgG(Crownbio,#C0002)作為陰性對照。陽性對照分子為表1-5中的分子。將細胞放置於4℃，避光培育1小時。之後，加入100 μL/孔預冷PBS洗滌細胞兩次，於500 g，4℃下離心5分鐘，棄上清液。再加入100 μL/孔螢光二抗(山羊抗人IgG(H+L)第二抗體,Alexa Fluor® 488 conjugate, Invitrogen，#A11013,1:1000稀釋)，4℃，避光培育30分鐘。用200 μL/孔預冷PBS洗滌細胞兩次，於500 g，4℃下離心5分鐘，棄上清液。最後，用200 μL/孔預冷PBS重新懸浮細胞。使用BD FACS CANTOII流式細胞儀或

ACEA NovoCyte流式細胞儀讀取螢光發光訊號值，並用軟體FlowJo v10(FlowJo,LLC)處理和分析數據。

【0077】 應用軟體GraphPad Prism 8進行數據處理和作圖分析，透過四參數非線性擬合，得到抗體對靶細胞的結合曲線及EC50值等參數。

實施例4.1 結合到人CD40細胞CHO-K1/hCD40

【0078】 圖1A、圖1B、圖1C和圖1D以及表5顯示了CD40抗體PR003379及其變異體分子結合CHO-K1/hCD40的活性。結果顯示PR003379及其變異體分子具有很好的人CD40的結合活性；而且，PR003379的結合活性與對照分子相比更強，例如，EC50優於Selicrelumab和CDX-1140，而MFI最大值高於APX005和CDX-1140。

表5：PR003379及其變異體分子結合CHO-K1/hCD40(對應圖1A-圖1D)

	抗體	EC50 (nM)	MFI 最大值		抗體	EC50(nM)	MFI 最大值
(A)	PR003379	6.345	81590	(B)	PR006239	6.675	88598
	Selicrelumab	10.28	84982		PR006492	8.87	92266
	APX005	2.831	25987		PR006493	5.264	83381
	CDX-1140	12.2	29214		PR006494	8.727	98839
					PR006495	4.902	79429
					PR006496	4.8	88167
					PR006497	5.092	92305
					PR006498	4.971	77721
					PR006499	4.651	84247
	抗體	EC50 (nM)	MFI 最大值		抗體	EC50 (nM)	MFI 最大值
(C)	PR006500	5.011	85885	(D)	PR006509	5.513	79637
	PR006501	5.285	90960		PR006510	4.981	82967
	PR006502	4.553	88464		PR006511	4.99	79406
	PR006503	6.067	84519		PR006512	5.182	81563
	PR006504	4.873	85950		PR006513	7.509	89193
	PR006505	6.077	82709		PR006514	5.079	86852
	PR006506	5.853	82769		PR006515	4.588	86329
	PR006507	5.576	81836		PR006516	5.08	86126

實施例4.2 結合到人CD40細胞Raji

【0079】 圖2A、圖2B、圖2C、圖2D和圖2E以及表6顯示了CD40抗體PR003379及其變異體分子結合Raji細胞的活性。結果顯示PR003379及其變異體分子能夠很強地結合Raji細胞；而且，PR003379的結合活性與對照分子相比更強。

表6：PR003379及其變異體分子結合Raji細胞(對應圖2A-圖2E)

	抗體	EC50 (nM)	MFI最大值				
(A)	PR003379	0.0699	3696				
	Selicrelumab	0.4837	2449				
	APX005	0.0347	2791				
	CDX-1140	0.028	614				
	抗體	**EC50 (nM)**	**MFI最大值**		**抗體**	**EC50 (nM)**	**MFI最大值**
(B)	PR006239	0.3319	9048	(C)	PR006500	0.3515	8975
	PR006492	0.4184	9073		PR006501	0.3521	9005
	PR006493	0.3769	9347		PR006502	0.2866	9035
	PR006494	0.3283	9175		PR006515	0.3219	8895
	PR006495	0.3556	8872		PR006516	0.3511	8897
	PR006496	0.2771	9297				
	PR006497	0.2524	9203				
	PR006498	0.3443	8985				
	PR006499	0.3014	8980				
	抗體	**EC50 (nM)**	**MFI最大值**		**抗體**	**EC50 (nM)**	**MFI最大值**
(D)	PR006503	0.3328	12171	(E)	PR006509	0.371	12204
	PR006504	0.3503	12152		PR006510	0.3762	12373
	PR006505	0.336	11935		PR006511	0.3859	11785
	PR006506	0.3879	12128		PR006512	0.4241	12067
	PR006507	0.3836	12332		PR006513	0.3734	11986
					PR006514	0.4546	12037

實施例4.3 結合到食蟹猴CD40細胞CHO-K1/cyCD40

【0080】 圖3A、圖3B、圖3C和圖3D以及表7顯示了CD40抗體PR003379及其變異體分子結合食蟹猴CD40細胞CHO-K1/cyCD40的活性。結果顯示PR003379及其變異體分子具有很好的食蟹猴CD40的結合活性；而且，PR003379的結合活性與對照分子相比更強。

表7：PR003379及其變異體分子結合CHO-K1/cyCD40(對應圖3A-圖3D)

	抗體	EC50 (nM)	MFI最大值		抗體	EC50 (nM)	MFI最大值
(A)	PR003379	3.878	116864	(B)	PR006239	4.408	51824
	Selicrelumab	5.97	105580		PR006492	6.256	52166
	APX005	4.721	93571		PR006493	4.061	48943
	CDX-1140	5.536	39735		PR006494	4.042	49590
					PR006495	4.406	48028
					PR006496	3.503	49738
					PR006497	3.544	51708
					PR006498	4.045	47335
					PR006499	3.199	49776
	抗體	EC50 (nM)	MFI最大值		抗體	EC50 (nM)	MFI最大值
(C)	PR006500	4.403	48505	(D)	PR006509	4.693	45342
	PR006501	4.189	48203		PR006510	4.554	44305
	PR006502	3.961	47725		PR006511	3.684	40321
	PR006503	3.988	49554		PR006512	4.546	45792
	PR006504	3.71	51016		PR006513	3.564	40200
	PR006505	4.619	48059		PR006514	4.233	45078
	PR006506	4.504	47308		PR006515	3.745	50571
	PR006507	5.009	49256		PR006516	5.293	51388

實施例5 與CD40蛋白的親和力

【0081】 為了檢測CD40抗體與抗原如人CD40蛋白的親和力，透過生物膜干涉(BLI)技術，使用Octet Red 96e(Fortebio)分子相互作用分析儀來進行抗原抗體之間的結合動力學分析。

【0082】 先將10×動力學緩衝液(ForteBio，#18-1105)稀釋至1×，用於親和力測試以及抗原、抗體的稀釋。測定抗原和抗體的親和力時，感測器轉動速度為1000轉/分鐘。先將置於一列的AHC感測器(Fortebio，#18-5060)在上述稀釋至1×的測試緩衝液中平衡

10分鐘，然後用AHC感測器捕獲CD40抗體，捕獲高度0.85 nm；將AHC感測器在緩衝液中平衡120秒後與2倍梯度稀釋的人CD40蛋白(與PR003379、CDX-1140結合的CD40濃度範圍為20-5 nM以及0 nM；與APX005M、Selicrelumab結合的CD40濃度範圍為120-30nM以及0 nM結合180秒，再解離500秒。最後將AHC感測器浸入10 mM甘胺酸-鹽酸pH 1.5溶液進行再生，以洗提結合在感測器上的蛋白。

【0083】 使用Octet Data Analysis軟體(Fortebio，版本11.0)進行數據分析時，以0 nM為參照孔，扣除參照訊號(reference subtraction)，選擇“1:1Global fitting”方法進行數據擬合，計算出抗原與CD40抗體結合的動力學參數，得到kon(1/Ms)值、kdis(1/s)值和KD(M)值。

【0084】 親和力測試結果如表 8所示，PR003379結合人CD40蛋白有很強的親和力(約138 pM)，親和力強於陽性對照抗體。

表 8：CD40抗體結合人CD40蛋白的親和力

抗體	抗原濃度	KD (M)	kon (1/Ms)	kdis (1/s)	Full R^2
PR003379	20－5 nM	1.38E-10	1.04E+06	1.44E-04	0.9703
Selicrelumab	120－30 nM	4.50E-09	1.07E+05	4.80E-04	0.9746
APX005M	120－30 nM	7.14E-09	3.69E+05	2.64E-03	0.9909
CDX-1140	20－5 nM	5.25E-10	1.09E+06	5.70E-04	0.9939

實施例6 在螢光報導基因實驗中的活性

【0085】 本實施例利用螢光報導基因實驗研究了CD40抗體在Fc交聯以及不交聯情況下對CD40的活化影響。利用高表現人

CD32B的細胞對抗體進行Fc媒介的交聯，研究交聯是否能進一步增強對CD40活化的能力。

【0086】 將表現人CD32B的CHO-K1細胞CHO-K1/hCD32B(Genscript，#M00600)以及CHO-K1細胞以1×10^4/孔以1×10^4/孔，100 μL/孔接種到96孔盤中(PerkinElmer，#6005181)，37℃在5% CO_2環境下培育過夜。去除上清液，將表現人CD40和NFkB-螢光素酶報導基因的HEK293-hCD40-NFkB報導基因細胞(BPS bioscience, #60626)收集後以5×10^4/孔，50 μL/孔加入到96孔盤中。加入50 μL/孔的待測抗體蛋白稀釋液，起始濃度為100 nM，5倍濃度稀釋，共8個濃度。37℃在5% CO_2環境下培養6小時。加入ONE-Glo™螢光素酶試劑 (Promega, #E6110)，室溫培育5分鐘，酵素標示讀取儀(PerkinElmer EnSpire)檢測發光值。應用軟體GraphPad Prism 8進行數據處理和作圖分析，透過四參數非線性擬合，得到抗體濃度依賴的相對螢光訊號單位(RLU)的曲線及EC50值等參數。CD40抗體與CHO-K1/hCD32B細胞培育的樣品稱為“交聯”(crosslinked)；CD40抗體與CHO-K1細胞培育的樣品沒有交聯。

【0087】 如圖4A、圖4B、圖4C和圖4D和表9所示，PR003379和對照抗體APX005M有非常明顯的“交聯增強”作用，即，在CD32B媒介抗體交聯的條件下，PR003379和APX005M能夠顯著地放大螢

光報導基因的訊號，說明顯著增強了對CD40分子的下游訊號分子的活化作用。

【0088】 如圖5A和圖5B及表10顯示了PR003379的變異體分子在有或者沒有CD32B細胞媒介交聯的條件下對報導基因細胞的活化的螢光強度增強倍數。結果說明，PR003379的變異體分子在交聯的情況下能顯著增強對CD40分子的活化作用，表現在其EC50值在交聯的情況下相比未交聯的情況下顯著減小(體現為“倍數(未交聯EC50/交聯EC50)”>1)。

【0089】 從表9和表10中RLU倍數/倍數均代表了抗體在兩種情況下的活化潛能的差異，或者治療範圍，反應了PR003379及其衍生抗體的倍數較現有抗體更佳，治療範圍更大。

表 9：CD40抗體活化HEK293-CD40-NFkB報導基因細胞的活性

抗體	EC50 (nM)	RLU 最大值	RLU 倍數(交聯/未交聯)
PR003379	0.3693	8252	2.38
PR003379 crosslinked(交聯)	0.1784	19664	
Selicrelumab	0.1628	13355	1.28
Selicrelumab crosslinked(交聯)	0.0413	17036	
APX005M	0.3551	11898	1.95
APX005M crosslinked(交聯)	0.0420	23207	
CDX-1140	0.0371	19955	1.13
CDX-1140 crosslinked(交聯)	0.0506	22605	

表10：PR003379變異體在交聯和未交聯條件下活化報導基因細胞活性

	交聯		未交聯		
PR003379變異體	**EC50 (nM)**	**倍數最大值 (fold)**	**EC50 (nM)**	**倍數最大值 (fold)**	**倍數（未交聯EC50/交聯EC50）**
PR006239	0.0980	5.76	0.1734	4.58	1.77
PR006495	0.1092	5.54	0.9047	4.92	8.28
PR006496	0.2172	5.03	0.4296	4.43	1.98
PR006497	0.1582	4.77	0.4786	4.61	3.03
PR006498	0.1958	5.53	0.4615	4.4	2.36
PR006499	0.4054	5.28	1.0440	3.92	2.58
PR006500	0.1689	5.55	0.3012	4.33	1.78
PR006502	0.1704	4.95	0.3212	4.63	1.88
PR006504	0.1572	5.21	0.7079	4.7	4.50
PR006510	0.0423	4.66	0.1253	4.54	2.96
PR006511	0.1600	5.19	0.8153	4.5	5.10
PR006515	0.0669	4.91	0.2683	4.54	4.01

實施例7 在DC細胞活化實驗中的活性

【0090】 本實施例利用高表現人CD32B的細胞對抗體進行Fc媒介的交聯，研究交聯是否能進一步增強CD40抗體活化DC細胞的能力。

【0091】 將表現人CD32B的CHO-K1細胞CHO-K1/hCD32B以及CHO-K1細胞分別以1×10^4/孔，50 μL/孔接種到96孔盤中(Corning，#3599)。加入50 μL/孔的待測抗體蛋白稀釋液，起始濃度為100 nM，5倍濃度稀釋，共8個濃度。加入從人PBMC分離得到的誘導成熟的DC細胞，2×10^4/孔，100 μL/孔，於37℃，5% CO_2

培養箱培育2天。收集第二天的上清液，採用人IL-12p40 ELISA套組(R&D system，#DY240)檢測上清液中IL-12p40的含量。應用軟體GraphPad Prism8進行數據處理和作圖分析，透過四參數非線性擬合，得到抗體濃度依賴的IL12p40釋放位準的曲線及EC50值等參數。CD40抗體與CHO-K1/hCD32B細胞培育的樣品稱為“交聯”(crosslinked)；CD40抗體與CHO-K1細胞培育的樣品沒有交聯。

【0092】 結果如圖6A、圖6B、圖6C和圖6D和表11所示，PR003379有非常明顯的“交聯增強”作用，即，在沒有CD32B媒介抗體交聯的條件下，PR003379活化DC細胞釋放IL-12p40位準有限；但是，在有CD32B媒介抗體交聯的條件下，PR003379能顯著增強DC細胞的活化，IL-12p40的最大值可以達到1243.0 pg/mL，遠超過其他對照抗體。

表 11：CD40抗體活化DC細胞釋放細胞激素IL-12p40

抗體	EC50(nM)	IL12p40 最大值 (pg/mL)	IL12p40 最大值倍數(交聯/未交聯)
PR003379	0.0102	179.2	6.94
PR003379 crosslinked(交聯)	0.6268	1243.0	
Selicrelumab	0.3800	318.7	1.75
Selicrelumab crosslinked(交聯)	0.3917	558.9	
APX005M	0.0735	242.5	2.75
APX005M crosslinked(交聯)	0.1695	666.1	
CDX-1140	0.0889	252.1	0.92
CDX-1140 crosslinked(交聯)	0.0886	231.6	

實施例8 阻斷CD40和CD40L的結合

【0093】 為了檢測CD40抗體對CD40和CD40L結合的影響，將CHO-K1/hCD40細胞以2×10^5/孔，100 μL/孔接種到96孔盤中(Corning，#3799)，離心取上清液，加入50 μL/孔的待測抗原結合蛋白稀釋液，起始濃度為500 nM，5倍濃度稀釋，共8個濃度。加入20 ug/mL人CD40L-his蛋白(Sino biological，#10239-H08E)，50 μL/孔，4度培育1小時後，用FACS緩衝液(1xPBS with 2%FBS)洗3次，加入1：400稀釋的抗組胺酸標籤的二抗(GenScript, #A01800)，4度培育1小時後用FACS緩衝液洗2次，用預冷PBS重新懸浮細胞。使用BD FACS CANTOII流式細胞儀或ACEA NovoCyte流式細胞儀讀取螢光發光訊號值，並用軟體FlowJo v10(FlowJo, LLC)處理和分析數據。

【0094】 應用軟體GraphPad Prism 8進行數據處理和作圖分析，透過四參數非線性擬合，得到抗體濃度依賴的抑制率曲線及IC50值等參數。

【0095】 如圖7和表12所示，PR003379呈現出部分抑制CD40和CD40L結合的活性，最大抑制率為41.9%。

表12：CD40抗體抑制CD40和CD40L的結合

抗體	IC50(nM)	最大抑制率(%)
CDX-1140	4.4	24.0
PR003379	17.0	41.9
APX005M	10.0	26.0
hIgG1	無	2.3

實施例9 利用BLI方法測定抗體結合CD40的表位競爭

【0096】 為了檢測CD40抗體的結合表位，使用Octet Red 96e(Fortebio)分子相互作用分析儀透過BLI技術對CD40抗體Selicrelumab、APX005M、PR003379進行表位競爭實驗。第一步，獲取抗體的100%訊號：用HIS1K感測器(Fortebio，#18-5120)捕獲CD40蛋白(Sino Biological，#10774-H08H)，捕獲高度為0.2nm。將感測器在緩衝液中平衡120秒後浸入稀釋至140 nM的各抗體中，時間220秒，將抗體與CD40結合的最終訊號記錄為該抗體的100%訊號。第二步，表位競爭：用HIS1K感測器捕獲CD40蛋白，捕獲高度為0.2 nm。將感測器浸入第一抗體中(濃度為140 nM)，時間220秒，再將HIS1K感測器浸入第一抗體和第二抗體的混合物中(兩種抗體的終濃度均為140 nM)，時間220秒，將感測器浸入抗體混合物後的訊號差，記錄為該抗體作為第二抗體的訊號。抑制率透過下式計算，

抑制率(%)=(A－B)/A*100

A：某抗體的100%訊號(從第一步中獲得)，B：該抗體作為第二抗體的訊號(從第二步獲得)。

若得到的抑制率大於80%，則意味著兩種抗體的表位幾乎完全重疊；若抑制率大於40%且小於80%，則意味著兩種抗體結合的表位不完全重疊或者表位很相近；若抑制率小於40%，則意味著兩種抗體的表位不同。

【0097】 結果如表13所示，PR003379和Selicrelumab的結合表位幾乎一致，但是和APX005M的表位不同。

表13：BLI表位競爭實驗

抑制率(%)		第二抗體		
		Selicrelumab	APX005M	PR003379
第一抗體	Selicrelumab	95.11	10.92	92.8
	APX005M	0.53	98.59	-0.12
	PR003379	98.87	9.56	96.74

實施例10 在MC38-hPD-L1/hCD40-C57BL/6J小鼠模型中的抗腫瘤活性和對小鼠體重的影響

【0098】 為檢測CD40抗體在體內的抗腫瘤功能，將過表現人PD-L1的MC38小鼠結腸癌細胞(MC38/hPD-L1，由上海南方模式生物公司提供)培養在37度，5% CO_2的培養箱中，培養基為含10%滅活胎牛血清的DMEM培養基，細胞每隔3至4天長滿即分皿傳代。取對數生長期MC38/hPD-L1，重新懸浮於PBS中，進行細胞計數，

調整細胞濃度到1.0×10^7/mL；用1 mL注射器將細胞懸液接種於CD40人源化基因轉殖小鼠(hCD40-C57BL/6J，由上海南方模式生物公司提供)的右側脅肋部皮下，100 μL/隻，每隻接種約1.0×10^6個腫瘤細胞。當平均腫瘤體積達到114 mm^3時，挑選個體腫瘤體積適中的小鼠入組，將小鼠按腫瘤體積隨機分配到各實驗組中，每組6隻，分組當天開始給藥。

【0099】 結果如圖8A和圖8B所示，給藥開始後第10天，對照組IgG1 (3 mg/kg)平均腫瘤體積為1409.41±205.02 mm^3。Selicrelumab (3 mg/kg)組、CDX-1104 (3 mg/kg)組、PR003379 (3 mg/kg)組的平均腫瘤體積分別為460.96±68.61 mm^3、1345.22±162.94 mm^3、447.89±50.74 mm^3，腫瘤抑制率分別為73.22%、4.92%、74.24%。整個實驗過程中，IgG1對照組、Selicrelumab、CDX-1104、PR003379小鼠的體重增長率分別為12.24%、7.31%、7.56%、1.86%。小鼠狀態正常。

【0100】 雖然以上描述了本發明的具體實施方式，但是本領域的技術人員應當理解，這些僅是舉例說明，在不背離本發明的原理和實質的前提下，可以對這些實施方式做出多種變更或修改。因此，本發明的保護範圍由所附申請專利範圍限定。

【符號說明】

【0101】 無

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【發明申請專利範圍】

【請求項1】 一種標靶CD40的抗原結合蛋白，所述抗原結合蛋白包含輕鏈可變區和重鏈可變區，所述輕鏈可變區(VL)包含LCDR1、LCDR2和LCDR3，所述重鏈可變區(VH)包含HCDR1、HCDR2和HCDR3；其中：

所述LCDR1包括如SEQ ID NO: 33所示的胺基酸序列，所述LCDR2包括如SEQ ID NO: 41所示的胺基酸序列，所述LCDR3包括如SEQ ID NO: 49-73任一項所示的胺基酸序列；所述HCDR1包括如SEQ ID NO: 7所示的胺基酸序列，所述HCDR2包括如SEQ ID NO: 15所示的胺基酸序列，所述HCDR3包括如SEQ ID NO: 23所示的胺基酸序列。

【請求項2】 如請求項1所述的標靶CD40的抗原結合蛋白，其特徵在於，所述輕鏈可變區包括如SEQ ID NO: 85所示的胺基酸序列或與SEQ ID NO: 85有至少85%、90%、92%、94%、95%、96%、97%、98%或99%相同性的胺基酸序列，所述重鏈可變區包括如SEQ ID NO: 81所示的胺基酸序列或與SEQ ID NO: 81有至少85%、90%、92%、94%、95%、96%、97%、98%或99%相同性的胺基酸序列。

【請求項3】 如請求項2所述的標靶CD40的抗原結合蛋白，其特徵在於，所述輕鏈可變區包括如SEQ ID NO: 85-109任一項所示的胺基酸序列，所述重鏈可變區包括如SEQ ID NO: 81 所示的胺基酸序列。

【請求項4】 如請求項1-3任一項所述的標靶CD40的抗原結合蛋白，其特徵在於，所述標靶CD40的抗原結合蛋白滿足以下三項中至少一項：

(1)所述標靶CD40的抗原結合蛋白為全長抗體、Fab、Fab’、F(ab’)2或Fv；

(2)所述標靶CD40的抗原結合蛋白為單特異性抗體、雙特異性抗體或多特異性抗體；

(3)所述標靶CD40的抗原結合蛋白為單株抗體或多株抗體。

【請求項5】 如請求項4所述的標靶CD40的抗原結合蛋白，其特徵在於，所述標靶CD40的抗原結合蛋白為全長抗體，所述全長抗體包含輕鏈和重鏈；所述輕鏈包括輕鏈恆定區(CL)，所述輕鏈恆定區為人源抗體輕鏈恆定區；所述重鏈包括重鏈恆定區(CH)，所述重鏈恆定區為hIgG1、hIgG2、hIgG3或hIgG4亞型的重鏈恆定區。

【請求項6】 如請求項5所述的標靶CD40的抗原結合蛋白，其特徵在於，所述重鏈恆定區為hIgG1亞型的重鏈恆定區。

【請求項7】 如請求項1所述的標靶CD40的抗原結合蛋白，其特徵在於，所述標靶CD40的抗原結合蛋白為全長抗體，所述全長抗體包含輕鏈和重鏈，所述重鏈包括如SEQ ID NO: 114所示的胺基酸序列，所述輕鏈包括如SEQ ID NO: 119所示的胺基酸序列；或，所述重鏈包括如SEQ ID NO: 115所示的胺基酸序列，所述輕鏈包括如SEQ ID NO: 119-143任一項所示的胺基酸序列。

【請求項8】 一種嵌合抗原受體，其特徵在於，所述嵌合抗原受體包含如請求項1-7任一項所述的標靶CD40的抗原結合蛋白。

【請求項9】 一種分離的核酸，其特徵在於，所述分離的核酸編碼如請求項1-7任一項所述的標靶CD40的抗原結合蛋白或如請求項8所述的嵌合抗原受體。

【請求項10】 一種重組表現載體，其特徵在於，所述重組表現載體包含如請求項9所述的分離的核酸。

【請求項11】 一種轉形株，其特徵在於，所述轉形株包含如請求項9所述的分離的核酸或如請求項10所述的重組表現載體。

【請求項12】 一種如請求項1-7任一項所述的標靶CD40的抗原結合蛋白的製備方法，其包括以下步驟：培養如請求項11所述的轉形株，從培養物中獲得所述標靶CD40的抗原結合蛋白。

【請求項13】 一種抗體藥物偶聯物，其特徵在於，所述抗體藥物偶聯物包含如請求項1-7任一項所述的標靶CD40的抗原結合蛋白和細胞毒性劑或標籤。

【請求項14】 一種基因修飾的細胞，其特徵在於，所述基因修飾的細胞表現如請求項8所述的嵌合抗原受體。

【請求項15】 一種藥物組成物，其特徵在於，所述藥物組成物包含如請求項1-7任一項所述的標靶CD40的抗原結合蛋白、如請求項9所述的分離的核酸、如請求項10所述的重組表現載體，如請求項13所述的抗體藥物偶聯物和如請

求項14所述的基因修飾的細胞中的一種或多種，以及藥學上可接受的載劑和/或藥學上可接受的佐劑。

【請求項16】 如請求項15所述的藥物組成物，其特徵在於，所述藥物組成物還包括其他抗腫瘤抗體作為活性成分。

【請求項17】 一種檢測試劑，其特徵在於，所述檢測試劑包含如請求項1-7任一項所述的標靶CD40的抗原結合蛋白和/或如請求項13所述的抗體藥物偶聯物。

【請求項18】 一種套裝藥盒，其特徵在於，所述套裝藥盒包含藥盒A，所述藥盒A含有如請求項1-7任一項所述的標靶CD40的抗原結合蛋白、如請求項15所述的藥物組成物、如請求項17所述的檢測試劑、如請求項13所述的抗體藥物偶聯物和如請求項14所述的基因修飾的細胞中的一種或多種。

【請求項19】 如請求項18所述的套裝藥盒，其特徵在於，所述套裝藥盒還包括藥盒B，所述藥盒B含有其他抗腫瘤抗體或者包含所述其他抗腫瘤抗體的藥物組成物，和/或由激素製劑、標靶小分子製劑、蛋白酶體抑制劑、成像劑、診斷劑、化療劑、溶瘤藥物、細胞毒性劑、細胞激素、共刺激分子的活化劑、抑制性分子的抑制劑以及疫苗組成的群組中的一種或多種。

【請求項20】 一種如請求項1-7任一項所述的標靶CD40的抗原結合蛋白、如請求項9所述的分離的核酸、如請求項10所述的重組表現載體，如請求項15所述的藥物組成物、如請求項17所述的檢測試劑、如請求項18所述的套裝藥盒、

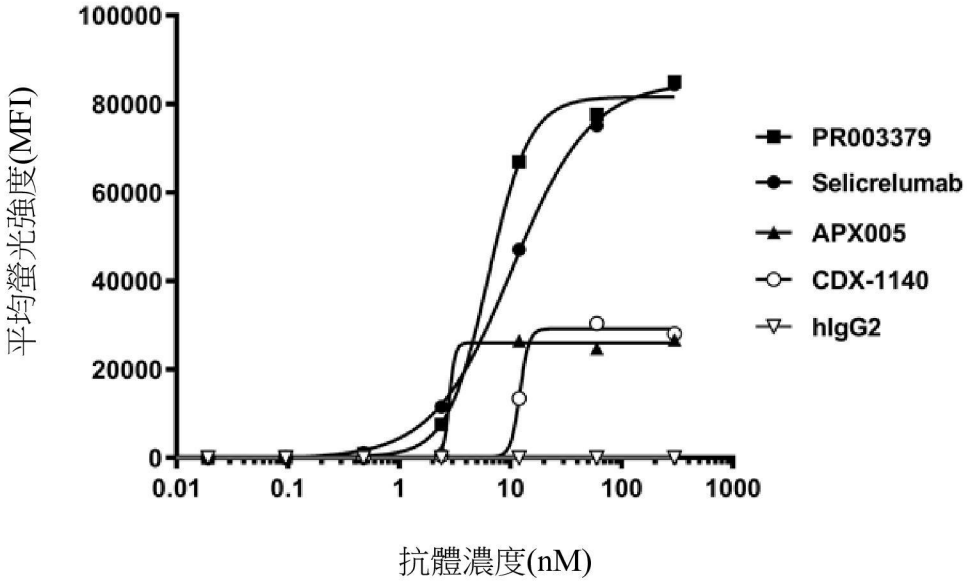
如請求項13所述的抗體藥物偶聯物和如請求項14所述的基因修飾的細胞中的一種或多種在製備診斷、預防和/或治療腫瘤的藥物中的用途。

【請求項21】 如請求項20所述的用途，其特徵在於，所述腫瘤包括B系NHL、慢性淋巴細胞性白血病(CLL)、多毛細胞白血病(HCL)、霍奇金病、多發性骨髓瘤、膀胱癌、腎癌、卵巢癌、子宮頸癌、乳腺癌、肺癌、鼻咽癌、惡性黑色素瘤、胰腺癌和結腸癌。

【請求項22】 一種檢測樣品中CD40的方法，其特徵在於，所述方法包括使用如請求項1-7任一項所述的標靶CD40的抗原結合蛋白、如請求項17所述的檢測試劑和/或如請求項13所述的抗體藥物偶聯物與所述樣品接觸的步驟。

【請求項23】 如請求項22所述的方法，其特徵在於，所述方法為非診斷和/或治療目的。

【發明圖式】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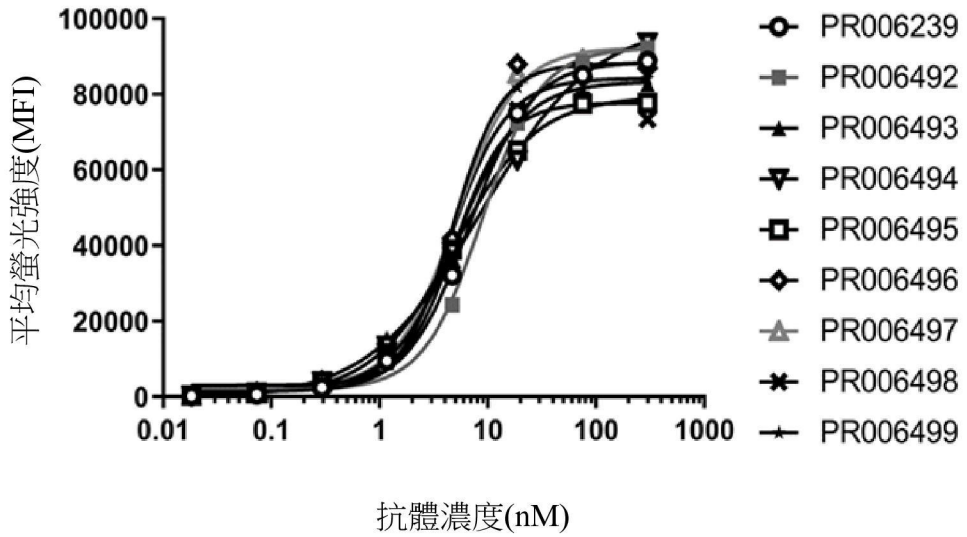
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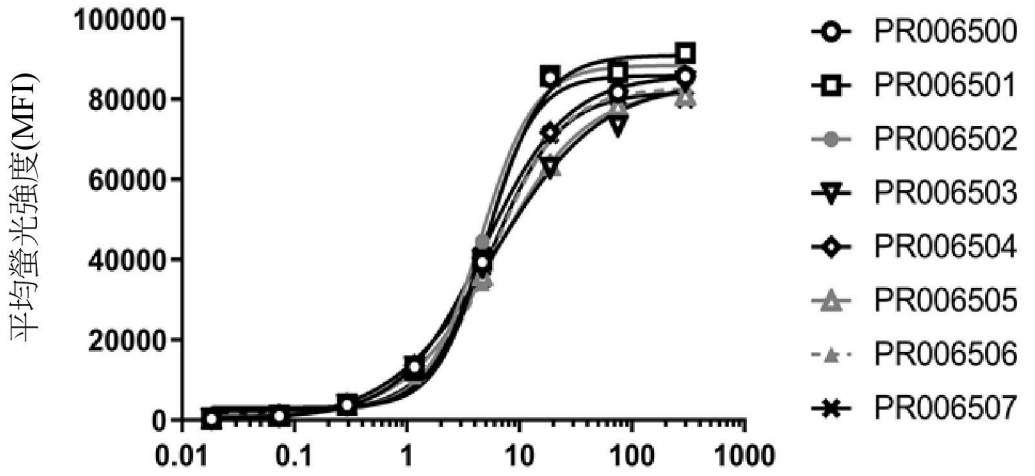
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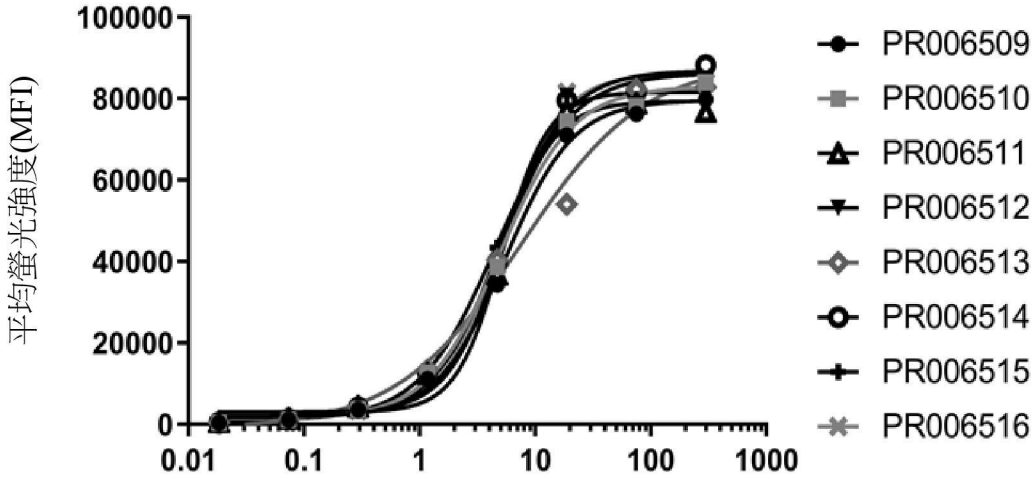
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圖 1D

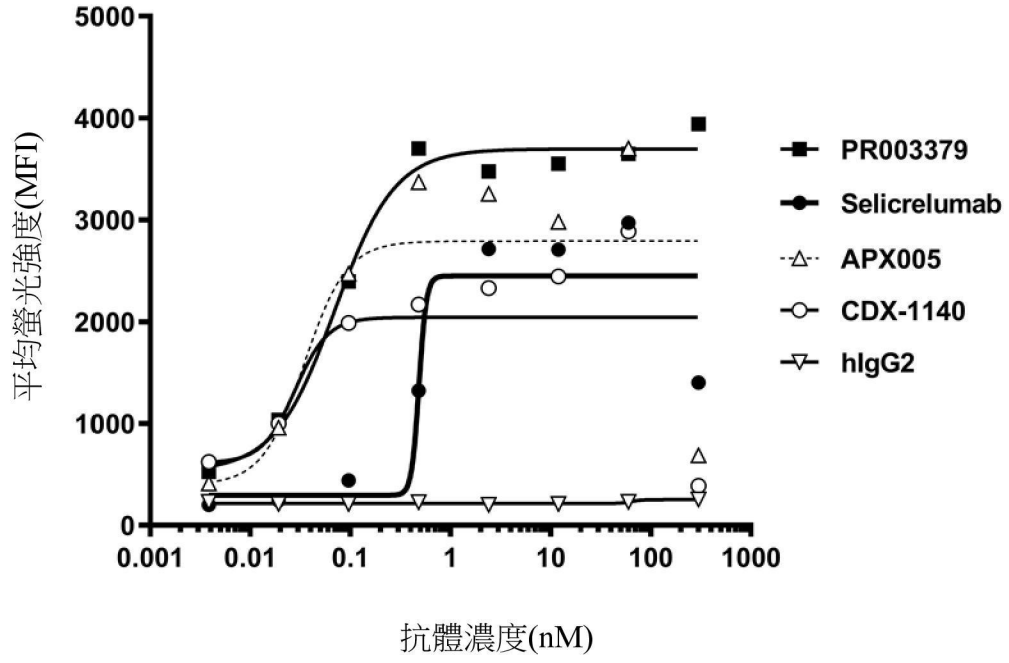
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圖 2A

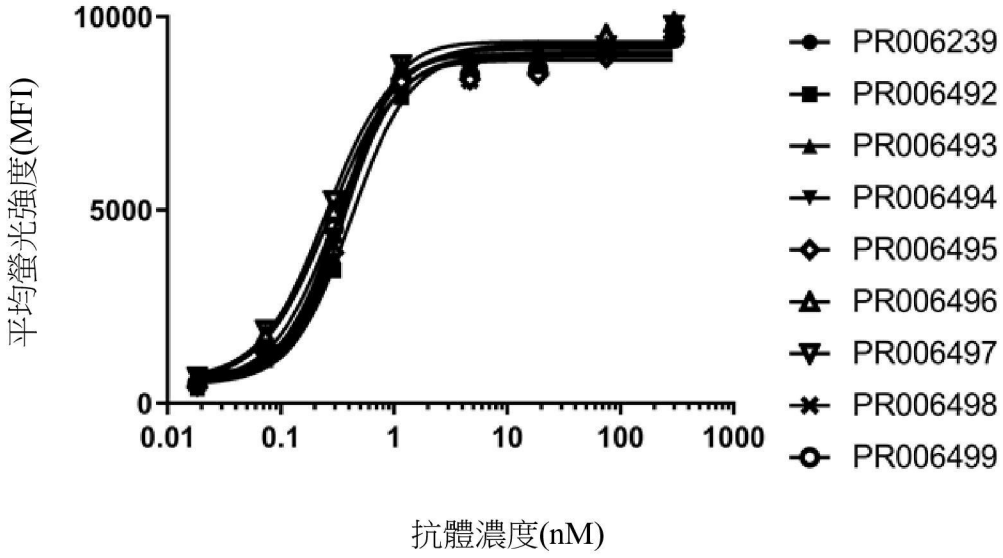
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圖 2B

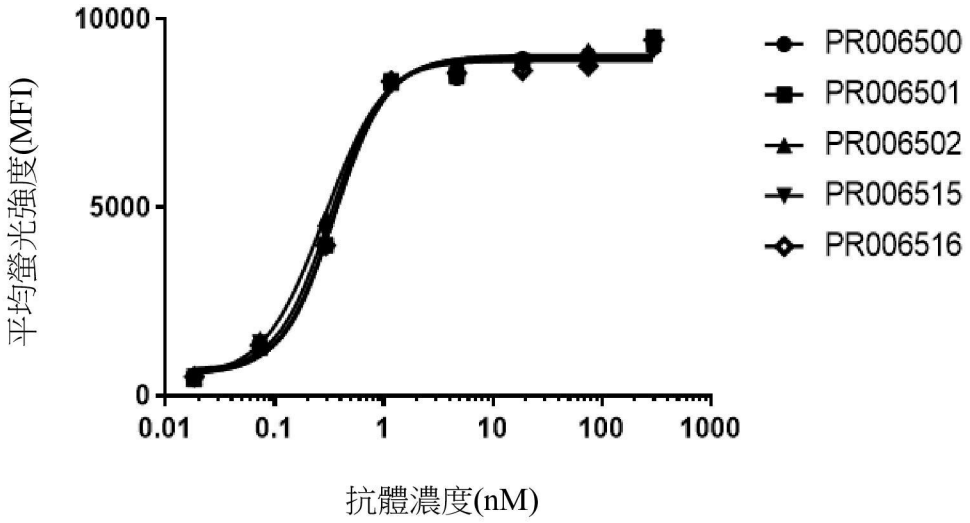
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圖 2C

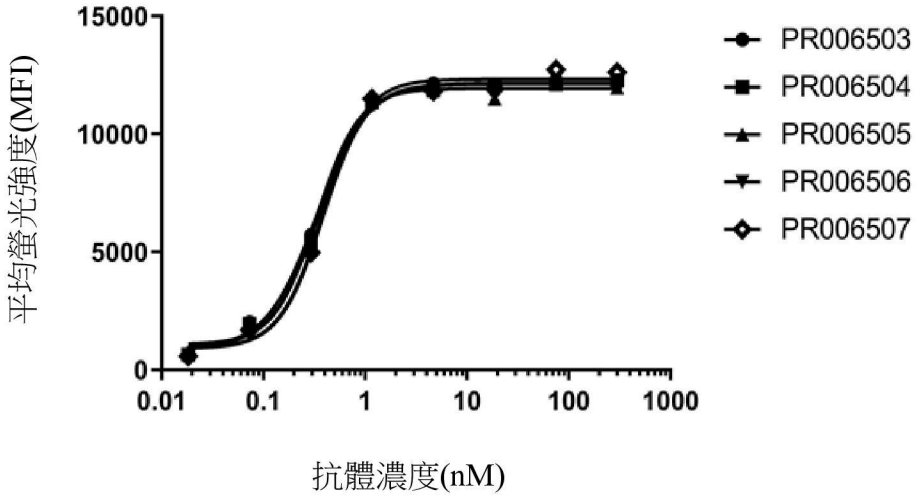
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圖 2D

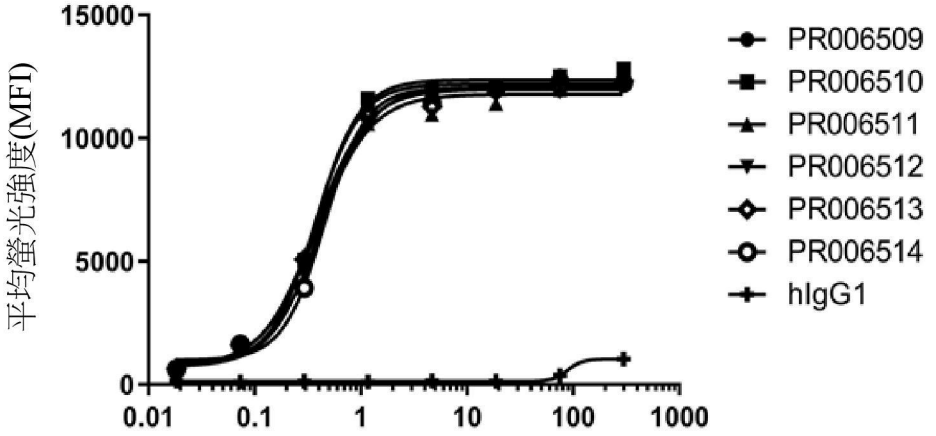
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圖 2E

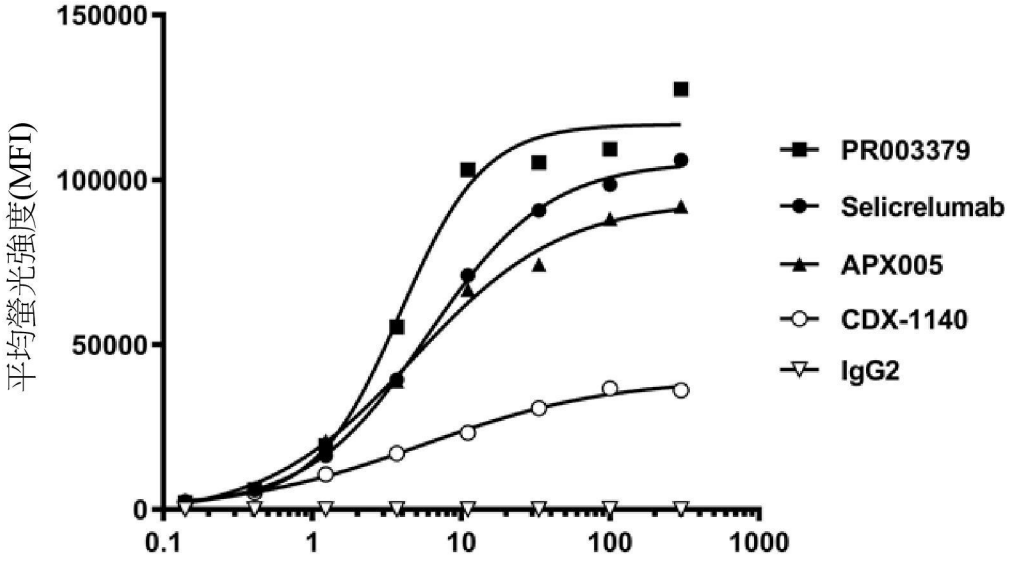
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圖 3A

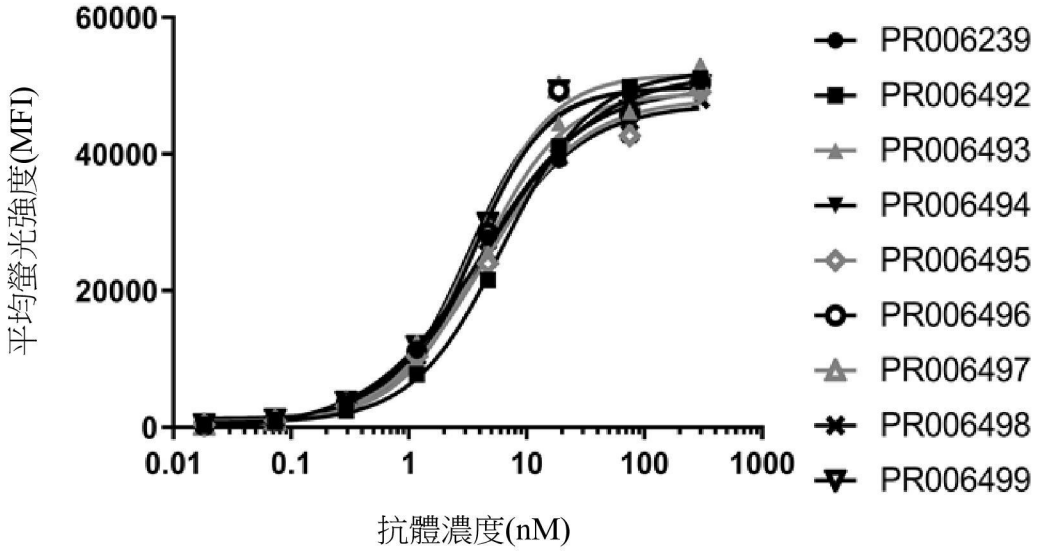
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圖 3B

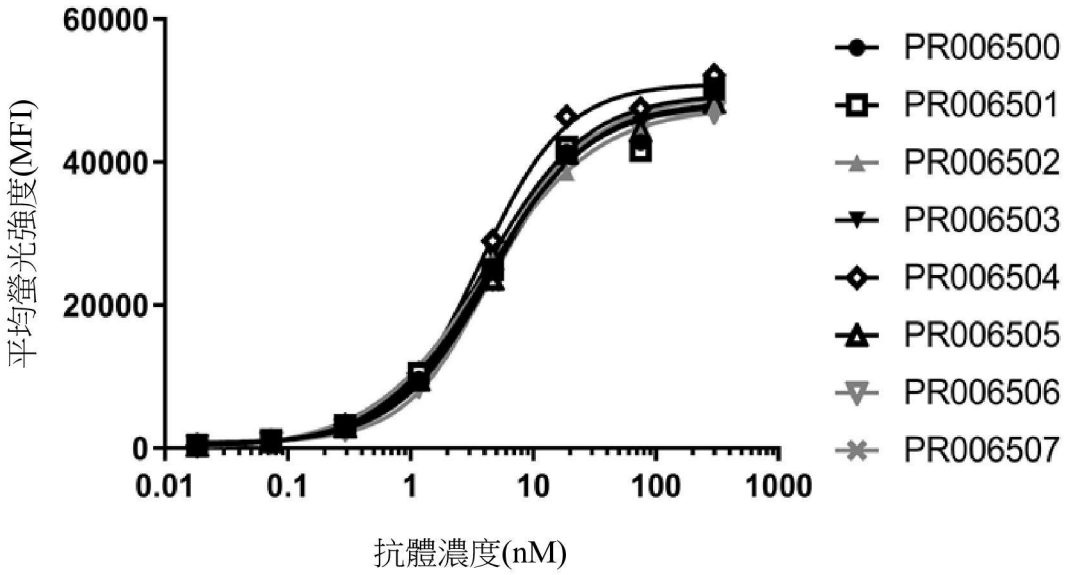
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圖 3C

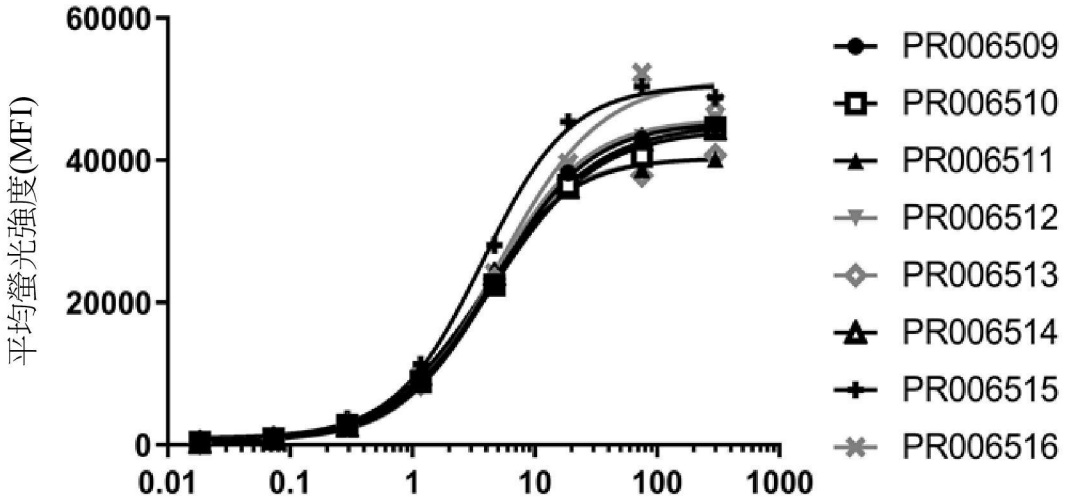
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圖 3D

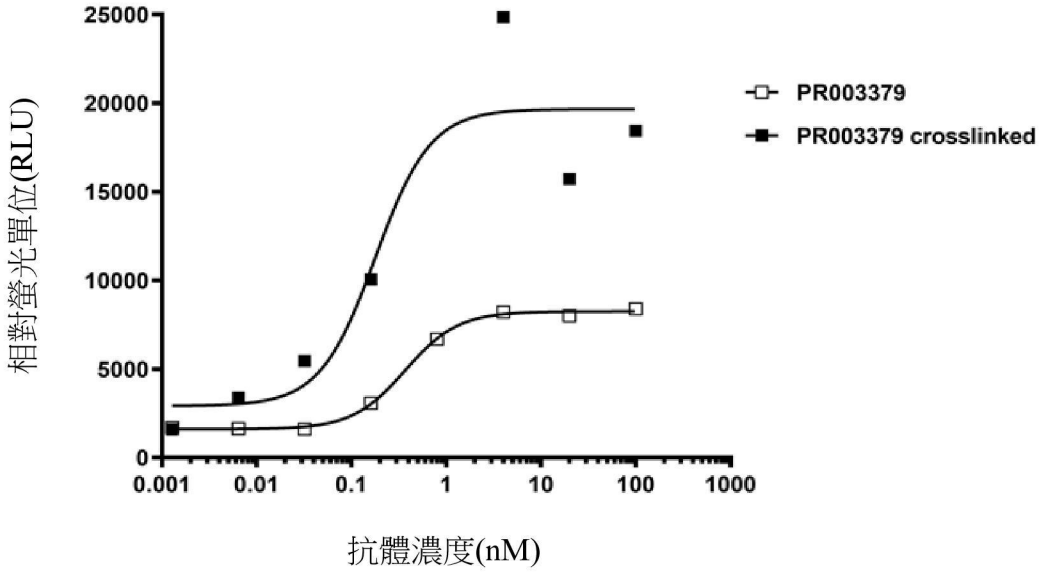
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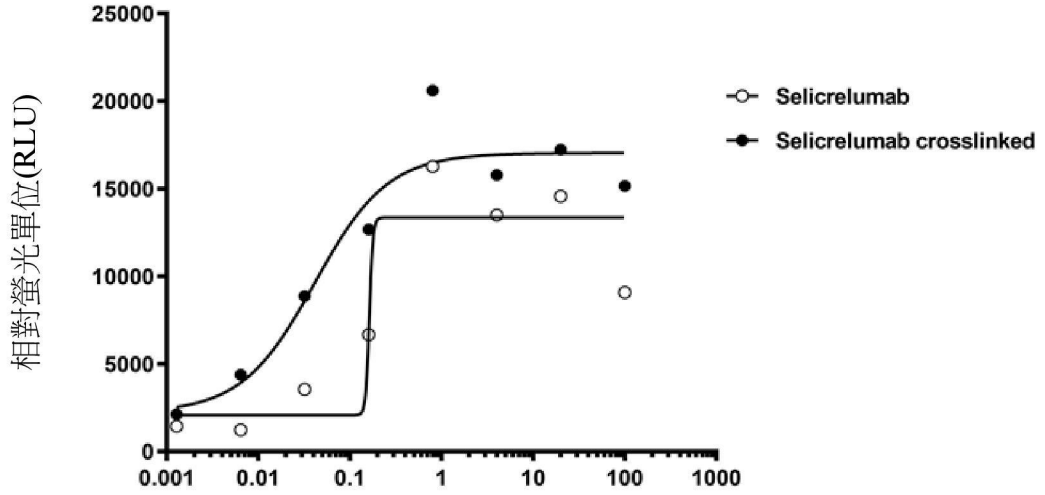
圖 4A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Selicrelumab crosslinked

圖 4B

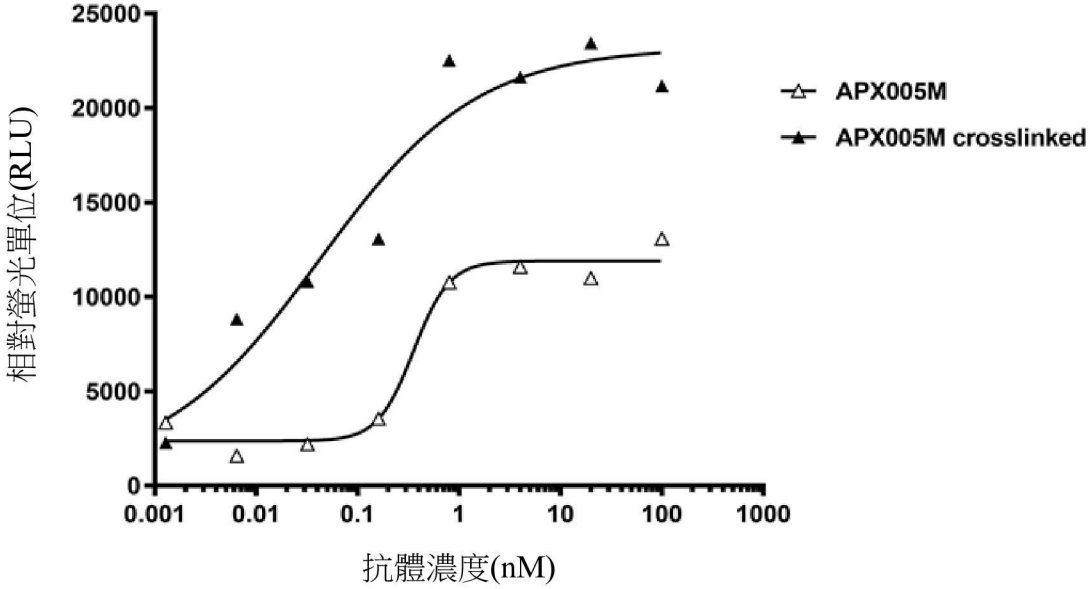

25000
20000
15000
10000
5000
0
0.001
0.01
0.1
1
10
100
1000
相對螢光單位(RLU)
抗體濃度(nM)
APX005M
APX005M crosslinked

圖 4C

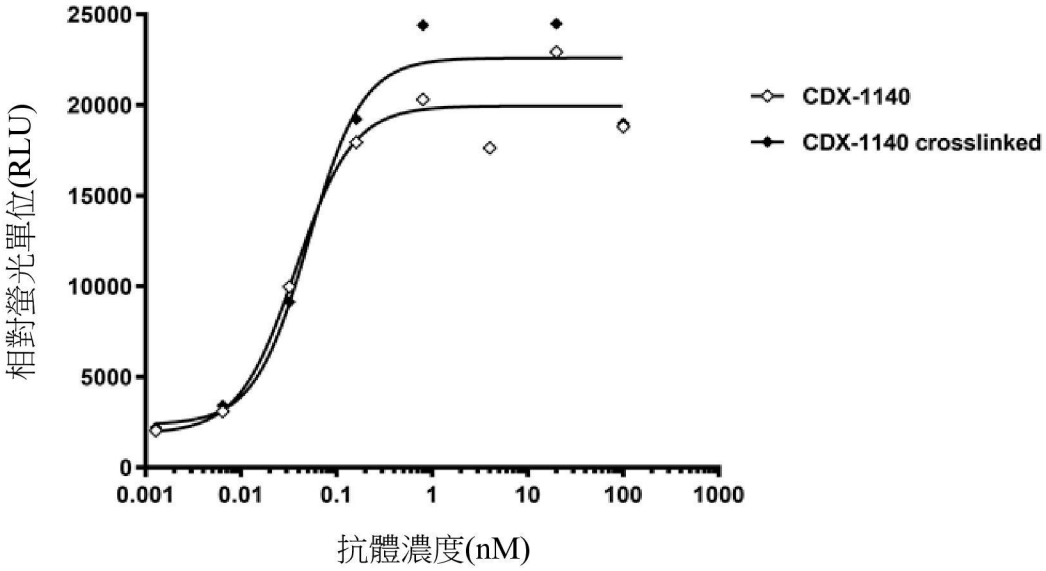

25000
20000
15000
10000
5000
0
0.001
0.01
0.1
1
10
100
1000
相對螢光單位(RLU)
抗體濃度(nM)
CDX-1140
CDX-1140 crosslinked

圖 4D

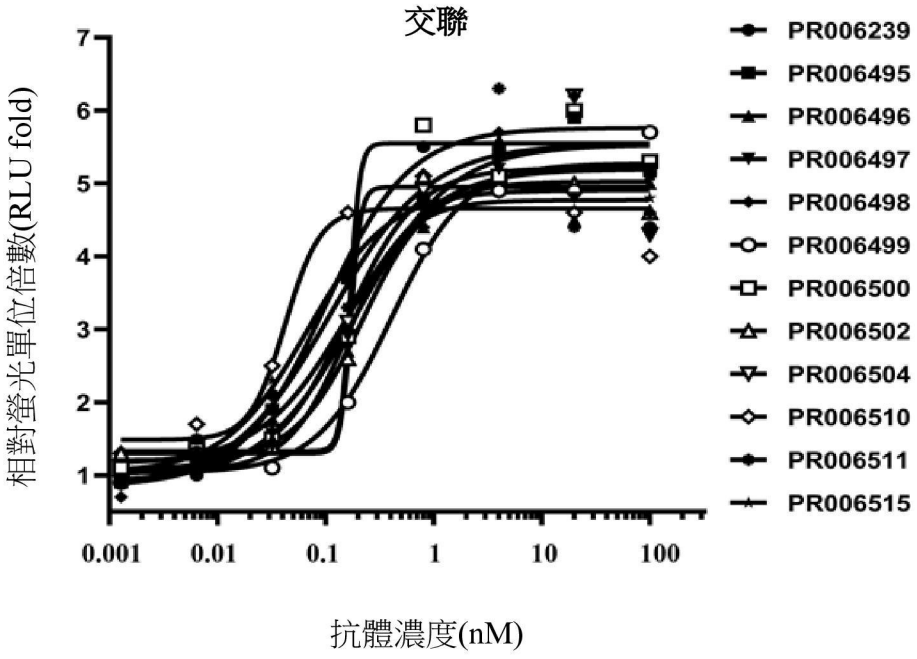

交聯
7
6
5
4
3
2
1
0.001
0.01
0.1
1
10
100
相對螢光單位倍數(RLU fold)
抗體濃度(nM)
PR006239
PR006495
PR006496
PR006497
PR006498
PR006499
PR006500
PR006502
PR006504
PR006510
PR006511
PR006515

圖 5A

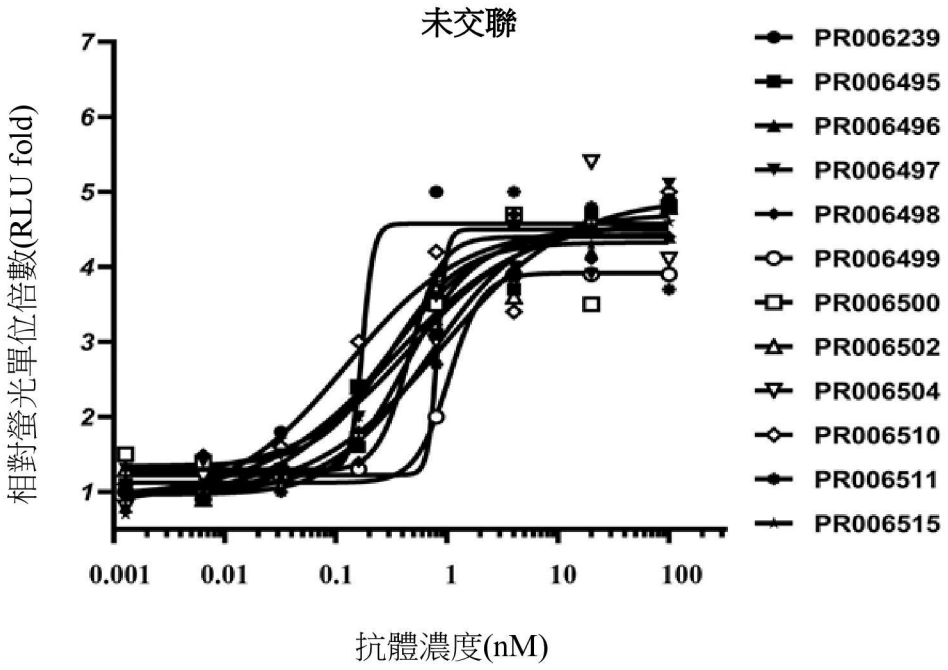

未交聯
相對螢光單位倍數(RLU fold)
7
6
5
4
3
2
1
0.001
0.01
0.1
1
10
100
PR006239
PR006495
PR006496
PR006497
PR006498
PR006499
PR006500
PR006502
PR006504
PR006510
PR006511
PR006515
抗體濃度(nM)

圖 5B

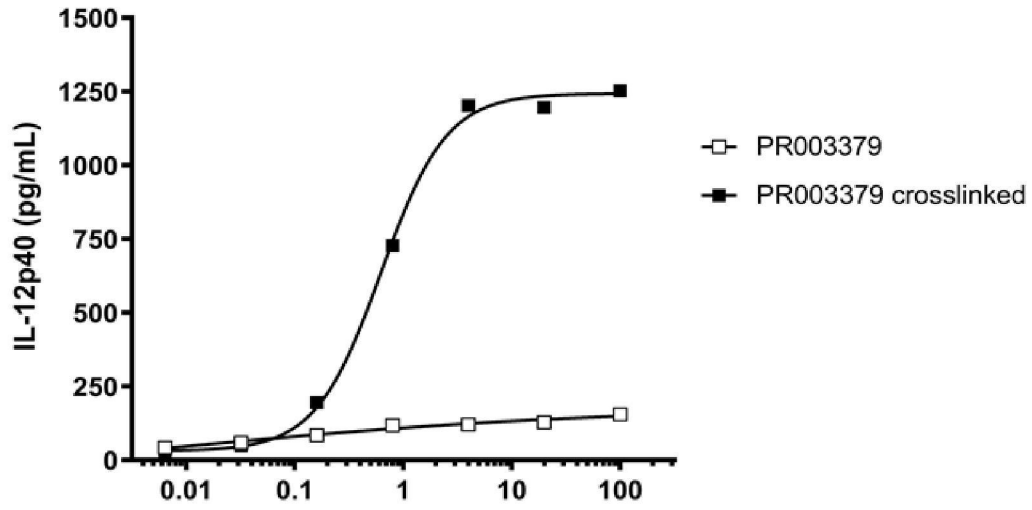

IL-12p40 (pg/mL)
1500
1250
1000
750
500
250
0
0.01
0.1
1
10
100
PR003379
PR003379 crosslinked
抗體濃度(nM)

圖 6A

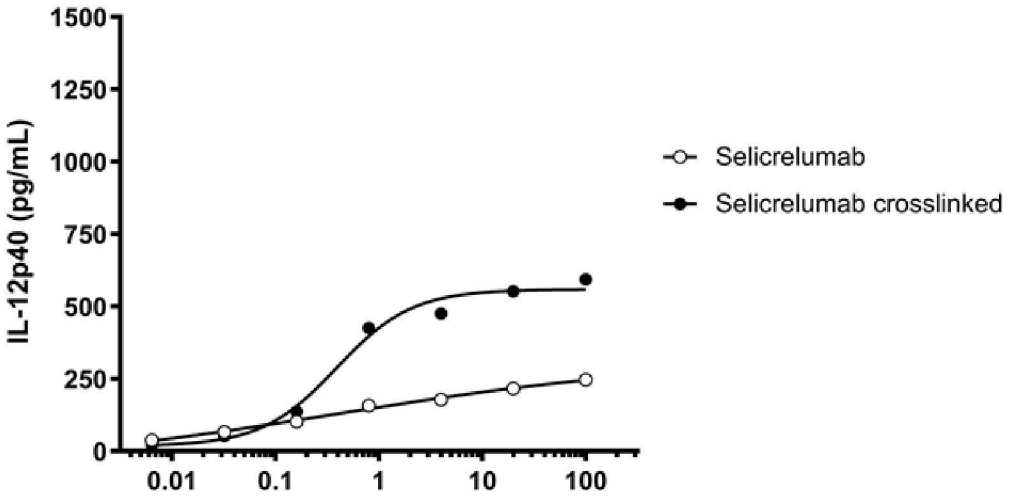

1500
1250
1000
750
500
250
0
IL-12p40 (pg/mL)
0.01
0.1
1
10
100
Selicrelumab
Selicrelumab crosslinked
抗體濃度(nM)

圖 6B

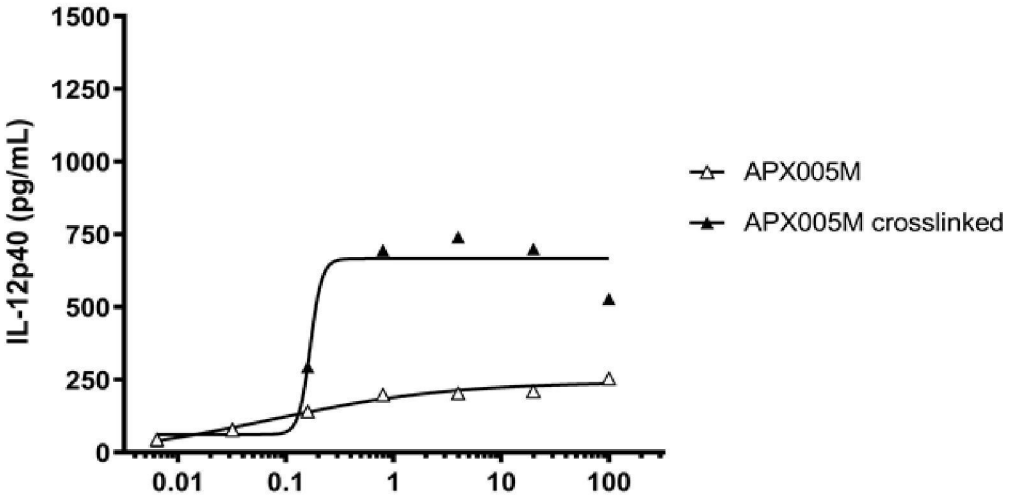
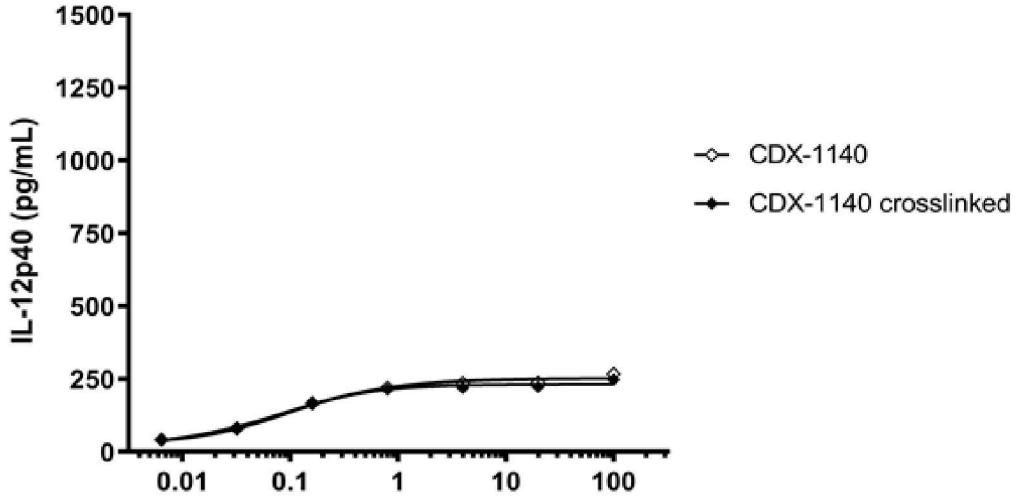
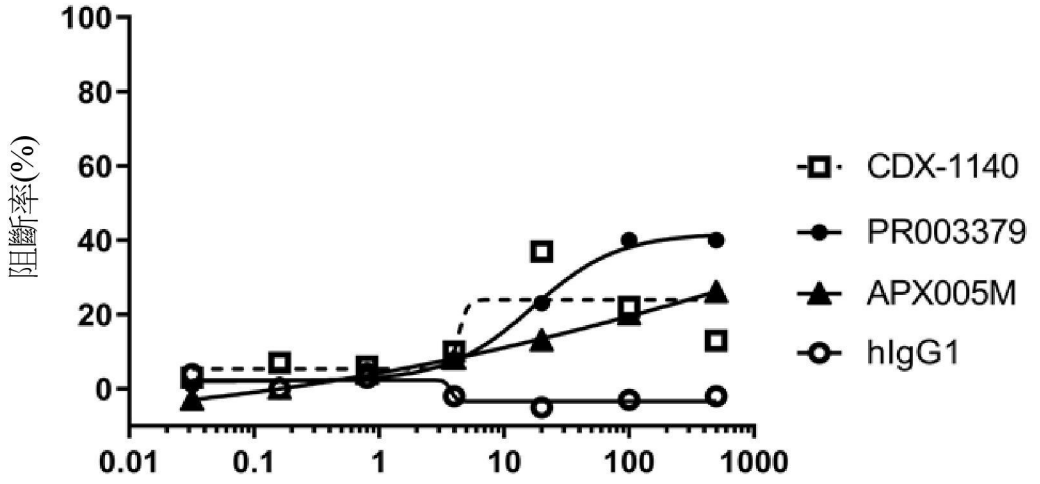

1500
1250
1000
750
500
250
0
IL-12p40 (pg/mL)
0.01
0.1
1
10
100
APX005M
APX005M crosslinked
抗體濃度(nM)

圖 6C



抗體濃度(nM)

圖 6D



抗體濃度(nM)

圖 7

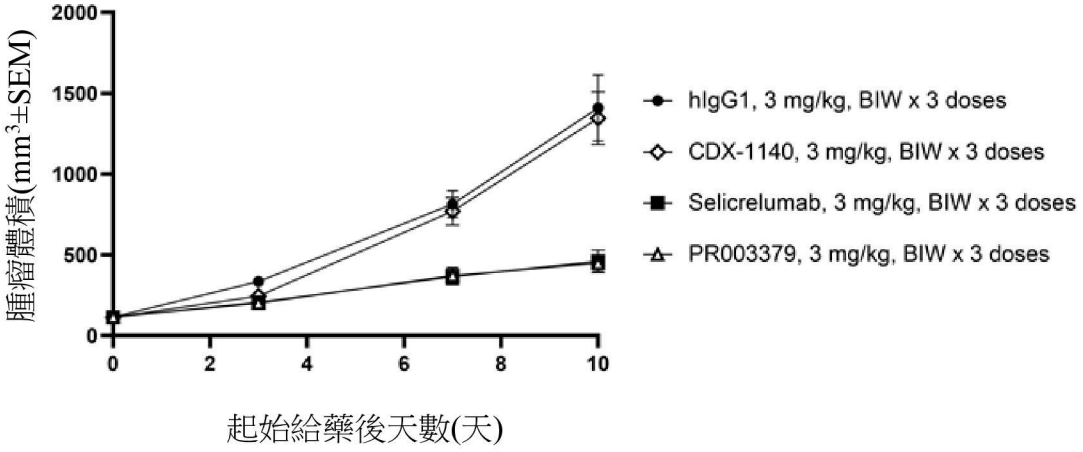

腫瘤體積(mm³±SEM)
2000
1500
1000
500
0
0
2
4
6
8
10
起始給藥後天數(天)
hIgG1, 3 mg/kg, BIW x 3 doses
CDX-1140, 3 mg/kg, BIW x 3 doses
Selicrelumab, 3 mg/kg, BIW x 3 doses
PR003379, 3 mg/kg, BIW x 3 doses

圖 8A

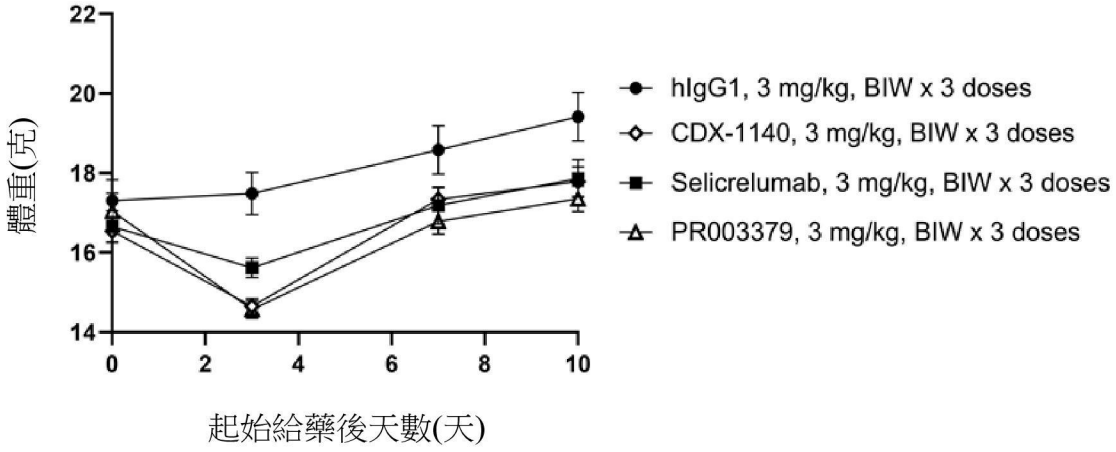

體重(克)
22
20
18
16
14
0
2
4
6
8
10
起始給藥後天數(天)
hIgG1, 3 mg/kg, BIW x 3 doses
CDX-1140, 3 mg/kg, BIW x 3 doses
Selicrelumab, 3 mg/kg, BIW x 3 doses
PR003379, 3 mg/kg, BIW x 3 doses

圖 8B