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(71)申請人：大陸商山東先聲生物製藥有限公司 (中國大陸) NO. 1, HEILONGJIANG ROAD,
YANTAI ECONOMIC AND TECHNOLOGICAL DEVELOPMENT ZONE, YANTAI,
SHAN (CN)

中國山東省煙臺市煙臺經濟技術開發區黑龍江路 1 號

(72)發明人：胡穎瑩 HU, YINGYING (CN)；付雅媛 FU, YAYUAN (CN)；劉雷 LIU, LEI

(CN)；曹卓曉 CAO, ZHUOXIAO (CN)；唐任宏 TANG, RENHONG (CN)；任晉

生 REN, JINSHENG (CN)

(74)代理人：王立成；余宗學

(56)參考文獻：

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審查人員：張維纓

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(54)名稱

SIRPa 突變體及其應用

(57)摘要

本發明提供了一種高親和力 SIRPa 多肽，其包含相對於野生型蛋白的至少一個胺基酸變化；和具有相對於野生型蛋白增加的對 CD47 的親和力。還提供了編碼 SIRPa 多肽的核酸分子以及表現該多肽的載體。還提供了藥物組合物和方法，用於治療表現 CD47 的腫瘤。

The application discloses a high affinity SIRPa polypeptide, which comprises at least one amino acid mutations compared with a wild type protein, the polypeptide also has an increased affinity for CD47 compared with the wild-type protein. The application also discloses the nucleic acid molecule which encoding the SIRPa polypeptide and the vector expressing the polypeptide. And the drug compositions and methods are also provided, for the treatment of CD47-expressing tumors.



公告本

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【發明摘要】

【中文發明名稱】 SIRPa突變體及其應用

【英文發明名稱】 SIRPa MUTANT AND APPLICATION THEREOF

【中文】

本發明提供了一種高親和力SIRPa多肽，其包含相對於野生型蛋白的至少一個胺基酸變化；和具有相對於野生型蛋白增加的對CD47的親和力。還提供了編碼SIRPa多肽的核酸分子以及表現該多肽的載體。還提供了藥物組合物和方法，用於治療表現CD47的腫瘤。

【英文】

The application discloses a high affinity SIRPa polypeptide, which comprises at least one amino acid mutations compared with a wild type protein, the polypeptide also has an increased affinity for CD47 compared with the wild-type protein. The application also discloses the nucleic acid molecule which encoding the SIRPa polypeptide and the vector expressing the polypeptide. And the drug compositions and methods are also provided, for the treatment of CD47-expressing tumors.

【指定代表圖】 無

【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】 SIRPa突變體及其應用

【英文發明名稱】 SIRPa MUTANT AND APPLICATION THEREOF

【技術領域】

【0001】 本發明關於生物醫藥領域，具體而言，關於SIRPa突變體及其應用。

【先前技術】

【0002】 CD47是一種具有醣基化的跨膜蛋白，活化後可以介導細胞增殖、遷移、吞噬以及細胞凋亡，免疫穩態等一系列過程。CD47的配體包括訊號調節蛋白（Signal regulatory protein α ，SIRPa）、血小板反應蛋白-1（TSP-1）和整合素。CD47在多種惡性腫瘤中表現普遍上調，CD47高表現程度與癌症惡化的治療反應和預後相關。CD47/SIRPa「別吃我」機制被認為是腫瘤免疫學中一個具有潛力的新機制。CD47在腫瘤細胞的高表現能夠抑制巨噬細胞的活化及避免後續對腫瘤細胞的吞噬作用。目前，一些針對CD47的免疫療法，包括單株抗體、融合蛋白、CAR-T細胞、ADC都已進入臨床研究階段，多種產品的作用機制、安全性和療效各有不同。

【0003】 現在已進行臨床研究階段的藥物包括多種CD47單抗、雙抗及SIRPa蛋白。其中開發最早，臨床進展最快的CD47抗體magrolimab為Forty Seven公司開發。現正在推進針對血液瘤和實體瘤的臨床II/III期試驗。但其引起一定的安全性問題，三級以上副作用包括14%左右的貧血事件，及16%左右的

中性粒細胞減少事件。SIRPa蛋白類藥物臨床進展最快的包括Trillium公司開發的TTI621、TTI622兩款藥物。TTI621為天然的SIRPa IgV結構域耦合人IgG1的Fc段，Trillium公司正在開發TTI621針對血液瘤的臨床I期試驗，單藥治療NHL有一定客觀反應率。三級以上副作用包括9%左右的貧血事件，20%的血小板減少症及9%左右的中性粒細胞減少事件。TTI622為天然的SIRPa IgV結構域耦合人IgG4的Fc段，現有療效及安全性數據優於TTI621。除此之外，多款免疫檢查點與CD47抗體的聯用或雙抗，腫瘤相關抗原抗體與CD47抗體的聯用或雙抗等也已陸續進入臨床。

【發明內容】

【0004】 除上述雙抗聯用機制外，提高SIRPa對CD47的親和力，提高阻斷CD47與SIRPa相互作用的效率，促進解除對巨噬細胞吞噬功能的抑制，可能對CD47標靶藥物領域提供新的研發思路和創新意義。有鑑於此，特提出本發明。

【0005】 本發明提供一種具有更高靶點結合活性的SIRPa變體及其融合蛋白，用於檢測CD47的存在或程度，阻斷SIRPa與CD47的結合，實現腫瘤的免疫治療。

【0006】 本發明的第一態樣提供了一種用於抑制CD47+疾病細胞的生長和/或增殖的多肽，其包含訊號調節蛋白a(SIRPa)突變體或其片段，所述突變體相對於野生型SIRPa在選自殘基31、殘基37、殘基51、殘基66、殘基68或殘基82具有至少一個胺基酸修飾；較佳地，所述胺基酸修飾為取代；較佳地，所述野生型SIRPa具有根據SEQ ID NO:1-2中任一個的序列。

【0007】 在一些實施例中，所述SIRPa突變體包含選自I31、Q37、N51、L66、K68或T82的至少一個胺基酸修飾。

【0008】 在一些實施例中，所述胺基酸修飾選自下列至少一個胺基酸修飾：（1）I31M；I31Y；（2）Q37T；（3）N51G；N51R；N51A；N51E；N51F；N51K；N51L；N51M；N51Q；N51T；N51W；（4）L66A；L66V；L66P；L66M；L66N；L66E；L66K；L66H；（5）K68D；K68M；K68Q；K68L；K68F；K68I；或（6）T82F；T82D；T82N；T82E；T82Q；T82G；T82H；T82L；T82I；T82K；T82M；T82P；T82R；T82V；T82W；T82Y。

【0009】 在一些實施例中，所述多肽，相對於具有SEQ ID NO：1的野生型SIRPa，包含選自下列群組的胺基酸突變：

（1）N51G；（2）N51R；（3）I31M；（4）I31Y；（5）I31M；N51G；（6）I31M；N51R；（7）I31Y；N51G；（8）I31Y；N51R；（9）Q37T；N51G；（10）Q37T；N51R；（11）I31Y；N51R；L66A；（12）I31Y；N51R；L66V；（13）I31Y；N51R；L66P；（14）I31Y；N51R；L66M；（15）I31Y；N51R；L66N；（16）I31Y；N51R；L66E；（17）I31Y；N51R；L66K；（18）I31Y；N51R；L66H；（19）N51A；（20）N51E；（21）N51F；（22）N51K；（23）N51L；（24）N51M；（25）N51Q；（26）N51T；（27）N51W；（28）I31M；N51R；L66N；K68D；（29）I31M；N51R；L66M；K68M；（30）I31Y；N51R；L66N；K68D；（31）I31M；N51R；L66N；K68Q；（32）I31M；N51R；L66N；K68L；（33）I31Y；N51R；L66N；K68F；（34）I31M；N51R；L66N；K68I；（35）I31Y；N51R；L66N；T82F；（36）I31Y；N51R；L66N；T82D；

(37) I31Y ; N51R ; L66N ; T82N ; (38) I31Y ; N51R ; L66N ; T82E ;
(39) I31Y ; N51R ; L66N ; T82Q ; (40) I31Y ; N51R ; L66N ; T82G ;
(41) I31Y ; N51R ; L66N ; T82H ; (42) I31Y ; N51R ; L66N ; T82L ;
(43) I31Y ; N51R ; L66N ; T82I ; (44) I31Y ; N51R ; L66N ; T82K ;
(45) I31Y ; N51R ; L66N ; T82M ; (46) I31Y ; N51R ; L66N ; T82P ;
(47) I31Y ; N51R ; L66N ; T82R ; (48) I31Y ; N51R ; L66N ; T82V ;
(49) I31Y ; N51R ; L66N ; T82W ; (50) I31Y ; N51R ; L66N ; T82Y ;
(51) I31M ; N51R ; L66N ; K68Q ; T82G ; (52) I31M ; N51R ; L66N ;
K68Q ; T82H ; (53) I31M ; N51R ; L66N ; K68Q ; T82L ; (54) I31M ;
N51R ; L66N ; K68Q ; T82V ; (55) I31M ; N51R ; L66N ; K68L ; T82G ;
(56) I31M ; N51R ; L66N ; K68L ; T82H ; (57) I31M ; N51R ; L66N ;
K68L ; T82L ; (58) I31M ; N51R ; L66N ; K68L ; T82V ; (59) I31M ;
N51R ; L66N ; K68I ; T82G ; (60) I31M ; N51R ; L66N ; K68I ; T82H ;
(61) I31M ; N51R ; L66N ; K68I ; T82L ; (62) I31M ; N51R ; L66N ;
K68I ; T82V 。

【0010】 或，相對於具有SEQ ID NO：2的野生型SIRPa，包含N51R；
N51M或N51W突變。

【0011】 在一些實施例中，所述多肽在其N端或C端與免疫球蛋白Fc區融合；較佳的，所述免疫球蛋白Fc區選自人IgG1、IgG2或IgG4的Fc區或其突變型；更佳的，所述免疫球蛋白Fc區選自人IgG1的Fc區或其突變型。

【0012】 在一些實施例中，所述Fc突變型包含相對於野生型人IgG1的以下胺基酸修飾中的至少一個：L234A、L235A、G237A和N297A；較佳的，所

述胺基酸修飾包含（1）N297A突變；（2）L234A、L235A以及G237A突變；或（3）L234A、L235A、G237A以及N297A突變。

【0013】 在一些實施例中，所述Fc突變型與人IgG Fc區的野生型相比展現消除或減少的效應功能，消除或降低的C1q結合和Fc γ 受體結合。

【0014】 在一些實施例中，所述多肽具有SEQ ID NO: 4-14，17-51，55-110中任一個的胺基酸序列。

【0015】 在一些實施例中，所述多肽具有至少 6×10^{-9} M的針對CD47的KD。

【0016】 在一些實施例中，所述多肽還連接有其他功能性分子，所述其他功能性分子可選自以下一種或多種：訊號肽、蛋白標籤、其他抗原結合分子、白血球介素、細胞激素、類固醇、抗炎劑、免疫調節劑或細胞毒素。

【0017】 在一些實施例中，所述多肽是單體的，或多聚體的。

【0018】 本發明的第二態樣提供了一種嵌合抗原受體（CAR），其至少包含細胞外抗原結合結構域、跨膜結構域和胞內訊號傳導結構域，所述細胞外抗原結合結構域包含上述任一種多肽。

【0019】 本發明的第三態樣提供了一種免疫作用細胞，其表現上述嵌合抗原受體，或包含編碼請求項12所述嵌合抗原受體的核酸片段；較佳地，所述免疫作用細胞選自T細胞、NK細胞（natural killer cell）、NKT細胞（natural killer T cell）、DNT細胞（double negative T cell）、單核細胞、巨噬細胞、樹突狀細胞或肥大細胞，所述T細胞較佳自細胞毒殺型T細胞、調節型T細胞或輔助型T細胞；較佳地，所述免疫作用細胞為自體免疫作用細胞或同種異體免疫作用細胞。

【0020】本發明的第四態樣提供了一種核酸分子，其編碼上述任一種多肽。

【0021】本發明的第五態樣提供了一種表現載體，其包含上述核酸片段。

【0022】本發明的第六態樣提供了一種宿主細胞，其包含上述載體；較佳地，所述細胞為原核細胞或真核細胞，例如細菌（大腸桿菌）、真菌（酵母）、昆蟲細胞或哺乳動物細胞（CHO細胞株或293T細胞株）。

【0023】本發明的第七態樣提供了一種製備上述任一種多肽的方法，其包括培養所述宿主細胞，以及分離所述宿主細胞表現的多肽。

【0024】本發明的第八態樣提供了一種製備上述免疫作用細胞的方法，其包括將編碼上述CAR的核酸片段導入所述免疫作用細胞，可選地，還包括啟動所述免疫作用細胞表現上述CAR。

【0025】本發明的第九態樣提供了一種藥物組合物，包含可藥用的載體和能夠有效地抑制CD47+疾病細胞的生長或增殖的量的上述任一種多肽，免疫作用細胞，核酸分子，表現載體，或上述任一項方法製備獲得的產品。

【0026】本發明的第十態樣提供了一種套組，其包含上述任一種多肽，免疫作用細胞，核酸分子，表現載體，宿主細胞，所述方法製備獲得的產品，或藥物組合物。

【0027】本發明的第十一態樣提供了上述任一種多肽，免疫作用細胞，核酸分子，表現載體，宿主細胞，所述方法製備獲得的產品，或藥物組合物用於製備治療表現CD47的腫瘤的藥物的用途；較佳地，所述腫瘤是CD47陽性血

液腫瘤或CD47陽性實體瘤，再較佳的，所述CD47陽性血液腫瘤包括白血病、淋巴瘤和骨髓瘤，所述CD47陽性實體瘤包括肉瘤。

【0028】 本發明的第十二態樣提供了一種治療表現CD47的腫瘤的方法，所述方法包括向受試者施用有效量的所述多肽，免疫作用細胞，核酸分子，表現載體，宿主細胞，所述方法製備獲得的產品，藥物組合物；較佳地，所述腫瘤是CD47陽性血液腫瘤或CD47陽性實體瘤，再較佳的，所述CD47陽性血液腫瘤包括白血病、淋巴瘤和骨髓瘤，所述CD47陽性實體瘤包括肉瘤。

【0029】 本發明的第十三態樣提供了所述多肽，免疫作用細胞，核酸分子，表現載體，宿主細胞，所述方法製備獲得的產品，或藥物組合物用於治療表現CD47的腫瘤；較佳地，所述腫瘤是CD47陽性血液腫瘤或CD47陽性實體瘤，再較佳的，所述CD47陽性血液腫瘤包括白血病、淋巴瘤和骨髓瘤，所述CD47陽性實體瘤包括肉瘤。

【0030】 本發明的第十四態樣提供了一種檢測生物學樣品中CD47表現的方法，其特徵在於，所述方法包括在所述多肽與CD47之間能夠形成複合物的條件下，使所述生物學樣品與所述多肽接觸；較佳地，所述方法還包括檢測所述複合物的形成，指示樣品中CD47的存在或表現程度。

【0031】 相關申請案的交叉引用：

本申請案請求以下2件中國發明專利申請案的權益和優先權，在此將它們的全部內容以援引的方式整體併入本文中：2021年10月31日向中國國家知識產權局提交的第202111283381.5號專利申請案；以及2022年7月7日向中國國家知識產權局提交的第202210800901.3號專利申請案。

【圖式簡單說明】**【0032】**

圖1、酵素結合免疫吸附分析（ELISA）方法檢測SIRPa-Fc融合蛋白與hCD47 ECD-His的結合活性；

圖2、酵素結合免疫吸附分析（ELISA）方法檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc的結合活性；

圖3、流式細胞實驗（FACS）檢測SIRPa-Fc融合蛋白與Jurkat細胞的結合活性；

圖4、流式細胞實驗（FACS）檢測SIRPa-Fc融合蛋白與Raji細胞的結合活性；

圖5、檢測SIRPa-Fc融合蛋白阻斷Raji與受體SIRPa V1的結合活性；

圖6、檢測SIRPa-Fc融合蛋白阻斷Raji與受體SIRPa V2的結合活性；

圖7、酵素結合免疫吸附分析（ELISA）方法檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc的結合活性；

圖8、流式細胞實驗（FACS）檢測SIRPa-Fc融合蛋白與Jurkat細胞的結合活性；

圖9、酵素結合免疫吸附分析（ELISA）方法檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc的結合活性；

圖10、流式細胞實驗（FACS）檢測SIRPa-Fc融合蛋白與Jurkat的結合活性；

圖11、檢測SIRPa-Fc融合蛋白介導的對Raji細胞的吞噬作用；

圖12、檢測SIRPa-Fc融合蛋白介導的對DLD1細胞的吞噬作用；

圖13、檢測SIRPa-Fc融合蛋白介導的對腫瘤生長的抑制作用。

【實施方式】

【0033】 除非本發明另外定義，與本發明相關的科學和技術術語應具有本發明所屬技術領域中具有通常知識者所理解的含義。

【0034】 此外，除非本文另有說明，本文單數形式的術語應包括複數形式，複數形式的術語應包括單數形式。更具體地，如在本說明書和所附請求項中所使用的，除非另外明確指出，否則單數形式「一種」和「這種」包括複數指示物。

【0035】 本文術語「包括」、「包含」和「具有」之間可互換使用，旨在表示方案的包含性，意味著所述方案可存在除所列出的元素之外的其他元素。同時應當理解，在本文中使用「包括」、「包含」和「具有」描述，也提供「由……組成」方案。示例性地，「一種組合物，包括A和B」，應當理解為以下技術方案：由A和B組成的組合物，以及除A和B外，還含有其他組分的組合物，均落入前述「一種組合物」的範圍內。

【0036】 本文術語「和/或」在本文使用時，包括「和」、「或」和「由所屬術語連結的要素的全部或任何其他組合」的含義。

【0037】 本文術語「SIRPa」是指在巨噬細胞上表現的細胞表面I型跨膜蛋白，它是Ig超家族中SIRP/SHPS(CD172)家族的成員。術語「SIRPa」可以與「訊號調節蛋白a」、「SIRP α 」或「SIRP-alpha」互換使用。SIRPa是CD47的受體。在人類中，發現SIRPa蛋白主要有兩種形式。一種形式(變體1或V1型)的胺基酸序列作為NCBI RefSeq NP_542970.1列出(殘基27-504構成成熟型)。另一種形式(變體2或V2型)有13個胺基酸不同並且胺基酸序列在GenBank中作為

CAA71403.1列出(殘基30-504構成成熟型)。這兩種形式的SIRPa構成了存在於人類中的大約80%的各種類型的SIRPa。

【0038】術語「CD47+」、「CD47陽性」通常是指在生物體或細胞表面表現CD47蛋白、其片段，或者其中經過1個或多個胺基酸取代的其突變體的特性。CD47陽性細胞可以為過表現CD47的細胞。所述CD47陽性細胞通常可以作為疾病的指示。例如在疾病情況下，所述CD47陽性細胞表面CD47蛋白密度會超過該種細胞在正常條件下所具有的CD47蛋白密度。在某些實施方式中，所述腫瘤或腫瘤細胞可為CD47陽性。例如，所述腫瘤可選自以下群組：CD47陽性血液腫瘤和/或CD47陽性實體瘤。

【0039】本文術語「CD47蛋白」通常是指整合素關聯蛋白(IAP)，其為一種屬於免疫球蛋白超家族的多次跨膜受體。例如，CD47蛋白可與膜整合素(membrane integrins)結合，並與其配體凝血栓蛋白-1(thrombospondin-1，TSP-1)和訊號調節蛋白 α (signal-regulatory protein alpha，SIRP α)結合。CD47蛋白廣泛表現於細胞膜表面。在本申請案中，所述CD47蛋白可包括人CD47的任何變體、同種型和物種同系物。

【0040】本文術語「突變體」通常是指與不具備任何突變/修飾的蛋白質具有序列同源性的蛋白質性分子，其保留至少一部分生物活性蛋白的治療和/或生物活性。例如，突變體蛋白質相較於參照生物活性蛋白可共享至少60%、65%、70%、75%、80%、85%、90%、95%、96%、97%、98%或99%的胺基酸序列同一性。在一些實施方案中，「突變體」可以包括經有意地修飾(例如透過定點突變、編碼基因的合成、插入或偶然透過突變)的蛋白質。

【0041】 在本發明中，某胺基酸序列中的某胺基酸殘基「相對於」另一胺基酸序列中的某胺基酸殘基通常是指，在最佳化條件下進行胺基酸序列比對時所獲得的胺基酸殘基對應關係。所述序列比對可透過本發明所屬技術領域中具有通常知識者瞭解的方式進行，例如，使用BLAST、BLAST-2、ALIGN、NEEDLE或Megalign(DNASTAR)軟體等。本發明所屬技術領域中具有通常知識者能夠確定用於比對的適當參數，包括在所比較的全長序列中實現最佳比對所需要的任何演算法。

【0042】 本申請案所述的胺基酸取代可以為非保守取代。所述非保守取代可包括以非保守的形式改變目標蛋白或多肽中的胺基酸殘基，例如將具有某種側鏈大小或某種特性(例如，親水性)的胺基酸殘基變為具有不同側鏈大小或不同特性(例如，疏水性)的胺基酸殘基。

【0043】 所述胺基酸取代也可以為保守取代。所述保守取代可包括以保守的形式改變目標蛋白或多肽中的胺基酸殘基，例如將具有某種側鏈大小或某種特性(例如，親水性)的胺基酸殘基變為具有相同或相似側鏈大小或者相同或相似特性(例如，仍為親水性)的胺基酸殘基。這樣的保守取代通常不會對所產生的蛋白質的結構或功能帶來很大影響。在本申請案中，作為所述融合蛋白、其片段，或者其中經過1個或多個胺基酸取代的其突變體的胺基酸序列變體可包括不顯著改變蛋白質結構或其功能(例如，阻斷CD47與其配體結合的能力)的保守胺基酸取代。

【0044】 作為示例，下述各群組中每群組內各胺基酸間的相互取代在本申請案中可被認為是保守取代：

1)丙胺酸(A)、絲胺酸(S)、蘇胺酸(T)；

- 2)天門冬胺酸(D)、穀胺酸(E)；
- 3)天門冬醯胺(N)、穀胺醯胺(Q)；
- 4)精胺酸(R)、離胺酸(K)、組胺酸(H)；
- 5)異白胺酸(I)、白胺酸(L)、甲硫胺酸(M)、纈胺酸(V)；和
- 6)苯丙胺酸(F)、酪胺酸(Y)、色胺酸(W)。

【0045】 本文術語「融合蛋白」通常指由兩個或更多個蛋白或多肽融合得到的蛋白。融合蛋白可透過重組DNA技術人工製備。例如，編碼所述兩個或更多個蛋白或多肽的基因或核酸分子可彼此連接而形成融合基因或融合的核酸分子，該融合基因或融合的核酸分子可編碼所述融合蛋白。所述融合基因的轉譯可以產生單一多肽，其可以具有融合前的所述兩個或更多個蛋白或多肽中至少一個、甚至每一個的性質。

【0046】 在本發明中，所述融合蛋白包括能夠特異性結合所述CD47蛋白的人SIRP α 結構域和免疫球蛋白Fc區，其中所述人SIRP α 結構域可以與所述免疫球蛋白Fc區直接或間接相連。例如，所述人SIRP α 結構域可位於所述免疫球蛋白Fc區的N端或C端。例如，所述人SIRP α 結構域的C端可以與所述免疫球蛋白Fc的N端直接或間接連接，或所述免疫球蛋白Fc的C端與人SIRP α 結構域的N端直接或間接連接。例如，所述人SIRP α 結構域可以與所述免疫球蛋白Fc透過連接子相連。

【0047】 本文術語「免疫球蛋白Fc區」通常是指抗體結構Y形結構的基座區域，又叫做片段可結晶區(Fragment crystallizable region, Fc region)。在IgG、IgA和IgD抗體同種型中，Fc區可由兩個相同的蛋白質片段組成，其來自抗體兩條重鏈的第二和第三恆定結構域；IgM和IgE的Fc區可在每條多肽鏈中含有三個

重鏈恆定結構域。IgG的Fc區具有高度保守的N-糖基化點位。在某些實施方式中，所述免疫球蛋白Fc區可包含IgG的Fc區。在某些實施方式中，所述免疫球蛋白Fc區可包含重鏈恆定區的CH2和CH3區域。在某些實施方式中，所述免疫球蛋白Fc區可包含鉸鏈區。例如，所述免疫球蛋白Fc區可包含選自下述任一項所示的胺基酸序列：SEQ ID NO：3。

【0048】 作為可選擇的實施方案，Fc區引入一個或多個改變，通常不多於約5個這樣的改變，包括影響某些Fc特性的胺基酸置換。

【0049】 本文術語「IgG」通常是指免疫球蛋白G(Immunoglobulin G)。IgG是人的免疫球蛋白之一。根據IgG分子中的 γ 鏈抗原性差異，人IgG有四個亞型：IgG1、IgG2、IgG3和IgG4。在本申請案中，術語「IgG1」通常是指IgG中佔比最高的一類亞型，與Fc受體有較高親和性。例如，所述IgG可為人IgG。又例如，所述IgG可選自以下群組：IgG1和/或IgG4。

【0050】 本文術語「KD」通常是指特定的抗體-抗原相互作用的解離平衡常數，單位為M(mol/L)，其中較低KD表示較高親和力。KD計算方式如下：KD = K_d/K_a ，其中Kd表示解離速率，Ka表示結合速率。可採用本領域習知的方法測量平衡解離常數KD，如表面電漿共振（例如Biacore）或平衡透析法測定，示例性地，可參見本文實施例4所示KD值獲得方法。

【0051】 本文術語「抗原結合分子」按最廣義使用，是指特異性結合抗原的分子。示例性地，抗原結合分子包括但不限於抗體或抗體模擬物。「抗體模擬物」是指能夠與抗原特異性結合，但與抗體結構無關的有機化合物或結合域，示例性地，抗體模擬物包括但不限於affibody、affitin、affilin、經設計的錨蛋白重複蛋白(DARPin)、核酸適體或Kunitz型結構域肽。

【0052】 本文術語「嵌合抗原受體（CAR）」是指經改造以在免疫作用細胞上表現並且特異性結合抗原的人工細胞表面受體，其包含至少(1)細胞外抗原結合結構域，例如抗體的可變重鏈或輕鏈，(2)錨定CAR進入免疫作用細胞的跨膜結構域，和(3)胞內訊號傳導結構域。CAR能夠利用細胞外抗原結合結構域以非MHC限制性的方式將T細胞和其它免疫作用細胞重定向至所選擇的標靶，例如癌細胞。

【0053】 本文術語「核酸分子」包括包含核苷酸的聚合物的任何化合物和/或物質。每個核苷酸由鹼基，特別是嘌呤或嘧啶鹼基(即胞嘧啶(C)、鳥糞嘌呤(G)、腺嘌呤(A)、胸腺嘧啶(T)或尿嘧啶(U))、糖(即去氧核糖或核糖)和磷酸基團組成。通常，核酸分子由鹼基的序列描述，由此所述鹼基代表核酸分子的一級結構(線性結構)。鹼基的序列通常表示為5'至3'。在本文中，術語核酸分子涵蓋去氧核糖核酸(DNA)，包括例如互補DNA(cDNA)和基因組DNA、核糖核酸(RNA)，特別是信使RNA(mRNA)、DNA或RNA的合成形式，以及包含兩種或更多種這些分子的混合的聚合物。核酸分子可以是線性的或環狀的。此外，術語核酸分子包括有義股和反義股二者，以及單股和雙股形式。而且，本文所述的核酸分子可含有天然存在的或非天然存在的核苷酸。非天然存在的核苷酸的例子包括具有衍生的糖或磷酸骨架鍵合或化學修飾的殘基的修飾的核苷酸鹼基。核酸分子還涵蓋DNA和RNA分子，其適合作為載體用於在體外和/或體內，例如在宿主或患者中，直接表現本發明的抗體。此類DNA(例如cDNA)或RNA(例如mRNA)載體可以是未修飾的或修飾的。例如，可以對mRNA進行化學修飾以增強RNA載體的穩定性和/或被編碼分子的表現，從而可以將mRNA注入到受試者內以在體內產生抗體(參見例如Stadler等人，Nature Medicine 2017，

published online 2017年6月12日，doi：10.1038/nm.4356或EP 2 101 823 B1)。本文「分離的」核酸指已經與其天然環境的組分分開的核酸分子。分離的核酸包括在下述細胞中含有的核酸分子，所述細胞通常含有該核酸分子，但該核酸分子存在於染色體外或存在於不同於其天然染色體位置的染色體位置處。

【0054】 本文術語「表現載體」是指能夠擴增與其連接的另一個核酸的核酸分子。該術語包括作為自我複製型核酸結構的載體以及整合入已引入該載體的宿主細胞的基因組中的載體。某些載體能夠指導與它們可操作連接的核酸的表現。這樣的載體在本文中稱為「表現載體」。

【0055】 本文術語「宿主細胞」是指細胞中引入外源核酸的細胞，包括這種細胞的後代。宿主細胞包括「轉型體」和「經轉型的細胞」，其包括初代的經轉型的細胞和來源於其的後代，而不考慮繼代的次數。後代在核酸內容物上可能與親代細胞不完全相同，而是可以包含突變。本文中包括具有與在初始轉型的細胞中篩選或選擇的相同功能或生物學活性的突變體後代。

【0056】 本文術語「藥物組合物」是指這樣的製劑，其以允許包含在其中的活性成分的生物學活性有效的形式存在，並且不含有對施用所述藥物組合物的受試者具有不可接受的毒性的另外的成分。

【0057】 本文術語「治療」是指外科手術或藥物處理（surgical or therapeutic treatment），其目的是預防、減緩（減少）治療對象中不希望的生理變化或病變，如癌症的進展。有益的或所希望的臨床結果包括但不限於症狀的減輕、疾病程度減弱、疾病狀態穩定（即，未惡化）、疾病進展的延遲或減慢、疾病狀態的改善或緩和、以及緩解（無論是部分緩解或完全緩解），無論是可檢測的或不可檢測的。需要治療的對象包括已患有病症或疾病的對象以及

易於患上病症或疾病的對象或打算預防病症或疾病的對象。當提到減緩、減輕、減弱、緩和、緩解等術語時，其含義也包括消除、消失、不發生等情況。

【0058】 本文術語「受試者」是指接受對如本發明所述的特定疾病或病症的治療的生物體。對象和患者的示例包括接受疾病或病症治療的哺乳動物，如人、靈長類動物（例如，猴）或非靈長類哺乳動物。

【0059】 本文術語「有效量」指單獨給予或與另一治療劑組合給予細胞、組織或對象時能有效防止或緩解疾病病症或該疾病進展的治療劑用量。

「有效量」還指足以緩解症狀，例如治療、治癒、防止或緩解相關醫學病症，或治療、治癒、防止或緩解這些病症的速度增加的化合物用量。當將活性成分單獨給予個體時，治療有效劑量單指該成分。當應用某一組合時，治療有效劑量指產生治療作用的活性成分的組合用量，而無論是組合、連續或同時給予。

【0060】 本文術語「癌症」指向或描述哺乳動物中典型地以不受調節的細胞生長為特徵的生理狀況。此定義中包括良性和惡性癌症。本文術語「腫瘤」或「瘤」是指所有贅生性(neoplastic)細胞生長和增殖，無論是惡性的還是良性的，及所有癌前(pre-cancerous)和癌性細胞和組織。術語「癌症」和「腫瘤」在本文中提到時並不互相排斥。

【0061】 在本申請案中，術語「CD47陽性血液腫瘤」通常是指過表現CD47的血液腫瘤，其中可包括各類白血病、淋巴瘤和骨髓瘤。所述「白血病」通常是指血液的一種癌症，其中產生了過多的對抵抗感染不產生作用的白血球，由此擠佔了組成血液的其他部分，如血小板和紅血球。白血病可分為急性或慢性白血病。

【0062】 在本申請案中，術語「CD47陽性實體瘤」通常是指過表現CD47的實體瘤或有形瘤，其可以透過臨床檢查，例如，X光攝影、電腦斷層攝影、超音波檢查或者觸診檢查出有形腫塊。主要類別可包括癌症(carcinoma)和肉瘤(sarcoma)。

【0063】 下面結合具體實施例來進一步描述本發明，本發明的優點和特點將會隨著描述而更為清楚。實施例中未註明具體條件者，按照常規條件或製造商建議的條件進行。所用試劑或儀器未註明生產廠商者，均為可以透過市售購買獲得的常規產品。

【0064】 本發明實施例僅是範例性的，並不對本發明的範圍構成任何限制。本發明所屬技術領域中具有通常知識者應該理解的是，在不偏離本發明的精神和範圍下可以對本發明技術方案的細節和形式進行修改或替換，但這些修改和替換均落入本發明的保護範圍內。

【0065】 實施例1 SIRPa突變的質體構築

【0066】 使用多種演算法獲得親和力提高的SIRPa突變體，設計合成相應序列，將編碼野生型SIRPa IgV和前述突變體的核酸片段複製至帶有不同Fc標籤的pTT5載體上，並按已建立的標準分子生物學方法製備質體，所述質體編碼SIRPa野生型/變體與Fc融合的蛋白。所述使用的SIRPa野生型及變體如下：

SIRPa V1、SIRPa V2、Mut10、Mut31、Mut33、Mut35、Mut38、Mut66、Mut67、Mut68、Mut69、Mut70、Mut71、Mut72、Mut73、Mut75、Mut80、Mut81、Mut83、Mut84、Mut86、Mut87、Mut88、Mut89、Mut90、Mut150、Mut152、Mut153、Mut156、Mut157、Mut158、Mut160、Mut162、Mut164、Mut174和Mut178。

【0067】 前述融合蛋白及各元件的具體序列資訊如表1所示，其中，

「SIRPa V1」表示野生型SIRPa V1的IgV片段，「SIRPa V2」表示野生型SIRPa V2的IgV片段，「Fc」表示野生型人IgG1的Fc片段，「inert Fc」表示人IgG1的Fc突變型，「MutXX」表示與野生型相比，發生突變的突變型SIRPa，「MutXX-Fc」表示突變型SIRPa與Fc的融合蛋白。「SIRPa V1/V2-Fc」表示野生型SIRPa V1/V2與SEQ ID NO：3所示的野生型Fc片段的融合蛋白。TTI621序列參考WO2019084692A1，如SEQ ID NO: 15所示。

【0068】 表1 SIRPa突變序列

突變號	序列編號	序列資訊
SIRPa V1	SEQ ID NO：1	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWF RGAGPGRELIYNQKEGHFPRVTTVSDLTKRNNMDFSIRI GNITPADAGTYCYVKFRKKGSPDDVEFKSGAGTELSVRA KPS
SIRPa V2	SEQ ID NO：2	EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQWFR GAGPARELIYNQKEGHFPRVTTVSESTKRENMDFSISIS NITPADAGTYCYVKFRKKGSPDTEFKSGAGTELSVRAKP S
Fc	SEQ ID NO：3	DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFNCSVMHEALHNHYTQKSLSLSPGK
Mut10 (V2，N51R)	SEQ ID NO：4	EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQWFR GAGPARELIYRQKEGHFPRVTTVSESTKRENMDFSISIS NITPADAGTYCYVKFRKKGSPDTEFKSGAGTELSVRAKP S
Mut31 (V1，N51G)	SEQ ID NO：5	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWF RGAGPGRELIYGQKEGHFPRVTTVSDLTKRNNMDFSIRI GNITPADAGTYCYVKFRKKGSPDDVEFKSGAGTELSVRA KPS
Mut33 (V1，N51R)	SEQ ID NO：6	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWF RGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDFSIRI GNITPADAGTYCYVKFRKKGSPDDVEFKSGAGTELSVRA KPS

突變號	序列編號	序列資訊
Mut35 (V1, I31M)	SEQ ID NO : 7	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQWFRGAGPGRELIYNQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut38 (V1, I31Y)	SEQ ID NO : 8	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFRGAGPGRELIYNQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut66 (V1, I31M/N51G)	SEQ ID NO : 9	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQWFRGAGPGRELIY GQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut67 (V1, I31M/N51R)	SEQ ID NO : 10	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQWFRGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut68 (V1, I31Y/N51G)	SEQ ID NO : 11	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFRGAGPGRELIY GQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut69 (V1, I31Y/N51R)	SEQ ID NO : 12	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFRGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut70 (V1, Q37T/N51G)	SEQ ID NO : 13	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPITWFRGAGPGRELIY GQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut71 (V1, Q37T/N51R)	SEQ ID NO : 14	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPITWFRGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
TTI621	SEQ ID NO : 15	EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQWFRGAGPARELIYNQKEGHFPRVTTVSESTKRENMDFSISISNITPADAGTY YCVKFRKGGSPDTEFKSGAGTELSVRAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Inert Fc	SEQ ID NO : 16	DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

突變號	序列編號	序列資訊
Mut72 (V1 , I31Y/N51R/L66 A)	SEQ ID NO : 17	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDATKRNNMDFSIRIGN ITPADAGTYTCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut73 (V1 , I31Y/N51R/L66 V)	SEQ ID NO : 18	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDVTKRNNMDFSIRIGN ITPADAGTYTCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut75 (V1 , I31Y/N51R/L66P)	SEQ ID NO : 19	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDPTKRNNMDFSIRIGNI TPADAGTYTCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut80 (V1 , I31Y/N51R/L66 M)	SEQ ID NO : 20	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDMTKRNNMDFSIRIGN ITPADAGTYTCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut81 (V1 , I31Y/N51R/L66 N)	SEQ ID NO : 21	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN ITPADAGTYTCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut83 (V1 , I31Y/N51R/L66E)	SEQ ID NO : 22	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDETKRNNMDFSIRIGNI TPADAGTYTCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut84 (V1 , I31Y/N51R/L66 K)	SEQ ID NO : 23	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDKTKRNNMDFSIRIGN ITPADAGTYTCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut86 (V1 , I31Y/N51R/L66 H)	SEQ ID NO : 24	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDHTKRNNMDFSIRIGN ITPADAGTYTCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut87 (V1 , I31M/N51G)	SEQ ID NO : 25	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQWFR GAGPGRELIYGQKEGHFPRVTTVSDLTKRNNMDFSIRIGNI TPADAGTYTCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut88 (V1 , I31M/N51R)	SEQ ID NO : 26	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQWFRGAGPG RELIYRQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTYTC VKFRKGGSPDDVEFKSGAGTELSVRAKPS

突變號	序列編號	序列資訊
Mut89 (V1 , I31Y/N51G)	SEQ ID NO : 27	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYGQKEGHFPRVTTVSDLTKRNNMDFSIRIGNI TPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut90 (V1 , I31Y/N51R)	SEQ ID NO : 28	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDFSIRIGNI TPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut10-Fc	SEQ ID NO : 29	EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQW FRGAGPARELIYRQKEGHFPRVTTVSESTKRENMDF SISISNITPADAGTY YCVKFRKGGSPDTEFKSGAGTELS VRAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGGSF FLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSL SLSPGK
Mut31-Fc	SEQ ID NO : 30	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQ WFRGAGPGRELIYGQKEGHFPRVTTVSDLTKRNNM DFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAG TELSVRAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYT QKSLSLSPGK
Mut33-Fc	SEQ ID NO : 31	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNM DFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAG TELSVRAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYT QKSLSLSPGK
Mut35-Fc	SEQ ID NO : 32	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYNQKEGHFPRVTTVSDLTKRNNM DFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAG TELSVRAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN

突變號	序列編號	序列資訊
		AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
Mut38-Fc	SEQ ID NO : 33	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYNQKEGHFPRVTTVSDLTKRNNMDFSI RIGNITPADAGTYYCVKFRKGSPDDVEFKSGAGTELSV RAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
Mut66-Fc	SEQ ID NO : 34	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYGQKEGHFPRVTTVSDLTKRNNMD FSIRIGNITPADAGTYYCVKFRKGSPDDVEFKSGAGTEL SVRAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
Mut67-Fc	SEQ ID NO : 35	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDF SIRIGNITPADAGTYYCVKFRKGSPDDVEFKSGAGTELS VRAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
Mut68-Fc	SEQ ID NO : 36	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYGQKEGHFPRVTTVSDLTKRNNMDFSI RIGNITPADAGTYYCVKFRKGSPDDVEFKSGAGTELSV RAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC

突變號	序列編號	序列資訊
		LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
Mut69-Fc	SEQ ID NO : 37	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDFSI RIGNITPADAGTYTCVKFRKGSPPDVEFKSGAGTELSV RAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
Mut70-Fc	SEQ ID NO : 38	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPITWF RGAGPGRELIYGQKEGHFPRVTTVSDLTKRNNMDFSI RIGNITPADAGTYTCVKFRKGSPPDVEFKSGAGTELSV RAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
Mut71-Fc	SEQ ID NO : 39	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPITWF RGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDFSI RIGNITPADAGTYTCVKFRKGSPPDVEFKSGAGTELSV RAKPSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
Mut72-Fc	SEQ ID NO : 40	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDATKRNNMDFSI RIGNITPADAGTYTCVKFRKGSPPDVEFKSGAGTELSV RAKPSDKTHTCPPCPAEEAAGAPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

突變號	序列編號	序列資訊
Mut73-Fc	SEQ ID NO : 41	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDVTKRNNMDFSI RIGNITPADAGTYTCVKFRKGSPPDVEFKSGAGTELSV RAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut75-Fc	SEQ ID NO : 42	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDPTKRNNMDFSI RIGNITPADAGTYTCVKFRKGSPPDVEFKSGAGTELSV RAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut80-Fc	SEQ ID NO : 43	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDMTKRNNMDFS IRIGNITPADAGTYTCVKFRKGSPPDVEFKSGAGTELS VRAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut81-Fc	SEQ ID NO : 44	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSI RIGNITPADAGTYTCVKFRKGSPPDVEFKSGAGTELSV RAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut83-Fc	SEQ ID NO : 45	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDETKRNNMDFSI RIGNITPADAGTYTCVKFRKGSPPDVEFKSGAGTELSV RAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY

突變號	序列編號	序列資訊
		PSDIAVEWESNGQPENNYKTTTPVLDSDGSSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut84-Fc	SEQ ID NO : 46	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDKTKRNNMDFS IRIGNITPADAGTY YCVKFRK GSPDDVEFKSGAGTELS VRAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut86-Fc	SEQ ID NO : 47	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDHTKRNNMDFS IRIGNITPADAGTY YCVKFRK GSPDDVEFKSGAGTELS VRAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut87-Fc	SEQ ID NO : 48	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYGQKEGHFPRVTTVSDLTKRNNMD FSIRIGNITPADAGTY YCVKFRK GSPDDVEFKSGAGTEL SVRAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut88-Fc	SEQ ID NO : 49	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDF SIRIGNITPADAGTY YCVKFRK GSPDDVEFKSGAGTELS VRAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut89-Fc	SEQ ID NO : 50	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYGQKEGHFPRVTTVSDLTKRNNMDFS IRIGNITPADAGTY YCVKFRK GSPDDVEFKSGAGTELS VRAKPSDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE

突變號	序列編號	序列資訊
		QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut90-Fc	SEQ ID NO : 51	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDLTKRNNMDFSIRIGNIT PADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut150 (V1 , N51A)	SEQ ID NO : 55	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRG AGPGRELIYAQKEGHFPRVTTVSDLTKRNNMDFSIRIGNIT PADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS
Mut152 (V1 , N51E)	SEQ ID NO : 56	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRG AGPGRELIYEQKEGHFPRVTTVSDLTKRNNMDFSIRIGNIT PADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS
Mut153 (V1 , N51F)	SEQ ID NO : 57	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRG AGPGRELIYFQKEGHFPRVTTVSDLTKRNNMDFSIRIGNIT PADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS
Mut156 (V1 , N51K)	SEQ ID NO : 58	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRG AGPGRELIYKQKEGHFPRVTTVSDLTKRNNMDFSIRIGNIT PADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS
Mut157 (V1 , N51L)	SEQ ID NO : 59	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRG AGPGRELIYLQKEGHFPRVTTVSDLTKRNNMDFSIRIGNIT PADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS
Mut158 (V1 , N51M)	SEQ ID NO : 60	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRG AGPGRELIYMQKEGHFPRVTTVSDLTKRNNMDFSIRIGNI TPADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS
Mut160 (V1 , N51Q)	SEQ ID NO : 61	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRG AGPGRELIYQQKEGHFPRVTTVSDLTKRNNMDFSIRIGNIT PADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS
Mut162 (V1 , N51T)	SEQ ID NO : 62	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRG AGPGRELIYTQKEGHFPRVTTVSDLTKRNNMDFSIRIGNIT PADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS
Mut164 (V1 , N51W)	SEQ ID NO : 63	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRG AGPGRELIYWQKEGHFPRVTTVSDLTKRNNMDFSIRIGNI TPADAGTYCYCVKFRKGSPDDVEFKSGAGTELSVRAKPS

突變號	序列編號	序列資訊
Mut174 (V2 , N51M)	SEQ ID NO : 64	EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQWFR GAGPARELIYMQKEGHFPRVTTVSESTKRENMDFSISIS NITPADAGTYCYCVKFRKGGSPDTEFKSGAGTELSVRAKPS
Mut178 (V2 , N51W)	SEQ ID NO : 65	EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQWFR GAGPARELIYWQKEGHFPRVTTVSESTKRENMDFSISIS NITPADAGTYCYCVKFRKGGSPDTEFKSGAGTELSVRAKPS
Mut150-Fc	SEQ ID NO : 66	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRGAGPGRELIYAQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSVRAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Mut152-Fc	SEQ ID NO : 67	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRGAGPGRELIYEQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSVRAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Mut153-Fc	SEQ ID NO : 68	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRGAGPGRELIYFQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSVRAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Mut156-Fc	SEQ ID NO : 69	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRGAGPGRELIYKQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSVRAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST

突變號	序列編號	序列資訊
		YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Mut157-Fc	SEQ ID NO : 70	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQW FRGAGPGRELIYLQKEGHFPRVTTVSDLTRNNMDFSI RIGNITPADAGTYICVKFRKGGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Mut158-Fc	SEQ ID NO : 71	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQW FRGAGPGRELIYMQKEGHFPRVTTVSDLTRNNMDFSI IRIGNITPADAGTYICVKFRKGGSPDDVEFKSGAGTELS VRAPKS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Mut160-Fc	SEQ ID NO : 72	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQW FRGAGPGRELIYQQKEGHFPRVTTVSDLTRNNMDFSI RIGNITPADAGTYICVKFRKGGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Mut162-Fc	SEQ ID NO : 73	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQW FRGAGPGRELIYTQKEGHFPRVTTVSDLTRNNMDFSI RIGNITPADAGTYICVKFRKGGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

突變號	序列編號	序列資訊
Mut164-Fc	SEQ ID NO : 74	EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQW FRGAGPGRELIYWQKEGHFPRVTTVSDLTKRNNMDFS IRIGNITPADAGTYYCVKFRKGSPPDVEFKSGAGTELS VRAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Mut174-Fc	SEQ ID NO : 75	EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQW FRGAGPARELIYMQKEGHFPRVTTVSESTKRENMDF SISISNITPADAGTYYCVKFRKGSPPDTEFKSGAGTELS VRAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Mut178-Fc	SEQ ID NO : 76	EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQW FRGAGPARELIYWQKEGHFPRVTTVSESTKRENMDF SISISNITPADAGTYYCVKFRKGSPPDTEFKSGAGTELS VRAKPS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

【0069】 實施例2 SIRPa-Fc融合蛋白的生產與純化

【0070】 對HEK293細胞（購自中國科學院細胞庫）瞬間轉染實施例1構
築的質體（PEI，Polysciences）並使用FreeStyle TM 293 Expression Medium（購
自Gibco）在37℃下進行擴大培養。7天後收集細胞培養液，離心去除細胞成
分，獲得含SIRPa V1-Fc、SIRPa V2-Fc、Mut10-Fc、Mut31-Fc、Mut33-Fc、
Mut35-Fc、Mut38-Fc、Mut66-Fc、Mut67-Fc、Mut68-Fc、Mut69-Fc、Mut70-
Fc、Mut71-Fc、Mut72-Fc、Mut73-Fc、Mut75-Fc、Mut80-Fc、Mut81-Fc、

Mut83-Fc、Mut84-Fc、Mut86-Fc、Mut87-Fc、Mut88-Fc、Mut89-Fc和Mut90-Fc的培養上清液。

【0071】 或將質體和轉染試劑（Thermofisher，貨號：A29133）加入OptiPRO SFM（Thermofisher，貨號：12309019）中混勻後靜置5分鐘，加入ExpiCHO-S™細胞（廠家：Thermofisher，貨號：A29127）中，放入5% CO₂，120 rpm，37℃振盪器培養。轉染第二天，加入補料，並將振盪器溫度調至32℃繼續培養。轉染第8~11天，收集含Mut174-Fc、Mut178-Fc、Mut150-Fc、Mut152-Fc、Mut153-Fc、Mut156-Fc、Mut157-Fc、Mut158-Fc、Mut160-Fc、Mut162-Fc和Mut164-Fc的細胞上清液。

【0072】 用10 mL蛋白A管柱（購自博格隆）純化細胞培養上清液中的融合蛋白。蛋白A管柱先用3~5倍柱體積的平衡緩衝液（PBS磷酸緩衝液，pH7.4）平衡，然後將澄清的培養上清液的樣品加入到蛋白A管柱，控制流速在10 mL/分鐘。樣品加入完畢後用平衡緩衝液清洗蛋白A管柱，平衡緩衝液的體積為蛋白A管柱柱床體積的3~5倍。用洗脫液（0.02 M檸檬酸緩衝液，0.1M甘氨酸，0.1M氯化鈉，pH3.0）洗脫結合在蛋白A管柱上的蛋白，用核酸蛋白檢測儀監測洗脫情況（A280紫外吸收峰）。收集洗脫的蛋白，加入Tris緩衝液中和pH，透析後緩衝體系為PBS，收集目的蛋白。用0.22 μm的過濾器進行無菌過濾，無菌保存，即得純化的SIRPa-Fc融合蛋白。

【0073】 將純化的SIRPa-Fc融合蛋白進行蛋白產量、蛋白濃度（A280/1.4）、SEC純度等檢測分析，純化後的SIRPa-Fc融合蛋白的品質合格。其中關於蛋白產量、蛋白濃度和純度的檢測資訊參見表2。

【0074】 表2 SIRPa-Fc融合蛋白的檢測分析

第 30 頁，共 65 頁(發明說明書)

突變號	蛋白產量 (mg/L)	蛋白 SEC 純度	蛋白濃度 (mg/mL)
SIRPa V1-Fc	71.7	98.157%	3.01
SIRPa V2-Fc	125.2	98.910%	6.31
Mut10-Fc	162.0	98.748%	4.86
Mut174-Fc	233.3	98.997%	6.23
Mut178-Fc	226.7	99.299%	5.00
Mut31-Fc	69.9	99.022%	2.84
Mut33-Fc	35.9	98.995%	1.81
Mut35-Fc	39.0	99.046%	1.52
Mut38-Fc	25.0	99.071%	1.11
Mut150-Fc	193.3	99.195%	7.71
Mut152-Fc	186.7	99.179%	8.50
Mut153-Fc	181.7	99.005%	7.96
Mut156-Fc	238.3	99.409%	6.47
Mut157-Fc	265.0	98.977%	5.68
Mut158-Fc	228.3	99.295%	8.62
Mut160-Fc	168.3	99.359%	5.40
Mut162-Fc	160.0	99.460%	3.93
Mut164-Fc	135.0	99.230%	4.15
Mut66-Fc	54.0	98.915%	1.39
Mut67-Fc	85.4	98.878%	3.47
Mut68-Fc	76.7	98.854%	3.22
Mut69-Fc	61.9	99.034%	2.60
Mut70-Fc	79.0	98.956%	3.21
Mut71-Fc	60.7	99.021%	2.47
Mut72-Fc	20.3	97.693%	1.17
Mut73-Fc	64.8	97.932%	2.94
Mut75-Fc	62.4	97.774%	1.7
Mut80-Fc	55.0	97.812%	2.04
Mut81-Fc	66.5	97.745%	2.79
Mut83-Fc	69.7	98.001%	1.27
Mut84-Fc	64.3	99.747%	2.7
Mut86-Fc	66.7	97.565%	2.8
Mut87-Fc	68.8	97.597%	2.89
Mut88-Fc	65.3	97.689%	1.83
Mut89-Fc	48.8	97.831%	2.05
Mut90-Fc	40.3	97.862%	2.54

【0075】 實施例3 酵素結合免疫吸附分析（ELISA）檢測SIRPa-Fc融合

蛋白與CD47蛋白結合程度

【0076】 A. CD47蛋白的生產和純化

【0077】 (1) hCD47 ECD-His蛋白的生產和純化

【0078】 將人的CD47細胞膜外區域（Extracellular Domain，ECD）胺基酸序列（NCBI中的基因登錄號為Q08722，第19-139位胺基酸，具體序列如SEQ ID NO：52所示）耦合6×His序列複製到pTT5載體。

【0079】 SEQ ID NO：52

QLLFNKTKSVEFTFCNDTVVIPCFVTNMEAQNTTEVYVKWKFKGRDIY
TFDGALNKSTVPTDFSSAKIEVSQLLKGDASLKMDKSDAVSHTGNYTCEVTE
LTREGETIHELKYRVVSWFSP

【0080】 將質體和轉染試劑PEI（Polysciences，貨號：24765-1）加入OPTI-MEM（Gibco，貨號：11058021）中混勻後靜置15分鐘，加入Expi293細胞（廠家：Thermofisher，貨號：A14527）中，放入5%CO₂，120 rpm，37℃振盪器培養。轉染第二天，加入OPM-293 ProFeed（上海奧浦邁，貨號：F081918-001）和6 g/L葡萄糖（廠家：Sigma，貨號：G7528）。轉染第六天，收集細胞上清液；離心去除細胞成分，獲得含CD47 ECD-His蛋白的培養上清液。用Ni親和性層析管柱（GE，貨號：17371206）純化細胞培養上清液中的蛋白。先用3~5倍管柱體積的平衡緩衝液（PBS磷酸緩衝液，pH7.4）（20× PBS緩衝劑500 ml，生工，貨號B548117-0500）平衡，然後將澄清的培養上清液樣品加入到Ni親和性層析管柱，控制流速在5 mL/分鐘。樣品加入完畢後用平衡緩衝液清洗蛋白A管柱，平衡緩衝液的體積為Ni親和性層析管柱柱床體積的3~5倍。用0-500 mM咪唑（國藥，貨號：30104961）進行梯度洗脫，用核酸蛋白檢測儀監測洗脫情況（A280紫外吸收峰）。收集洗脫的蛋白，用透析卡（購自Thermo

Scientific，貨號：88252）在4℃下將蛋白透析到PBS磷酸緩衝液。用0.22 μm的過濾器（Millipore，貨號SLGVR13SL）進行無菌過濾，無菌保存，即得純化的hCD47 ECD-His蛋白。將純化的hCD47 ECD-His進行蛋白產量、蛋白濃度（A280/1.4）、SEC純度等檢測分析，純化蛋白品質合格。其中關於蛋白產量、蛋白濃度和純度的檢測資訊參見表3。

【0081】 (2) hCD47 ECD-mFc蛋白的生產和純化

【0082】 將人的CD47細胞膜外區域（Extracellular Domain，ECD）胺基酸序列（具體序列如SEQ ID NO：52所示）耦合小鼠Fc序列複製到pTT5載體。

【0083】 將質體和轉染試劑PEI（Polysciences，貨號：24765-1）加入OPTI-MEM（Gibco，貨號：11058021）中混勻後靜置15分鐘，加入Expi293細胞（廠家：Thermofisher，貨號：A14527）中，放入5%CO₂，120 rpm，37℃振盪器培養。轉染第二天，加入OPM-293 ProFeed（上海奧浦邁，貨號：F081918-001）和6 g/L葡萄糖（廠家：Sigma，貨號：G7528）。轉染第六天，收集細胞上清液；離心去除細胞成分，獲得含hCD47 ECD-mFc蛋白的培養上清液。用10 mL蛋白A管柱（GE，貨號：17549802）純化細胞培養上清液中的蛋白。蛋白A管柱先用3~5倍管柱體積的平衡緩衝液（PBS磷酸緩衝液，pH7.4）（20× PBS緩衝劑500 ml，生工，貨號B548117-0500）平衡，然後將澄清的培養上清液樣品加入到蛋白A管柱，控制流速在10 mL/分鐘。樣品加入完畢後用平衡緩衝液清洗蛋白A管柱，平衡緩衝液的體積為蛋白A管柱柱床體積的3~5倍。用洗脫液（0.02 M檸檬酸緩衝液，pH3.5）洗脫結合在蛋白A管柱上的蛋白，用核酸蛋白檢測儀監測洗脫情況（A280紫外吸收峰）。收集洗脫的蛋白，加入Tris緩衝液（國藥，貨號：30188336）中和pH，透析後緩衝體系為PBS，

收集目的蛋白。用0.22 μm的過濾器（Millipore，貨號SLGVR13SL）進行無菌過濾，無菌保存，即得純化的hCD47 ECD-mFc蛋白。將純化的hCD47 ECD-mFc進行蛋白產量、蛋白濃度（A280/1.4）、SEC純度等檢測分析，純化蛋白質合格。其中關於蛋白產量、蛋白濃度和純度的檢測資訊參見表3。

【0084】 表3 CD47蛋白的檢測分析

蛋白名稱	蛋白產量 (mg/L)	蛋白 SEC 純度	蛋白濃度 (mg/mL)
hCD47 ECD-His	39.6	96.7%	1.13
hCD47 ECD-mFc	88.4	82.7%	2.21

【0085】 B. 檢測SIRPa-Fc融合蛋白與hCD47 ECD-His蛋白結合程度

【0086】 生物素標記hCD47 ECD-His。按照Biotin Labeling kit說明書（貨號LK03，購自DO JINDO）向Filtration tube中加入100 μL WS緩衝液和200 μg hCD47 ECD-His蛋白，混勻後以8000 g離心10分鐘；加10 μL DMSO到NH2-Reactive Biotin Tube混勻備用；離心結束後加100 μL反應溶液和8 μL NH2-Reactive Biotin溶液到Filtration tube，混勻後在37度恆溫培養箱放置10分鐘後加入100 μL WS緩衝液以8000 g離心10分鐘，丟棄濾液後再加入200 μL WS緩衝液以8000 g離心10分鐘，重複上步驟一次後加入100 μL WS緩衝液以回收標記好的hCD47 ECD-His到新的離心管中，測濃度後備用。

【0087】 先將鏈黴抗生物素蛋白（streptavidin，下稱SA，貨號S4762，購自Sigma）用PBS稀釋到終濃度3 μg/mL，然後以50 μL每孔加到96孔ELISA盤中，4℃孵育過夜。第二天拋棄上清液，加入阻斷液，即含有5%（w/w）脫脂奶粉（購自Sangon，貨號: A100777 -0500）的PBS緩衝液，37℃阻斷2小時。倒掉阻斷液，用含有0.1%（v/v）Tween20（購自Sangon，貨號A100777 -0500）的

PBS緩衝液PBST洗盤3次。每孔加入2 μg/mL生物素標記的hCD47 ECD-His，50 μL/孔，37℃孵育1小時，用PBST洗滌3次。每孔加入實施例2所得的純化的SIRPa-Fc融合蛋白50 μL，濃度為50 nM起始，5倍梯度稀釋，37℃孵育1小時後，用PBST洗板3次。每孔加入1:5000稀釋的山葵過氧化酶（HRP）標記的二級抗體（購自Bethyl，貨號A80-304P）50 μL，稀釋液為含有1%（w/w）BSA（購自Sangon，貨號A500023-0100）的PBS，室溫孵育1小時後，用PBST洗盤5次。每孔加入50 μL TMB受質，室溫孵育5分鐘，每孔加入50 μL終止液（1.0N HCl）。用微量盤偵測儀（Ensign-HH3400，購自PerkinElmer）讀取A450 nm數值，結果如圖1和表4所示，結果說明純化後的SIRPa-Fc融合蛋白與hCD47 ECD-His的結合活性均優於野生型V1或者V2，優於TTI621。陰性對照為非相關Fc融合蛋白，下同。其中表中的數據為OD450 nm值。

【0088】 表4 ELISA檢測SIRPa-Fc融合蛋白與hCD47 ECD-His的結合活性

OD450 nm	蛋白濃度(nM)							
蛋白名稱	50	10	2	0.4	0.08	0.016	0.0032	0.00064
Mut10-Fc	2.679	2.237	2.208	2.178	1.697	0.877	0.270	0.104
SIRPa V2-Fc	2.497	2.191	2.119	1.895	1.279	0.373	0.086	0.054
TTI621	2.329	2.352	2.170	1.945	1.255	0.359	0.088	0.055
Mut31-Fc	3.107	3.039	2.904	2.724	1.744	0.647	0.169	0.081
SIRPa V1-Fc	3.199	2.723	2.508	1.383	0.542	0.132	0.061	0.057
TTI621	3.176	3.082	2.933	2.302	1.107	0.258	0.076	0.067
Mut33-Fc	2.809	2.411	2.357	2.258	1.502	0.631	0.166	0.091
Mut35-Fc	2.701	2.295	2.292	2.139	1.322	0.449	0.127	0.070
Mut38-Fc	2.470	2.309	2.321	2.163	1.395	0.488	0.132	0.088
SIRPa V1-Fc	2.873	2.177	2.063	1.396	0.401	0.153	0.065	0.062
TTI621	2.438	2.240	2.150	1.905	0.960	0.233	0.076	0.062
陰性對照	0.064	0.046	0.042	0.044	0.043	0.046	0.044	0.061
Mut33-Fc	1.730	1.714	1.693	1.540	1.032	0.491	0.147	0.102

Mut66-Fc	1.647	1.441	1.540	1.391	0.837	0.300	0.117	0.061
Mut67-Fc	1.698	1.563	1.476	1.351	0.888	0.336	0.116	0.067
Mut68-Fc	1.659	1.511	1.507	1.196	0.780	0.292	0.122	0.070
Mut69-Fc	1.649	1.615	1.638	1.340	0.809	0.291	0.113	0.078
TTI621	1.461	1.460	1.240	0.807	0.580	0.133	0.061	0.048
陰性對照	0.050	0.044	0.039	0.045	0.039	0.039	0.043	0.045
Mut72-Fc	2.081	1.983	1.971	1.746	1.039	0.411	0.132	0.073
Mut73-Fc	2.552	2.423	2.532	2.080	1.046	0.371	0.130	0.066
Mut75-Fc	2.268	2.206	1.985	1.913	1.119	0.379	0.126	0.070
Mut80-Fc	2.101	1.838	1.845	1.623	0.899	0.379	0.149	0.066
Mut81-Fc	1.931	1.768	1.796	1.564	1.009	0.369	0.117	0.069
TTI621	2.457	2.400	2.048	1.642	0.894	0.256	0.091	0.049
Mut83-Fc	1.372	1.518	1.491	1.441	0.843	0.349	0.119	0.075
Mut84-Fc	1.673	1.861	1.729	1.536	1.086	0.349	0.116	0.067
Mut86-Fc	1.630	1.280	1.600	1.445	0.789	0.307	0.107	0.067
Mut87-Fc	1.750	1.840	1.639	1.478	0.921	0.338	0.103	0.064
Mut88-Fc	1.391	1.709	1.729	1.337	0.949	0.360	0.116	0.058
Mut89-Fc	1.687	1.774	1.833	1.489	0.995	0.449	0.120	0.068
Mut90-Fc	1.508	1.542	1.541	1.307	1.016	0.425	0.144	0.072
TTI621	1.425	1.599	1.345	1.084	0.593	0.187	0.065	0.046
陰性對照	0.047	0.046	0.038	0.038	0.039	0.041	0.046	0.047
Mut150-Fc	1.762	1.665	1.481	1.152	0.616	0.223	0.094	0.057
Mut152-Fc	1.683	1.596	1.571	1.360	0.817	0.274	0.091	0.052
Mut153-Fc	1.758	1.787	1.820	1.507	0.833	0.285	0.098	0.060
Mut156-Fc	1.719	1.827	1.791	1.554	0.914	0.254	0.093	0.058
Mut157-Fc	1.639	1.640	1.629	1.435	0.836	0.227	0.073	0.053
SIRPa V1-Fc	1.711	1.556	1.546	1.369	0.756	0.116	0.073	0.051
TTI621	1.762	1.714	1.537	1.249	0.641	0.152	0.073	0.054
陰性對照	0.066	0.054	0.045	0.043	0.042	0.050	0.056	0.064
Mut158-Fc	1.794	1.800	1.785	1.621	1.031	0.420	0.145	0.072
Mut160-Fc	1.707	1.645	1.739	1.387	0.812	0.381	0.100	0.059
Mut162-Fc	1.667	1.892	1.681	1.448	0.822	0.486	0.164	0.056
Mut164-Fc	1.811	1.802	1.990	1.496	0.809	0.295	0.109	0.060
SIRPa V1-Fc	1.360	1.685	1.742	1.318	0.669	0.241	0.057	0.050
TTI621	1.607	1.609	1.690	1.363	0.781	0.253	0.075	0.051
陰性對照	0.064	0.049	0.077	0.114	0.062	0.043	0.046	0.046

Mut174-Fc	1.833	1.807	1.733	1.396	0.816	0.293	0.090	0.059
Mut178-Fc	1.776	1.798	1.804	1.469	0.816	0.287	0.090	0.053
SIRPa V2-Fc	1.869	1.803	1.775	1.437	0.780	0.223	0.072	0.052
TTI621	1.772	1.728	1.776	1.393	0.782	0.244	0.085	0.051
陰性對照	0.069	0.055	0.043	0.040	0.041	0.042	0.051	0.049

【0089】 C. 檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc蛋白結合程度

【0090】 先將anti-mFc（購自Jackson，貨號115-006-071）用PBS稀釋到終濃度2 μg/mL，然後以50 μL每孔加到96孔ELISA盤中，4℃孵育過夜。第二天拋棄上清液，加入阻斷液，即含有5%（w/w）脫脂奶粉（購自Sangon，貨號A600669-0250）的PBS緩衝液，37℃阻斷2小時。倒掉阻斷液，用PBST洗盤3次。每孔加入0.5 μg/mL hCD47 ECD-mFc，50 μL/孔，37℃孵育1小時，用PBST洗滌3次。每孔加入實施例2所得的純化的SIRPa-Fc融合蛋白50 μL，濃度為50 nM起始，5倍梯度稀釋，37℃孵育1小時後，用PBST洗盤3次。每孔加入1:5000稀釋的山葵過氧化酶（HRP）標記的二級抗體（購自Bethyl，貨號A80-304P）50 μL，稀釋液為含有1%（w/w）BSA（購自Sangon，貨號A500023-0100）的PBS，室溫孵育1小時後，用PBST洗盤5次。每孔加入50 μL TMB受質，室溫孵育5分鐘，每孔加入50 μL終止液（1.0 N HCl）。用微量盤偵測儀（Ensign-HH3400，購自PerkinElmer）讀取A450 nm數值，結果如圖2和表5所示，結果說明純化後的SIRPa-Fc融合蛋白與hCD47 ECD-mFc的結合活性均優於野生型V1或者V2，優於TTI621。表中的數據為OD450 nm值。

【0091】 表5 ELISA檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc的結合活性

OD450 nm	蛋白濃度(nM)							
蛋白名稱	50	10	2	0.4	0.08	0.016	0.0032	0.00064
Mut10-Fc	2.409	2.114	2.103	2.053	1.713	0.925	0.314	0.116
SIRPa V2-Fc	2.184	1.942	1.855	1.653	1.006	0.329	0.097	0.063

TTI621	1.995	1.987	1.935	1.724	1.013	0.336	0.090	0.062
Mut31-Fc	2.758	2.771	2.751	2.644	1.811	0.706	0.187	0.092
SIRPa V1-Fc	2.969	2.565	2.319	1.892	0.859	0.227	0.084	0.068
TTI621	2.608	2.668	2.550	2.215	1.233	0.383	0.136	0.068
Mut33-Fc	2.567	2.292	2.217	2.117	1.588	0.629	0.192	0.104
Mut35-Fc	2.658	2.100	2.005	1.939	1.244	0.510	0.145	0.100
Mut38-Fc	2.452	2.098	2.056	2.038	1.409	0.557	0.165	0.092
SIRPa V1-Fc	2.355	1.905	1.574	1.118	0.507	0.143	0.071	0.065
TTI621	2.188	1.966	1.848	1.588	0.799	0.228	0.087	0.078
陰性對照	0.184	0.082	0.053	0.054	0.049	0.053	0.049	0.058
Mut33-Fc	1.669	1.468	1.518	1.301	0.987	0.417	0.155	0.092
Mut66-Fc	1.240	1.519	1.306	1.144	0.762	0.250	0.095	0.062
Mut67-Fc	1.329	1.430	1.593	1.415	0.920	0.309	0.108	0.061
Mut68-Fc	1.344	1.621	1.474	1.203	0.831	0.285	0.118	0.063
Mut69-Fc	1.328	1.612	1.418	1.347	0.907	0.333	0.116	0.078
TTI621	0.796	0.836	0.751	0.422	0.204	0.074	0.047	0.047
陰性對照	0.048	0.037	0.036	0.037	0.0036	0.036	0.039	0.047
Mut72-Fc	1.267	1.463	1.142	1.227	0.964	0.415	0.145	0.076
Mut73-Fc	1.269	1.349	1.428	1.185	0.894	0.331	0.132	0.078
Mut75-Fc	1.432	1.506	1.397	1.277	1.078	0.373	0.147	0.069
Mut80-Fc	1.392	1.369	1.460	1.178	0.966	0.396	0.165	0.085
Mut81-Fc	1.267	1.291	1.281	1.295	0.993	0.373	0.150	0.071
TTI621	1.295	1.567	1.439	0.997	0.500	0.162	0.074	0.054
Mut83-Fc	1.139	1.430	1.288	1.384	0.731	0.288	0.127	0.062
Mut84-Fc	1.265	1.459	1.480	1.353	0.883	0.360	0.144	0.068
Mut86-Fc	1.309	1.571	1.479	1.454	0.863	0.296	0.125	0.062
Mut87-Fc	1.104	1.419	1.306	1.194	0.919	0.313	0.128	0.070
Mut88-Fc	1.251	1.258	1.287	1.263	0.838	0.308	0.121	0.066
Mut89-Fc	1.286	1.459	1.115	1.330	0.877	0.334	0.146	0.074
Mut90-Fc	1.334	1.374	1.159	1.252	0.816	0.382	0.158	0.087
TTI621	1.005	1.210	0.866	0.759	0.367	0.134	0.059	0.040
陰性對照	0.046	0.038	0.036	0.035	0.037	0.043	0.043	0.039
Mut153-Fc	1.473	1.185	1.363	1.019	0.716	0.269	0.105	0.065
Mut156-Fc	1.405	0.978	1.153	0.7	0.404	0.146	0.075	0.061
Mut157-Fc	1.039	1.402	1.335	0.521	0.239	0.105	0.063	0.061

SIRPa V1-Fc	0.763	0.638	0.614	0.316	0.113	0.061	0.053	0.057
TTI621	1.219	0.949	0.957	0.56	0.308	0.116	0.064	0.07
陰性對照	0.084	0.068	0.055	0.054	0.05	0.056	0.055	0.059
Mut158-Fc	1.844	1.74	1.603	1.44	1.079	0.47	0.174	0.097
Mut160-Fc	1.421	1.403	1.407	1.294	0.835	0.295	0.119	0.069
Mut162-Fc	1.222	1.26	1.469	1.105	0.697	0.229	0.115	0.067
Mut164-Fc	2.194	1.959	1.878	1.935	1.018	0.362	0.133	0.075
SIRPa V1-Fc	0.870	1.288	1.017	0.318	0.107	0.060	0.055	0.057
TTI621	1.133	1.008	1.128	0.778	0.33	0.115	0.069	0.059
陰性對照	0.063	0.053	0.046	0.044	0.043	0.047	0.049	0.056
Mut178-Fc	1.625	1.73	1.872	1.557	0.898	0.304	0.116	0.061
SIRPa V2-Fc	1.638	1.568	1.386	0.764	0.384	0.139	0.067	0.056
TTI621	1.292	1.33	1.632	0.876	0.309	0.112	0.07	0.056
陰性對照	0.073	0.063	0.059	0.052	0.049	0.052	0.058	0.053

【0092】 實施例4 表面電漿共振（SPR）檢測SIRPa-Fc融合蛋白與CD47

蛋白親和力

【0093】 應用BIAcore 8K儀器，採用多循環動力學法測定與抗原的親和力。首先，根據Human Antibody Capture Kit（購自cytiva，29234600）的方法指導，將Anti-human IgG Fc抗體固定到CM5晶片上（購自cytiva，BR100530），根據Amine Coupling Kit套組（購自cytiva，BR100633）的指導，以HBS-EP+ pH7.4為流動相，將NHS和EDC混合後，活化晶片約600 s，用10 mM乙酸鈉 pH5.0將抗-人類IgG Fc稀釋至15 µg/mL，注射420 s，最後用乙醇胺對剩餘的活化點位進行阻斷。然後，採用多循環動力學法測定與抗原的親和力，在每一個循環中，首先用抗-人類IgG Fc晶片捕獲SIRPa-Fc融合蛋白，然後注入單一濃度的抗原，記錄SIRPa-Fc融合蛋白和抗原蛋白的結合和解離過程，最後用3M MgCl₂完成晶片再生，其中流動相為HBS-EP+ (10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.05%表面活性劑P20)，流速30 µL/分鐘，再生時間為30 s，檢測溫

度為25℃；最後，根據1:1 結合(binding)模型，對數據進行分析，擬合抗體抗原結合動力學參數，包括結合速率常數ka、解離速率常數kd、平衡解離常數KD、最大結合訊號Rmax。結果如表6所示，結果說明純化後的SIRPa-Fc融合蛋白與hCD47 ECD-mFc的親和力均優於野生型或者TTI621，其中Mut10-Fc、Mut33-Fc、Mut67-Fc、Mut69-Fc、Mut80-Fc、Mut81-Fc、Mut86-Fc、Mut153-Fc、Mut158-Fc、Mut160-Fc、Mut164-Fc融合蛋白親和力提高較為明顯。

【0094】 表6 SPR檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc的親和力

SIRPa-Fc 融合蛋白	ka (1/Ms)	kd (1/s)	KD (M)
Mut10-Fc	1.16E+06	8.66E-04	7.48E-10
TTI621	6.75E+05	1.57E-03	2.32E-09
Mut31-Fc	3.04E+05	1.19E-03	3.92E-09
Mut33-Fc	4.52E+05	8.74E-04	1.94E-09
Mut35-Fc	2.91E+05	1.19E-03	4.09E-09
Mut38-Fc	3.25E+05	1.17E-03	3.60E-09
SIRPa V1-Fc	1.36E+05	1.94E-03	1.42E-08
TTI621	1.80E+05	1.64E-03	9.13E-09
Mut33-Fc	1.68E+06	3.58E-03	2.13E-09
Mut66-Fc	1.28E+06	7.48E-03	5.82E-09
Mut67-Fc	1.62E+06	4.33E-03	2.66E-09
Mut68-Fc	1.42E+06	6.64E-03	4.68E-09
Mut69-Fc	1.57E+06	4.52E-03	2.88E-09
Mut71-Fc	1.39E+06	5.98E-03	4.29E-09
TTI621	7.18E+05	6.93E-03	9.65E-09
Mut72-Fc	8.45E+05	1.15E-03	1.36E-09
Mut73-Fc	8.28E+05	7.45E-03	9.00E-09
Mut75-Fc	8.78E+05	6.53E-03	7.45E-09
Mut80-Fc	8.47E+05	6.49E-04	7.67E-10
Mut81-Fc	8.29E+05	2.83E-04	3.42E-10
Mut83-Fc	8.28E+05	1.14E-03	1.37E-09
Mut84-Fc	8.81E+05	6.87E-03	7.80E-09
Mut86-Fc	8.18E+05	7.27E-04	8.89E-10
Mut87-Fc	7.63E+05	9.42E-03	1.24E-08

Mut88-Fc	8.46E+05	5.89E-03	6.97E-09
Mut89-Fc	9.09E+05	7.74E-03	8.51E-09
Mut90-Fc	1.17E+06	5.82E-03	4.99E-09
Mut150-Fc	4.36E+05	1.78E-03	4.09E-09
Mut152-Fc	2.90E+05	1.74E-03	5.98E-09
Mut153-Fc	7.10E+05	1.52E-03	2.15E-09
Mut156-Fc	4.96E+05	1.68E-03	3.39E-09
Mut157-Fc	4.06E+05	1.77E-03	4.35E-09
Mut158-Fc	8.66E+05	1.45E-03	1.67E-09
Mut160-Fc	6.60E+05	1.62E-03	2.45E-09
Mut162-Fc	5.15E+05	1.78E-03	3.46E-09
Mut164-Fc	9.34E+05	1.38E-03	1.48E-09
SIRPa V1-Fc	2.22E+05	1.63E-03	7.34E-09
TTI621	4.30E+05	1.80E-03	4.19E-09
Mut174-Fc	4.65E+05	1.79E-03	3.86E-09
Mut178-Fc	5.72E+05	1.68E-03	2.94E-09
SIRPa V2-Fc	3.88E+05	2.00E-03	5.15E-09

【0095】 實施例5 流式細胞實驗（FACS）檢測SIRPa-Fc融合蛋白與細胞的結合活性

【0096】 A. 檢測SIRPa-Fc融合蛋白與Jurkat細胞結合程度

【0097】 將Jurkat細胞在T-75細胞培養瓶中擴大培養，室溫條件下以1000 rpm離心5分鐘，拋棄培養基，用PBS緩衝液（購自Hyclone，貨號SH30256.01）洗滌2次，將細胞用PBS重新懸浮並計數。按每孔 1×10^5 個細胞，每孔50 μ L加入到U型底96孔FACS 反應盤中（購自Corning，貨號3795），放在4℃備用。用含有1%（w/w）BSA（購自Sangon，貨號A500023-0100）的PBS稀釋待測SIRPa-Fc融合蛋白，按每孔50 μ L加入細胞中混勻，4℃孵育1小時。每孔加入200 μ L FACS緩衝液（含有1%（w/w）BSA的PBS緩衝液），洗滌2次，以1500 rpm離心5分鐘。去掉上清液後，每孔加入100 μ L稀釋的螢光標記的二級抗體（購自Jackson ImmunoResearch，貨號109-605-098），4℃孵育1小時。用FACS緩衝液

離心洗滌2次，用100 μL的PBS懸浮細胞。用FACS儀（FACS Canto II，購自BD公司）檢測和分析結果。結果如圖3和表7所示。結果顯示，SIRPa-Fc融合蛋白可結合Jurkat細胞表面的CD47，SIRPa-Fc融合蛋白與Jurkat結合活性均優於野生型V1或者V2，優於TTI621。表中數據MFI為所測細胞群的平均螢光強度值。

【0098】 表7 FACS檢測SIRPa-Fc融合蛋白與Jurkat的結合活性

MFI	蛋白濃度(nM)							
蛋白名稱	500	100	20	4	0.8	0.16	0.032	0.0064
Mut10-Fc	29421	29435	27944	26359	20067	5994	1359	342
SIRPa V2-Fc	23854	18974	15977	13447	9025	3268	811	248
TTI621	23468	19197	15960	13191	8722	3036	715	218
陰性對照	247	94	45	33	36	31	54	38
Mut31-Fc	19581	20410	18106	16359	12517	4406	1092	241
Mut33-Fc	21417	24570	23371	22807	20429	6754	1472	334
Mut35-Fc	20879	21465	19055	17479	12776	4040	922	203
Mut38-Fc	20841	20669	17422	16337	13240	4716	1092	249
SIRPa V1-Fc	15935	11319	6613	3123	1222	311	98	31
TTI621	17556	14974	10285	8896	6198	2492	704	144
陰性對照	34	29	22	22	20	23	24	209
MFI	蛋白濃度（nM）							
蛋白名稱	1000	200	40	8	1.6	0.32	0.064	0.0128
Mut66-Fc	16478	27464	26727	25467	25216	23873	8938	2500
Mut67-Fc	13809	29021	27758	27161	26909	26165	8281	1792
Mut68-Fc	14670	27125	26078	25219	24530	23355	7932	2118
Mut69-Fc	14615	28442	28054	27286	26992	24980	7805	2020
Mut70-Fc	13997	19865	15690	12195	9923	6502	3526	2289
Mut71-Fc	13607	25644	25819	24005	23564	21379	9698	3135
Mut33-Fc	17151	26777	26336	24440	24129	21791	9270	3284
TTI621	15633	17641	14387	10577	8202	5294	1952	533
陰性對照	163	91	38	30	24	24	23	24

【0099】 B. 檢測SIRPa-Fc融合蛋白與Raji細胞結合程度

【0100】 將Raji細胞在T-75細胞培養瓶中擴大培養，計數，室溫條件下以1000 rpm離心5分鐘，拋棄培養基，用PBS緩衝液（購自Hyclone，貨號

SH30256.01) 洗滌2次，將細胞用25 µg/ml的Fc阻斷劑(購自BD，貨號564220)重新懸浮，室溫阻斷20分鐘。按每孔1×10⁵個細胞，每孔50 µL加入到U型底96孔FACS 反應盤中(購自Corning，貨號3795)，放在4℃備用。用含有1% (w/w) BSA(購自Sangon，貨號A500023-0100)的PBS稀釋待測SIRPa-Fc融合蛋白，按每孔50 µL加入細胞中混勻，4℃ 孵育1小時。每孔加入200 µL FACS緩衝液(含有1% (w/w) BSA的PBS緩衝液)，洗滌2次，以1500 rpm離心5分鐘。去掉上清液後，每孔加入100 µL 稀釋的螢光標記的二級抗體(購自Jackson ImmunoResearch，貨號109-605-098)，4℃ 孵育1小時。用FACS緩衝液離心洗滌2次，用100 µL的PBS懸浮細胞。用FACS儀(FACS Canto II，購自BD公司)檢測和分析結果。結果如圖4和表8所示。結果顯示，SIRPa-Fc融合蛋白可結合Raji細胞表面的CD47，SIRPa-Fc融合蛋白與Raji結合活性均優於野生型V1或者V2，優於TTI621。表中數據MFI為所測細胞群的平均螢光強度值。

【0101】 表8 FACS檢測SIRPa-Fc融合蛋白與Raji的結合活性

MFI	蛋白濃度(nM)							
蛋白名稱	500	100	20	4	0.8	0.16	0.032	0.0064
Mut10-Fc	920	969	822	769	696	548	246	106
SIRPa V2-Fc	680	777	516	348	254	156	87	67
TTI621	724	792	557	392	268	175	97	64
陰性對照	123	139	83	66	64	64	59	59
Mut31-Fc	204	207	158	137	120	79	37	24
Mut33-Fc	220	238	222	214	204	152	54	29
Mut35-Fc	208	215	169	154	132	79	39	26
Mut38-Fc	205	211	170	133	129	90	44	26
SIRPa V1-Fc	166	146	76	44	30	20	18	20
TTI621	178	169	114	82	63	44	31	22
陰性對照	57	50	27	23	22	22	22	24
MFI	蛋白濃度 (nM)							

蛋白名稱	200	40	8	1.6	0.32	0.064	0.0128	0.00256
Mut33-Fc	205	208	204	194	173	103	60	50
Mut66-Fc	211	211	205	196	148	69	46	39
Mut67-Fc	218	223	220	215	178	84	52	45
Mut68-Fc	212	215	207	203	156	75	48	41
Mut69-Fc	222	230	224	217	185	88	52	48
陰性對照	58	53	49	46	46	41	41	42
MFI	蛋白濃度（nM）							
蛋白名稱	100	20	4	0.8	0.16	0.032	0.0064	0.00128
Mut72-Fc	194	197	201	194	152	71	52	37
Mut73-Fc	177	178	178	170	141	72	50	41
Mut75-Fc	193	200	199	199	162	73	54	42
Mut80-Fc	192	205	203	203	156	79	52	48
Mut81-Fc	192	197	205	201	162	83	60	46
TTI621	136	113	84	69	54	50	53	48
陰性對照	48	46	46	46	48	45	49	-
Mut83-Fc	192	190	193	189	137	68	46	37
Mut84-Fc	177	178	180	173	143	73	50	45
Mut86-Fc	194	200	196	199	159	76	50	46
Mut87-Fc	180	181	175	170	131	69	50	44
Mut88-Fc	181	193	189	188	158	78	57	50
Mut89-Fc	169	178	175	165	140	80	53	53
Mut90-Fc	178	188	190	190	158	80	56	50
TTI621	141	114	88	73	57	49	45	46
陰性對照	42	48	50	48	49	42	46	46

【0102】 實施例6 檢測SIRPa-Fc融合蛋白阻斷Raji與受體SIRPa的結合

【0103】 A. SIRPa蛋白的生產和純化

【0104】 將人的SIRPa V1細胞膜外區域（Extracellular Domain，ECD）胺基酸序列（NCBI中的基因登錄號為NP_542970.1，第31-370位胺基酸，具體序列如SEQ ID NO：53所示）和SIRPa V2細胞膜外區域（Extracellular Domain，ECD）胺基酸序列（NCBI中的基因登錄號為AAH38510.1，第31-369位胺基酸，具體序列如SEQ ID NO：54所示）分別耦合6×His序列複製到pTT5載體。

【0105】 SEQ ID NO : 53

EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRGAGPGRELIY
NQKEGHFPRVTTVSDLTKRNNMDFSIRIGNITPADAGTYCYCVKFRKGGSPDDV
EFKSGAGTELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRDITLKWF
KNGNELSDFQTNVDPVGESVSYSIHSTAKVVLTRDVDHSQVICEVAHVTLQG
DPLRG TANLSETIRVPPTLEVTTQQPVRAENQVNVTCQVRKFYPQRLQLTWLE
NGNVSRTETASTVTENKDGTYNWMSWLLVNVSAHRDDVKLTCQVEHDGQP
AVSKSHDLKVS AHPKEQGSNTAAENTGSNER

【0106】 SEQ ID NO : 54

EEELQVIQPDKSVSVAAGESAILHCTVTSIPVGPIQWFRGAGPARELIY
NQKEGHFPRVTTVSESTKRENMDFSISISNITPADAGTYCYCVKFRKGGSPDTEF
KSGAGTELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRDITLKWFKN
GNELSDFQTNVDPVGESVSYSIHSTAKVVLTRDVDHSQVICEVAHVTLQGGP
LRGTANLSETIRVPPTLEVTTQQPVRAENQVNVTCQVRKFYPQRLQLTWLENG
NVSRTETASTVTENKDGTYNWMSWLLVNVSAHRDDVKLTCQVEHDGQPAV
SKSHDLKVS AHPKEQGSNTAAENTGSNER

【0107】 將所得質體和轉染試劑PEI（Polysciences，貨號：24765-1）加入OPTI-MEM（Gibco，貨號：11058021）中混勻後靜置15分鐘，加入Expi293細胞（廠家：Thermofisher，貨號：A14527）中，放入5%CO₂，120 rpm，37℃振盪器培養。轉染第二天，加入OPM-293 ProFeed（上海奧浦邁，貨號：F081918-001）和6 g/L葡萄糖（廠家：Sigma，貨號：G7528）。轉染第六天，收集細胞上清液；離心去除細胞成分，分別獲得含hSIRPa V1 ECD-His和hSIRPa V2 ECD-His蛋白的培養上清液。用Ni親和性層析管柱（GE，貨號：

17371206) 純化細胞培養上清液中的蛋白。先用3~5倍管柱體積的平衡緩衝液 (PBS磷酸緩衝液, pH7.4) (20× PBS緩衝劑500 ml, 生工, 貨號B548117-0500) 平衡, 然後將澄清的培養上清液樣品加入到Ni親和性層析管柱, 控制流速在5 mL/分鐘。樣品加入完畢後用平衡緩衝液清洗蛋白A管柱, 平衡緩衝液的體積為Ni親和性層析管柱柱床體積的3~5倍。用0-500 mM咪唑 (國藥, 貨號: 30104961) 進行梯度洗脫, 用核酸蛋白檢測儀監測洗脫情況 (A280紫外吸收峰)。收集洗脫的蛋白, 用透析卡 (購自Thermo Scientific貨號: 88252) 在4℃下將蛋白透析到PBS磷酸緩衝液。用0.22 μm的過濾器 (Millipore, 貨號SLGVR13SL) 進行無菌過濾, 無菌保存, 即得純化的hSIRPa V1 ECD-His和hSIRPa V2 ECD-His蛋白。將純化的hSIRPa V1 ECD-His和hSIRPa V2 ECD-His進行蛋白產量、蛋白濃度 (A280/1.4)、SEC純度等檢測分析, 純化蛋白品質合格。其中關於蛋白產量、蛋白濃度和純度的檢測資訊參見表9。

【0108】 表9 SIRPa蛋白的檢測分析

蛋白名稱	蛋白產量 (mg/L)	蛋白 SEC 純度	蛋白濃度 (mg/mL)
hSIRPa V1 ECD-His	241.56	99.31	3.355
hSIRPa V2 ECD-His	234.24	99.39	2.928

【0109】 B. 檢測SIRPa-Fc融合蛋白阻斷Raji與受體SIRPa V1的活性

【0110】 生物素標記hSIRPa V1 ECD-His, 方法同實施例3。將Raji細胞在T-75細胞培養瓶中擴大培養, 收集培養基, 計數, 室溫條件下以1000 rpm離心5分鐘, 拋棄培養基, 用PBS緩衝液 (購自Hyclone, 貨號SH30256.01) 洗滌2次, 將細胞用25 μg/ml的Fc阻斷劑 (購自BD, 貨號564220) 重新懸浮, 室溫阻斷20分鐘。按每孔1×10⁵個細胞, 每孔50 μL加入到U型底96孔FACS反應盤中

（購自Corning，貨號3795），放在4℃備用。在PBS磷酸緩衝液中加入1%（w/w）BSA作為FACS緩衝液，將純化的不同濃度的SIRPa-Fc融合蛋白和生物素化的hSIRRPa V1 ECD-His混合，hSIRRPa V1 ECD-His終濃度為4 μg/mL，室溫孵育15分鐘。之後每孔加入50 μL混合物，冰上孵育1小時。用FACS緩衝液離心洗滌2次，每孔加入100 μL螢光標記的鏈黴抗生物素蛋白（購自Biolegend，貨號405243），冰上孵育1小時。用FACS緩衝液離心洗滌2次。用100 μL的PBS懸浮細胞，用FACS（FACS Canto II，購自BD公司）檢測和分析結果。結果如圖5和表10所示，SIRPa-Fc融合蛋白能夠有效阻斷Raji與SIRPa V1的結合活性，並且阻斷活性均優於TTI621或野生型。表中數據MFI為所測細胞群的平均螢光強度值。

【0111】 表10 FACS檢測SIRPa-Fc融合蛋白阻斷Raji與SIRPa V1的結合活性

MFI	蛋白濃度(nM)							
蛋白名稱	200	40	8	1.6	0.32	0.064	0.0128	0.00256
Mut10-Fc	47	49	52	58	112	279	356	394
Mut31-Fc	48	48	57	95	194	333	371	389
Mut33-Fc	47	51	48	49	65	242	351	388
Mut35-Fc	47	48	56	89	197	346	380	401
Mut38-Fc	49	50	56	86	181	317	382	385
TTI621	48	52	86	183	304	378	389	398
陰性對照	349	368	383	363	383	386	-	-
Mut33-Fc	23	24	23	23	24	76	99	102
Mut66-Fc	16	16	16	16	16	41	88	98
Mut67-Fc	18	18	18	18	16	54	95	102
Mut68-Fc	19	19	18	15	18	60	88	99
Mut69-Fc	20	19	19	16	15	49	90	103
TTI621	23	22	31	53	84	95	99	102
陰性對照	92	101	106	101	102	99	99	94

MFI	蛋白濃度(nM)							
蛋白名稱	100	20	4	0.8	0.16	0.032	0.0064	0.00128
Mut150-Fc	25	45	104	186	237	256	270	235
Mut153-Fc	23	23	35	89	180	245	262	252
Mut156-Fc	25	42	102	184	222	248	271	247
Mut157-Fc	25	51	117	207	240	248	281	226
Mut158-Fc	21	23	23	39	150	240	266	242
Mut160-Fc	22	25	50	126	205	255	293	255
SIRPa V1-Fc	38	85	167	234	251	263	297	241
TTI621	23	30	70	159	216	259	286	250
陰性對照	278	282	270	261	264	273	279	261
Mut162-Fc	24	29	63	125	192	207	249	227
Mut164-Fc	21	22	23	40	153	193	229	229
SIRPa V1-Fc	37	80	151	193	219	204	231	222
Mut174-Fc	23	26	51	110	181	202	212	206
Mut178-Fc	22	23	38	89	170	206	217	218
SIRPa V2-Fc	24	30	67	134	190	194	221	210
TTI621	24	31	68	132	193	203	220	221
陰性對照	193	216	206	213	215	197	210	208

【0112】 C. 檢測SIRPa-Fc融合蛋白阻斷Raji與受體SIRPa V2的活性

【0113】 生物素標記hSIRPa V2 ECD-His，方法同實施例3。將Raji細胞在T-75細胞培養瓶中擴大培養，收集培養基，計數，室溫條件下以1000 rpm離心5分鐘，拋棄培養基，用PBS緩衝液（購自Hyclone，貨號SH30256.01）洗滌一次，將細胞用25 µg/ml的Fc阻斷劑（購自BD，貨號564220）重新懸浮，室溫阻斷20分鐘。按每孔1×10⁵個細胞，每孔50 µL加入到U型底96孔FACS反應盤中（購自Corning，貨號3795），放在4℃備用。在PBS磷酸緩衝液中加入1%（w/w）BSA作為FACS緩衝液，將純化的不同濃度的SIRPa-Fc融合蛋白和生物素化的hSIRPa V2 ECD-His混合，hSIRPa V2 ECD-His終濃度為4 µg/mL，室溫孵育15分鐘。之後每孔加入50 µL混合物，冰上孵育1小時。用FACS緩衝液離心洗滌2次，每孔加入100 µL螢光標記的鏈黴抗生物素蛋白（購自

Biolegend，貨號405243），冰上孵育1小時。用FACS緩衝液離心洗滌2次。用100 μL的PBS懸浮細胞，用FACS（FACS Canto II，購自BD公司）檢測和分析結果。結果如圖6A-6B和表11所示，SIRPa-Fc融合蛋白能夠有效阻斷Raji與SIRPa V2的結合活性，並且阻斷活性均優於TTI621。表中數據MFI為所測細胞群的平均螢光強度值。

【0114】 表11 FACS檢測SIRPa-Fc融合蛋白阻斷Raji與SIRPa V2的結合活性

MFI	蛋白濃度(nM)							
蛋白名稱	200	40	8	1.6	0.32	0.064	0.0128	0.00256
Mut10-Fc	49	49	55	71	143	290	331	335
Mut31-Fc	51	50	68	120	204	318	346	362
Mut33-Fc	49	48	49	56	87	258	339	366
Mut35-Fc	51	50	64	114	220	347	362	372
Mut38-Fc	49	52	62	111	213	324	362	362
TTI621	50	65	116	215	327	368	377	381
陰性對照	322	349	342	367	401	386	-	-
Mut33-Fc	22	26	22	23	31	78	98	106
Mut66-Fc	26	24	22	24	20	46	91	101
Mut67-Fc	23	26	27	22	23	67	99	109
Mut68-Fc	22	27	24	26	23	64	101	109
Mut69-Fc	22	20	22	24	24	61	99	99
TTI621	26	27	38	67	95	109	105	105
陰性對照	98	95	103	105	114	95	102	97

【0115】 實施例7 SIRPa-Fc融合蛋白親和力成熟

【0116】 以Mut87-Fc、Mut88-Fc、Mut89-Fc、Mut90-Fc四個質體為模板，分別構築4個突變文庫；每個文庫包含針對重點突變點位的單點胺基酸突變及多點突變的組合。理論突變總數： 4.7×10^8 ，構築總文庫庫容 $> 3.8 \times 10^9$ 。經過2-3輪淘選後，將第2輪或第3輪噬菌體進行親和力鑒定。

【0117】 類似實施例1，將編碼突變體的核酸片段複製至帶有Fc標籤的pTT5載體上，並按已建立的標準分子生物學方法製備質體。所述使用的SIRPa變體如下：Mut113、Mut114和Mut117。前述融合蛋白及各元件的具體序列資訊如表12所示，其中，「MutXX-Fc」表示突變型SIRPa與Fc的融合蛋白。

【0118】 表12 SIRPa突變序列

突變號	序列編號	序列資訊
Mut113 (Mut88+L66N+K68Q)	SEQ ID NO : 77	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDNTQRNNMD FSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTE LSVRAKPS
Mut114 (Mut88+L66N+K68L)	SEQ ID NO : 78	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDNTLRNNMD FSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTE LSVRAKPS
Mut117 (Mut88+L66N+K68I)	SEQ ID NO : 79	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDNTIRNNMDF SIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSGAGTEL SVRAKPS
Mut113-Fc	SEQ ID NO : 80	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPI QWFRGAGPGRELIYRQKEGHFPRVTTVSDNTQRN NMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKS GAGTELSVRAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
Mut114-Fc	SEQ ID NO : 81	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPI QWFRGAGPGRELIYRQKEGHFPRVTTVSDNTLRN NMDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKS GAGTELSVRAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF

突變號	序列編號	序列資訊
		FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
Mut117-Fc	SEQ ID NO : 82	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPI QWFRGAGPGRELIYRQKEGHFPRVTTVSDNTIRNN MDFSIRIGNITPADAGTY YCVKFRKGGSPDDVEFKSG AGTELSVRAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG

【0119】 類似實施例2，用Expi293F系統表現突變蛋白，將純化的SIRPa-Fc融合蛋白進行蛋白產量、蛋白濃度（A280/1.4）、SEC純度等檢測分析，純化後的SIRPa-Fc融合蛋白的品質合格。其中關於蛋白產量、蛋白濃度和純度的檢測資訊參見表13。

【0120】 表13 SIRPa-Fc融合蛋白的檢測分析

突變號	蛋白產量 (mg/L)	蛋白 SEC 純度	蛋白濃度 (mg/mL)
Mut113-Fc	76.3	98.191%	4.81
Mut114-Fc	66.3	97.992%	3.98
Mut117-Fc	91.3	97.990%	2.81

【0121】 類似實施例4，利用表面電漿共振（SPR）檢測SIRPa-Fc融合蛋白與CD47蛋白親和力結果如表14所示，結果說明親和力成熟後SIRPa-Fc融合蛋白與hCD47 ECD-mFc的親和力均優於野生型或者TTI621。

【0122】 表14 SPR檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc的親和力

SIRPa-Fc 融合蛋白	ka (1/Ms)	kd (1/s)	KD (M)
Mut88-Fc	1.11E+06	9.92E-04	8.97E-10
Mut113-Fc	9.47E+05	2.16E-04	2.28E-10
Mut114-Fc	1.25E+06	2.53E-04	2.03E-10
Mut117-Fc	1.35E+06	4.39E-04	3.25E-10

SIRPa V1-Fc	1.76E+05	7.64E-04	4.34E-09
TTI621	2.50E+05	1.19E-03	4.76E-09

【0123】 類似實施例3C，檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc蛋白結合程度。結果如圖7和表15所示，結果說明親和力成熟後SIRPa-Fc融合蛋白與hCD47 ECD-mFc的結合活性均優於野生型或者TTI621。

【0124】 表15 ELISA檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc的結合活性

OD450 nm	蛋白濃度(nM)							
蛋白名稱	50	10	2	0.4	0.08	0.016	0.0032	0.00064
Mut88-Fc	2.007	2.083	2.250	1.939	1.466	0.643	0.247	0.091
Mut113-Fc	1.892	1.949	2.164	2.098	1.315	0.625	0.355	0.091
Mut114-Fc	1.874	1.958	2.136	2.012	1.267	0.526	0.200	0.075
Mut117-Fc	2.021	2.013	2.185	1.976	1.294	0.528	0.216	0.071
SIRPa V1-Fc	1.556	1.348	1.300	0.864	0.400	0.143	0.061	0.057
TTI621	1.652	1.470	1.586	1.300	0.699	0.296	0.132	0.082
陰性對照	0.056	0.053	0.046	0.044	0.042	0.048	0.051	0.067

【0125】 類似實施例5A，流式細胞實驗（FACS）檢測SIRPa-Fc融合蛋白與細胞的結合活性。結果如圖8和表16所示，結果說明親和力成熟後SIRPa-Fc融合蛋白與Jurkat細胞結合程度均優於野生型或者TTI621。表中數據MFI為所測細胞群的平均螢光強度值。

【0126】 表16 FACS檢測SIRPa-Fc融合蛋白與Jurkat的結合活性

MFI	蛋白濃度(nM)							
蛋白名稱	500	100	20	4	0.8	0.16	0.032	0.0064
Mut88-Fc	5300	5083	4986	4932	4586	1268	463	37
Mut113-Fc	5460	5261	5265	5235	3635	1192	367	34
Mut114-Fc	5563	5353	5292	5258	3921	1327	384	36
Mut117-Fc	5574	5357	5227	5260	3775	1242	390	36
SIRPa V1-Fc	2478	1322	576	211	90	47	36	30
TTI621	2928	2184	1360	792	429	173	73	31
陰性對照	178	66	39	35	33	33	31	29

【0127】 實施例8 篩選去醣基化突變

【0128】 為保證後續生產製程的可控性，我們在Mut81、Mut113、

Mut114和Mut117的基礎上進一步對82位胺基酸進行突變以保證該點位不引起醣基化修飾。類似實施例1，將編碼突變體的核酸片段複製至帶有Fc標籤的pTT5載體上，並按已建立的標準分子生物學方法製備質體。融合蛋白及各元件的具體序列資訊如表17所示，其中，「MutXX-Fc」表示突變型SIRPa與Fc的融合蛋白。

【0129】 表17 SIRPa突變序列

突變號	序列編號	序列資訊
Mut92 (Mut81+T82F)	SEQ ID NO : 83	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN IFPADAGTYCYVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut93 (Mut81+T82D)	SEQ ID NO : 84	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN IDPADAGTYCYVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut94 (Mut81+T82N)	SEQ ID NO : 85	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN INPADAGTYCYVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut95 (Mut81+T82E)	SEQ ID NO : 86	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN IEPADAGTYCYVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut97 (Mut81+T82G)	SEQ ID NO : 87	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN IGPADAGTYCYVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut98 (Mut81+T82H)	SEQ ID NO : 88	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN IHPADAGTYCYVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut99 (Mut81+T82L)	SEQ ID NO : 89	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN ILPADAGTYCYVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut100 (Mut81+T82I)	SEQ ID NO : 90	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN IIPADAGTYCYVKFRKGGSPDDVEFKSGAGTELSVRAKPS
Mut105 (Mut81+T82V)	SEQ ID NO : 91	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSIRIGN IVPADAGTYCYVKFRKGGSPDDVEFKSGAGTELSVRAKPS

突變號	序列編號	序列資訊
Mut107 (Mut81+T82Y)	SEQ ID NO : 92	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQWFR GAGPGRELIYRQKEGHFPRVTTVSDNTRNNMDFSIRIGN IYPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSVR AKPS
Mut139 (Mut113+T82H)	SEQ ID NO : 93	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTQRNNMDFSIR RIGNIHPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSV RAKPS
Mut141 (Mut113+T82V)	SEQ ID NO : 94	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTQRNNMDFSIR RIGNIVPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSV RAKPS
Mut142 (Mut114+T82G)	SEQ ID NO : 95	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTRLRNNMDFSIR IGNIGPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSVR AKPS
Mut146 (Mut117+T82G)	SEQ ID NO : 96	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTIRNNMDFSIR IGNIGPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSVR AKPS
Mut92-Fc	SEQ ID NO : 97	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTRNNMDFSIR RIGNIFPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut93-Fc	SEQ ID NO : 98	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTRNNMDFSIR RIGNIDPADAGTYCYCVKFRKGGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut94-Fc	SEQ ID NO : 99	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTRNNMDFSIR

突變號	序列編號	序列資訊
		RIGNINPADAGTYTCVKFRKGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut95-Fc	SEQ ID NO : 100	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSI RIGNIEPADAGTYTCVKFRKGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut97-Fc	SEQ ID NO : 101	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSI RIGNIGPADAGTYTCVKFRKGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut98-Fc	SEQ ID NO : 102	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSI RIGNIHPADAGTYTCVKFRKGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut99-Fc	SEQ ID NO : 103	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSI RIGNILPADAGTYTCVKFRKGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK

突變號	序列編號	序列資訊
		AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut100-Fc	SEQ ID NO : 104	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSI RIGNIIPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut105-Fc	SEQ ID NO : 105	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSI RIGNIVPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut107-Fc	SEQ ID NO : 106	EEELQVIQPDKSVLVAAGETATLRCTATSLYPVGPIQW FRGAGPGRELIYRQKEGHFPRVTTVSDNTKRNNMDFSI RIGNIYPADAGTY YCVKFRKGGSPDDVEFKSGAGTELSV RAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut139-Fc	SEQ ID NO : 107	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDNTQQRNM DFSIRIGNIHPADAGTY YCVKFRKGGSPDDVEFKSGAG TELSVRAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK

突變號	序列編號	序列資訊
		GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut141-Fc	SEQ ID NO : 108	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDNTQRNNM DFSIRIGNIVPADAGTYYCVKFRKGSPPDDVEFKSGAG TELSVRAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut142-Fc	SEQ ID NO : 109	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDNTLRNNM DFSIRIGNIGPADAGTYYCVKFRKGSPPDDVEFKSGAG TELSVRAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
Mut146-Fc	SEQ ID NO : 110	EEELQVIQPDKSVLVAAGETATLRCTATSLMPVGPIQ WFRGAGPGRELIYRQKEGHFPRVTTVSDNTIRNNMD FSIRIGNIGPADAGTYYCVKFRKGSPPDDVEFKSGAGT ELSVRAKPS DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

【0130】 類似實施例2，用Expi293F或ExpiCHO系統表現純化突變蛋白，其中Mut92-Fc、Mut93-Fc、Mut94-Fc、Mut95-Fc、Mut97-Fc、Mut98-Fc、Mut99-Fc、Mut100-Fc、Mut105-Fc和Mut107-Fc透過Expi293F系統表現，Mut139-Fc、Mut141-Fc、Mut142-Fc和Mut146-Fc透過ExpiCHO系統表現。將純化的SIRPa-Fc融合蛋白進行蛋白產量、蛋白濃度（A280/1.4）、SEC純度等檢

測分析，純化後的SIRPa-Fc融合蛋白的品質合格。其中關於蛋白產量、蛋白濃度和純度的檢測資訊參見表18。

【0131】 表18 SIRPa-Fc融合蛋白的檢測分析

突變號	蛋白產量 (mg/L)	蛋白 SEC 純度	蛋白濃度 (mg/mL)
Mut92-Fc	16.3	97.866%	1.03
Mut93-Fc	48.7	98.266%	1.98
Mut94-Fc	64.0	97.704%	1.72
Mut95-Fc	53.5	97.920%	3.38
Mut97-Fc	64.3	97.770%	4.06
Mut98-Fc	53.5	97.812%	2.18
Mut99-Fc	38.3	98.104%	2.42
Mut100-Fc	40.7	97.766%	1.32
Mut105-Fc	44.8	97.210%	2.46
Mut107-Fc	20.3	98.106%	0.92
Mut139-Fc	188.3	91.768%	5.58
Mut141-Fc	141.7	94.182%	3.70
Mut142-Fc	193.3	93.930%	5.88
Mut146-Fc	158.3	93.527%	4.35

【0132】 類似實施例4，利用表面電漿共振（SPR）檢測SIRPa-Fc融合蛋白與CD47蛋白親和力結果如表19所示，結果說明去糖基化SIRPa-Fc融合蛋白與hCD47 ECD-mFc的親和力均優於野生型或者TTI621。

【0133】 表19 SPR檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc的親和力

SIRPa-Fc 融合蛋白	ka (1/Ms)	kd (1/s)	KD (M)
Mut81-Fc	1.06E+06	2.33E-04	2.20E-10
Mut92-Fc	9.23E+05	2.63E-04	2.85E-10
Mut93-Fc	9.70E+05	2.35E-04	2.42E-10
Mut94-Fc	9.06E+05	2.30E-04	2.54E-10
Mut95-Fc	9.61E+05	2.41E-04	2.50E-10
Mut97-Fc	9.19E+05	2.27E-04	2.47E-10
Mut98-Fc	9.41E+05	2.45E-04	2.60E-10
Mut99-Fc	9.98E+05	2.29E-04	2.29E-10
Mut100-Fc	9.32E+05	2.51E-04	2.70E-10
Mut105-Fc	9.60E+05	2.19E-04	2.28E-10
Mut107-Fc	8.59E+05	2.85E-04	3.31E-10

Mut88-Fc	1.11E+06	9.92E-04	8.97E-10
Mut139-Fc	1.14E+06	2.45E-04	2.14E-10
Mut141-Fc	1.16E+06	2.35E-04	2.02E-10
Mut142-Fc	8.99E+05	2.66E-04	2.96E-10
Mut146-Fc	9.82E+05	3.84E-04	3.90E-10
SIRPa V1-Fc	1.76E+05	7.64E-04	4.34E-09
TTI621	2.50E+05	1.19E-03	4.76E-09

【0134】 類似實施例3C，檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc蛋白結合程度。結果如圖9A-9C和表20所示，結果說明去醣基化SIRPa-Fc融合蛋白與hCD47 ECD-mFc的結合活性均優於野生型或者TTI621。

【0135】 表20 ELISA檢測SIRPa-Fc融合蛋白與hCD47 ECD-mFc的結合活性

OD450 nm	蛋白濃度(nM)							
蛋白名稱	50	10	2	0.4	0.08	0.016	0.0032	0.00064
Mut81-Fc	2.157	2.050	2.096	2.110	1.901	0.477	0.186	0.100
Mut92-Fc	2.158	2.039	2.175	2.038	1.115	0.401	0.155	0.112
Mut93-Fc	2.154	2.059	2.146	2.020	1.091	0.399	0.144	0.109
Mut94-Fc	2.128	2.099	2.111	2.073	1.164	0.462	0.193	0.113
Mut95-Fc	2.190	2.175	2.228	2.090	1.233	0.522	0.217	0.119
Mut97-Fc	2.109	2.252	2.185	1.874	0.946	0.345	0.143	0.120
Mut98-Fc	2.055	2.103	2.239	2.266	1.890	0.907	0.361	0.123
Mut99-Fc	2.164	2.138	2.060	2.130	1.854	0.852	0.363	0.124
SIRPa V1-Fc	1.689	1.550	1.423	0.882	0.406	0.121	0.063	0.117
TTI621	1.852	1.726	1.545	1.272	0.748	0.228	0.098	0.099
陰性對照	0.061	0.056	0.048	0.045	0.049	0.048	0.055	0.098
Mut81-Fc	1.931	1.806	1.867	1.835	1.125	0.527	0.258	0.135
Mut100-Fc	1.952	1.784	1.989	1.662	0.877	0.321	0.135	0.122
Mut105-Fc	1.785	1.765	1.833	1.859	1.086	0.395	0.166	0.123
Mut107-Fc	1.839	1.876	1.919	1.913	1.112	0.446	0.185	0.124
SIRPa V1-Fc	1.431	1.239	0.973	0.775	0.367	0.136	0.077	0.117
TTI621	1.585	1.404	1.275	1.094	0.590	0.232	0.108	0.121
陰性對照	0.046	0.045	0.039	0.040	0.037	0.069	0.048	0.125
Mut88-Fc	2.007	2.083	2.250	1.939	1.466	0.643	0.247	0.091
Mut139-Fc	2.062	2.004	2.120	2.033	1.358	0.583	0.228	0.067
Mut141-Fc	1.963	1.961	2.088	1.957	1.383	0.603	0.380	0.081

Mut142-Fc	1.959	2.010	2.105	2.056	1.347	0.684	0.335	0.060
Mut146-Fc	1.929	2.137	2.246	2.084	1.187	0.531	0.277	0.061
SIRPa V1-Fc	1.556	1.348	1.300	0.864	0.400	0.143	0.061	0.057
TTI621	1.652	1.470	1.586	1.300	0.699	0.296	0.132	0.082
陰性對照	0.056	0.053	0.046	0.044	0.042	0.048	0.051	0.067

【0136】 類似實施例5A，流式細胞實驗（FACS）檢測SIRPa-Fc融合蛋白與細胞的結合活性。結果如圖10A-10C和表21所示，結果說明去醣基化SIRPa-Fc融合蛋白與Jurkat細胞結合程度均優於野生型或者TTI621。

【0137】 表21 FACS檢測SIRPa-Fc融合蛋白與Jurkat的結合活性

MFI	蛋白濃度(nM)							
蛋白名稱	500	100	20	4	0.8	0.16	0.032	0.0064
Mut81-Fc	5405	5316	5236	5179	4794	1342	421	36
Mut92-Fc	5248	5368	5278	5217	4284	1045	306	66
Mut93-Fc	5225	5030	5030	5105	4464	1076	393	36
Mut94-Fc	5294	5158	5152	5142	4120	957	372	36
Mut95-Fc	5421	5265	5233	5209	4177	1138	334	34
Mut97-Fc	5456	5117	5323	5218	4517	1128	459	34
Mut98-Fc	5486	5260	5229	5224	4523	1203	394	35
Mut99-Fc	5281	5394	5330	5272	4208	1109	458	34
SIRPa V1-Fc	2012	1231	543	214	88	47	36	33
TTI621	2759	1981	1255	758	392	165	72	35
陰性對照	121	52	36	35	34	34	31	33
Mut81-Fc	5957	5738	5583	5551	5319	2468	755	48
Mut100-Fc	5547	5514	5506	5398	4605	1633	484	42
Mut105-Fc	5582	5519	5430	5314	5307	2763	850	39
Mut107-Fc	5469	5421	5424	5324	4980	1904	584	39
SIRPa V1-Fc	2020	1240	606	227	94	53	39	36
TTI621	2596	1943	1190	694	372	157	75	38
陰性對照	134	53	42	36	38	36	35	33
Mut88-Fc	5300	5083	4986	4932	4586	1268	463	37
Mut139-Fc	5630	5405	5318	5337	4590	1521	514	36
Mut141-Fc	5780	5494	5365	5380	4479	1616	493	34
Mut142-Fc	5733	5441	5424	5337	4222	1394	533	34
Mut146-Fc	5607	5469	5366	5349	4399	1635	527	33
SIRPa V1-Fc	2478	1322	576	211	90	47	36	30

TTI621	2928	2184	1360	792	429	173	73	31
陰性對照	178	66	39	35	33	33	31	29

【0138】 實施例9 檢測SIRPa-Fc融合蛋白介導的對腫瘤細胞的吞噬作用

【0139】 PBMC自液態氮中取出後，置於37℃水浴中解凍。以EasySep™ Buffer（購自Stemcell，貨號20144）重新懸浮PBMC，以300xg離心5分鐘後，棄去上清液。以單核細胞分選套組（購自Miltenyi Biotec，貨號130-096-537）富集單核細胞，並以rhM-CSF（購自R&D systems，貨號216-MC-100）進行誘導分化，每兩天換液一次，至第七天收集巨噬細胞備用。

【0140】 將Raji細胞在T-75培養瓶中擴大培養至1×10⁶細胞/mL。離心去除培養基，用PBS（購自Hyclone，貨號SH30256.01）洗滌兩次，將細胞密度調整為1×10⁶細胞/mL。以CellTrace™ Violet（購自Thermo Fisher，貨號C34557）對Raji細胞進行染色。按同樣方法，以CellTrace™ Far Red（購自Thermo Fisher，貨號C34572）對巨噬細胞進行染色。將染色後的Raji與巨噬細胞按照E:T=1:2加入96孔盤（購自Corning，貨號3474），與SIRPa-Fc融合蛋白共同孵育3小時。

【0141】 實驗結束後，向細胞中加入PI（購自Thermo Fisher，貨號P3566），孵育5分鐘後，進行流式檢測（FACS Canto Plus，購自BD公司）。結果如圖11A-11B和表22所示，表中數據吞噬比例計算公式為：CellTrace™ Violet+ CellTrace™ Far Red+ / CellTrace™ Far Red+。根據結果，SIRPa-Fc融合蛋白能夠有效介導巨噬細胞吞噬Raji細胞，且吞噬程度均優於TTI621介導的吞噬程度。

【0142】 表22 FACS檢測SIRPa-Fc融合蛋白介導的對Raji細胞的吞噬作用

吞噬比例%	蛋白濃度(nM)					
蛋白名稱	6	1.2	0.24	0.048	0.0096	0.0019
Mut10-Fc	43.9	37.6	30.9	16.4	3.4	1.3

Mut31-Fc	43.8	38.2	28.4	15.5	4.0	1.4
Mut33-Fc	43.5	42.9	36.3	22.1	10.4	2.2
Mut35-Fc	41.5	43.7	31.0	15.0	2.6	1.0
Mut38-Fc	42.9	38.8	31.3	15.3	3.4	1.3
TTI621	36.2	31.6	22.0	12.1	2.6	0.8
陰性對照	1.7	-	-	-	-	-
Mut33-Fc	14.7	14.2	14.3	12.4	7.0	3.4
Mut66-Fc	14.4	15.1	15.1	11.1	5.8	3.2
Mut67-Fc	15.6	15.2	14.9	13.2	8.2	4.3
Mut68-Fc	15.4	14	14.8	12.2	5.8	3.7
Mut69-Fc	16.8	16.6	14.9	12.1	7.2	4.6
TTI621	15.7	14.8	11.5	6.2	3.9	3.3
陰性對照	3.5	-	-	-	-	-

【0143】 將DLD1細胞在T-75培養瓶中擴大培養至 1×10^6 細胞/mL。離心去除培養基，用PBS（購自Hyclone，貨號SH30256.01）洗滌兩次，將細胞密度調整為 1×10^6 細胞/mL。以CellTrace™ Violet（購自Thermo Fisher，貨號C34557）對DLD1細胞進行染色。按同樣方法，以CellTrace™ Far Red（購自Thermo Fisher，貨號C34572）對巨噬細胞進行染色。將染色後的DLD1與巨噬細胞按照E:T=1:2加入96孔盤（購自Corning，貨號3474），與SIRPa-Fc融合蛋白以及0.04 nM Cetuximab共同孵育3小時。

【0144】 實驗結束後，向細胞中加入PI（購自Thermo Fisher，貨號P3566），孵育5分鐘後，進行流式檢測（FACS Canto Plus，購自BD公司）。結果如圖12A-12B和表23所示，SIRPa-Fc融合蛋白能夠有效促進Cetuximab介導巨噬細胞吞噬DLD1細胞。

【0145】 表23 FACS檢測SIRPa-Fc融合蛋白促進的對DLD1細胞的吞噬作用

吞噬比例%	蛋白濃度(nM)								
蛋白名稱	20	4	0.8	0.16	0.032	0.0064	0.00128	0.000256	0.0000512

Mut81-Fc	53.8	55.1	56.6	53.3	49.6	48.7	50.3	51.7	48.9
Mut97-Fc	54.6	56.8	55.5	53.4	50.4	50.0	50.8	50.7	51.2
Mut98-Fc	55.9	55.5	56.6	54.1	50.4	52.5	51.4	51.1	51.1
Mut99-Fc	55.6	55.0	55.4	53.5	49.7	50.1	50.8	50.4	50.6
Mut105-Fc	54.5	56.3	55.4	52.8	50.6	49.1	50.8	50.8	49.2
Cetuximab (0.04nM)	50.5	-	-	-	-	-	-	-	-
Mut98-Fc	41.8	42.9	40.9	40.1	36.4	33.4	33.4	31.5	33.5
Mut99-Fc	42.4	42.8	40.6	41.3	37.1	34.1	33.7	32.8	34.1
Mut139-Fc	43.1	42.0	41.5	39.3	34.6	33.9	33.8	33.2	32.6
Mut142-Fc	43.7	43.0	43.0	41.1	33.7	35.1	34.0	35.2	33.8
Mut146-Fc	42.3	40.0	41.8	40.9	35.9	34.1	33.0	34.8	35.1
Cetuximab (0.04 nM)	33.9	-	-	-	-	-	-	-	-

【0146】 實施例10 檢測SIRPa-Fc融合蛋白介導的對腫瘤生長抑制

【0147】 雌性NOD-SCID小鼠（約6-8周齡，購自北京維通利華實驗動物技術有限公司），接收後適應至少1周後開始實驗。保證OE19細胞存活率大於90%，按照每隻鼠 $8 \times 10^6 / 100 \mu\text{L}$ （1640:matrigel=1:1，corning，356237）的體積接種於NOD-SCID小鼠軀幹右側皮下。小鼠接種後根據成瘤體積分組。SIRPa-Fc融合蛋白單用組：小鼠在分組後第0、7、14天腹腔注射30 mg/kg；Trastuzumab抗體單用組：小鼠在分組後第0、3、7、14天腹腔注射10 mg/kg（組別1），或在分組後第0、7、14天腹腔注射5 mg/kg（組別2）；SIRPa-Fc融合蛋白和Trastuzumab抗體聯用組：按照上述兩種藥物各自的給藥方式，結合給藥。每天觀察小鼠並記錄小鼠體重，每週2-3次測量接種腫瘤體積。當小鼠的腫瘤體積超過終點，即腫瘤體積 $>2000 \text{ mm}^3$ ，則麻醉犧牲小鼠。腫瘤體積透過如下公式計算： $\text{tumor volume} = (\text{length} \times \text{width}^2) / 2$ ，length為腫瘤的長徑，width為腫瘤的短徑。腫瘤抑制率(Tumor growth inhibition rate，TGI%)透過如下公式計

算： $TGI\% = (1 - TV_i / TV_{vi}) \times 100\%$ ， TV_i 是特定天數給藥組小鼠的腫瘤體積平均值， TV_{vi} 是特定天數對照組小鼠的腫瘤體積平均值。根據結果如圖13A-13B和表24所示，SIRPa-Fc融合蛋白聯用Trastuzumab抗體能夠有效抑制腫瘤生長。

【0148】 表24 SIRPa-Fc融合蛋白對腫瘤生長的影響

	腫瘤抑制率，TGI%				
組別 1：	D7	D10	D14	D17	D21
Trastuzumab 抗體單用組	96.75%	98.02%	94.53%	89.50%	87.15%
Mut81-Fc 單用組	-2.88%	3.65%	13.83%	8.28%	12.09%
Mut98-Fc 單用組	-30.43%	-2.49%	2.15%	0.74%	-8.93%
Mut99-Fc 單用組	-38.73%	-16.28%	-8.31%	-12.63%	-12.89%
Mut81-Fc 和 Trastuzumab 抗體聯用組	119.24%	117.02%	111.13%	108.63%	106.79%
Mut98-Fc 和 Trastuzumab 抗體聯用組	121.99%	119.17%	111.48%	108.96%	106.54%
Mut99-Fc 和 Trastuzumab 抗體聯用組	123.63%	118.43%	111.52%	108.79%	106.95%
組別 2：	D6	D10	D13	D17	D20
Trastuzumab 抗體單用組	78.08%	89.09%	80.88%	73.17%	66.14%
Mut139-Fc 單用組	-28.94%	-9.40%	-3.08%	-6.28%	-5.29%
Mut142-Fc 單用組	2.92%	16.25%	21.00%	22.14%	15.66%
Mut146-Fc 單用組	3.05%	9.71%	13.86%	17.18%	13.68%
Mut139-Fc 和 Trastuzumab 抗體聯用組	117.44%	116.29%	109.83%	102.56%	97.81%
Mut142-Fc 和 Trastuzumab 抗體聯用組	115.93%	105.47%	100.80%	95.05%	92.51%
Mut146-Fc 和 Trastuzumab 抗體聯用組	112.75%	112.32%	105.45%	98.34%	92.86%

【符號說明】

【0149】 無

【生物材料寄存】

【0150】 無

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【發明申請專利範圍】

【請求項1】 一種多肽，其為訊號調節蛋白a(SIRPa)突變體，所述突變體相對於具有SEQ ID NO：1的野生型SIRPa，進一步具有選自下列組的胺基酸突變：

(1) I31Y；N51R；L66N；及T82H；或

(2) I31Y；N51R；L66N；及T82L。

【請求項2】 如請求項1所述的多肽，其中所述多肽在其N端或C端與免疫球蛋白Fc區融合。

【請求項3】 如請求項2所述的多肽，所述免疫球蛋白Fc區選自人IgG1、IgG2或IgG4的Fc區或其突變型。

【請求項4】 如請求項3所述的多肽，其中所述人IgG1的Fc突變型包含相對於野生型人IgG1的以下胺基酸修飾中的至少一個：L234A、L235A、G237A和/或N297A。

【請求項5】 如請求項4所述的多肽，其中所述胺基酸修飾具體為：

(1) N297A突變；或

(2) L234A、L235A以及G237A突變；或

(3) L234A、L235A、G237A以及N297A突變。

【請求項6】 如請求項3所述的多肽，其中所述Fc突變型與人IgG Fc區的野生型相比展現消除或減少的效應功能，消除或降低的C1q結合和Fcγ受體結合。

【請求項7】 如請求項1-6中任一項所述的多肽，其中所述多肽具有SEQ ID NO: 88、89、102、103中任一個的胺基酸序列。

【請求項8】 一種核酸分子，其編碼如請求項1-7中任一項所述的多肽。

【請求項9】 一種包含如請求項8所述的核酸分子的表現載體。

【請求項10】 一種宿主細胞，其包含如請求項9所述的載體。

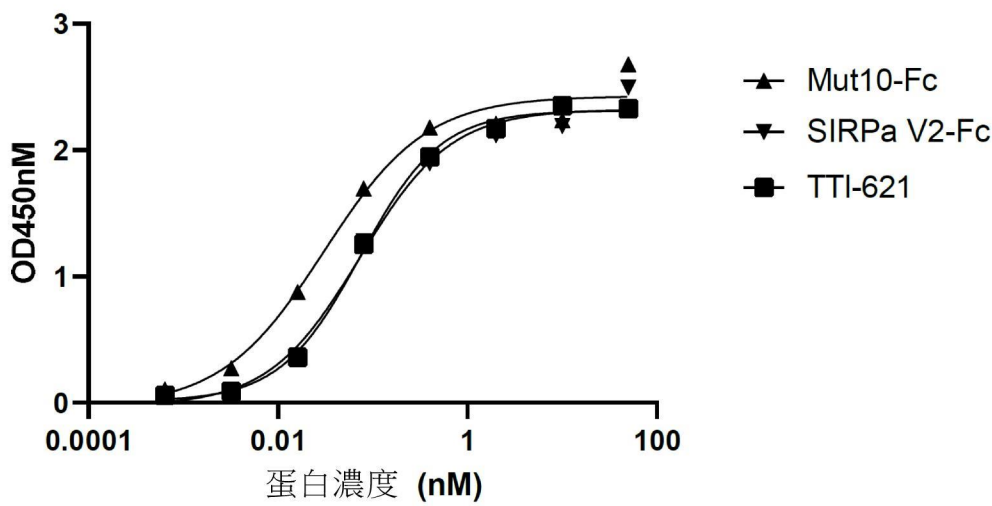
【請求項11】 如請求項10所述的宿主細胞，其中所述細胞為原核細胞或真核細胞；所述原核細胞為大腸桿菌、酵母；所述真核細胞為CHO細胞或293T細胞。

【請求項12】 一種製備如請求項1-7中任一項所述的多肽的方法，其包括培養如請求項10或11的宿主細胞，以及分離所述宿主細胞表現的多肽。

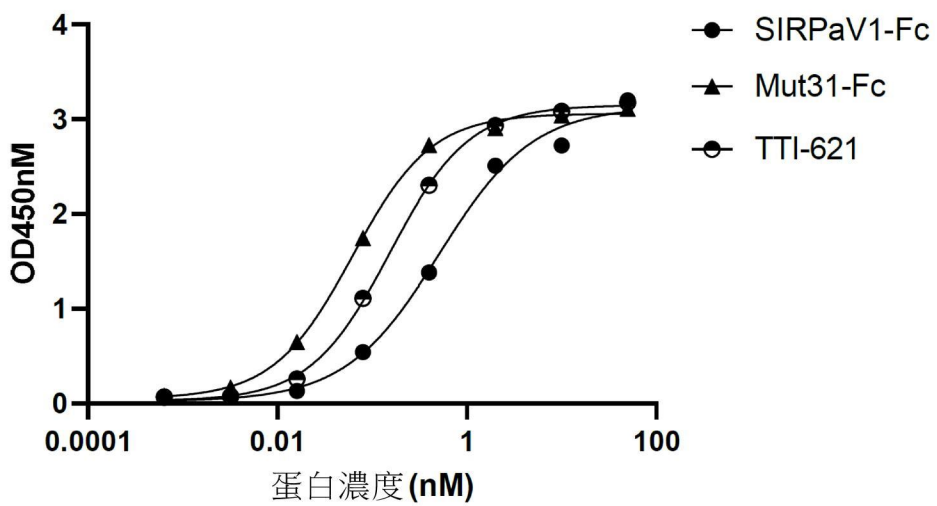
【請求項13】 一種藥物組合物，包含可藥用的載體和能夠有效地抑制CD47+疾病細胞的生長或增殖的量的如請求項1-7中任一項所述的多肽，或如請求項8的核酸分子，或如請求項9的載體。

【請求項14】 一種檢測生物學樣品中CD47表現的方法，其特徵在於，所述方法包括在如請求項1-7中任一項所述的多肽與CD47之間能夠形成複合物的條件下，使所述生物學樣品與如請求項1-7中任一項所述的多肽接觸。

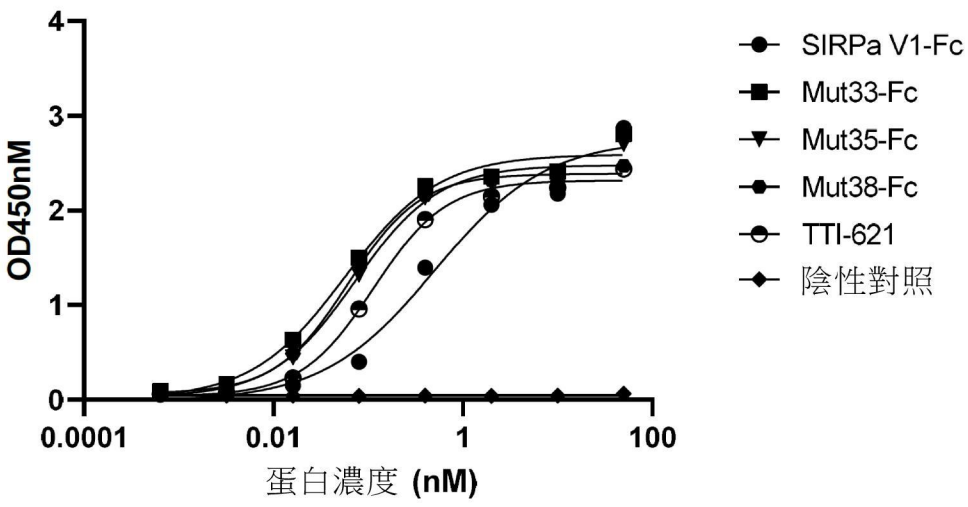
【發明圖式】



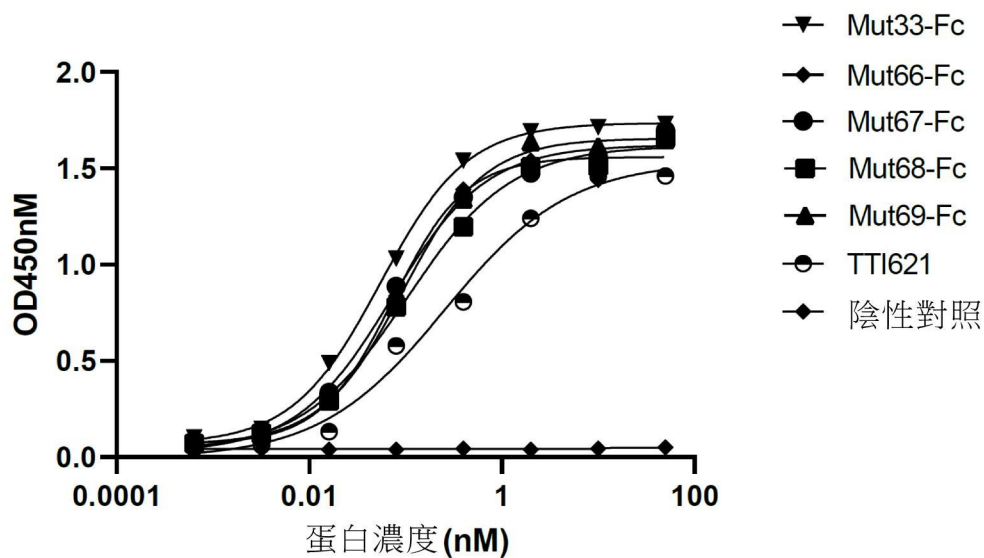
【圖1A】



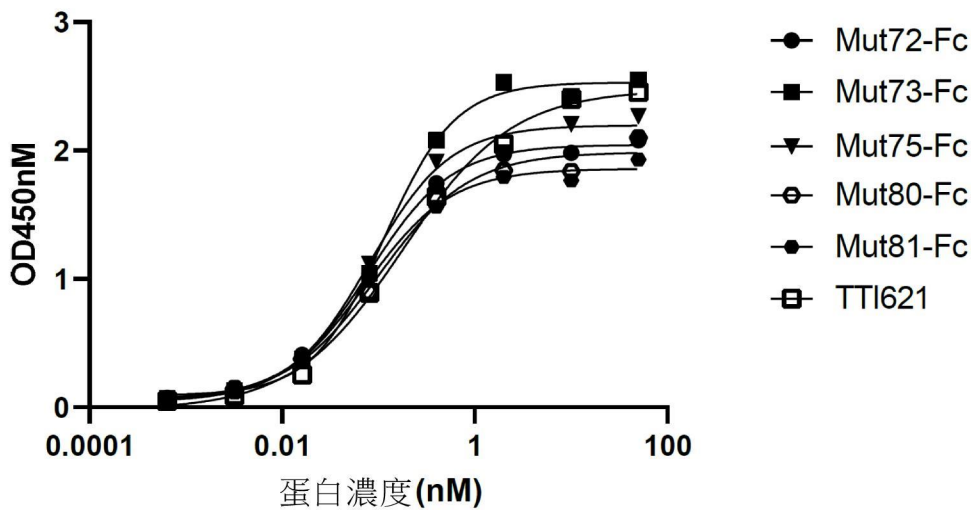
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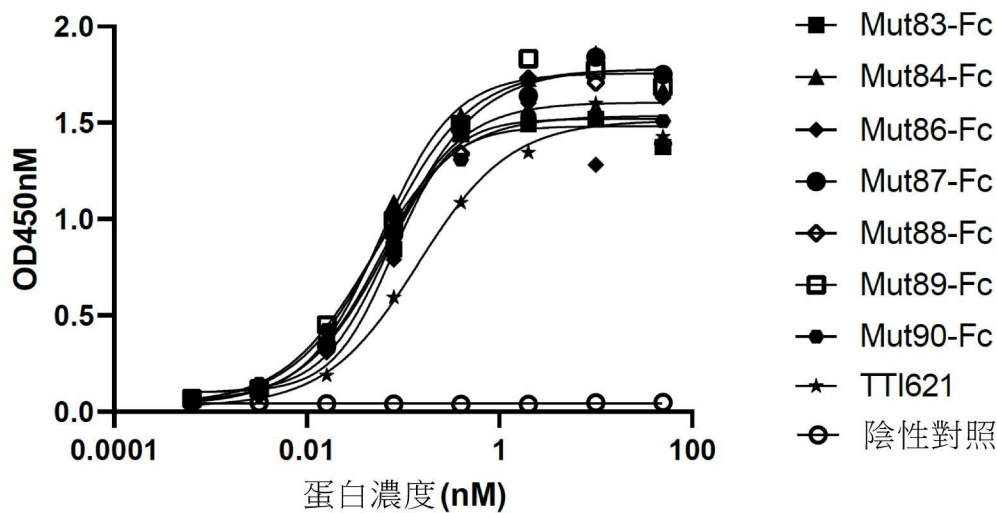
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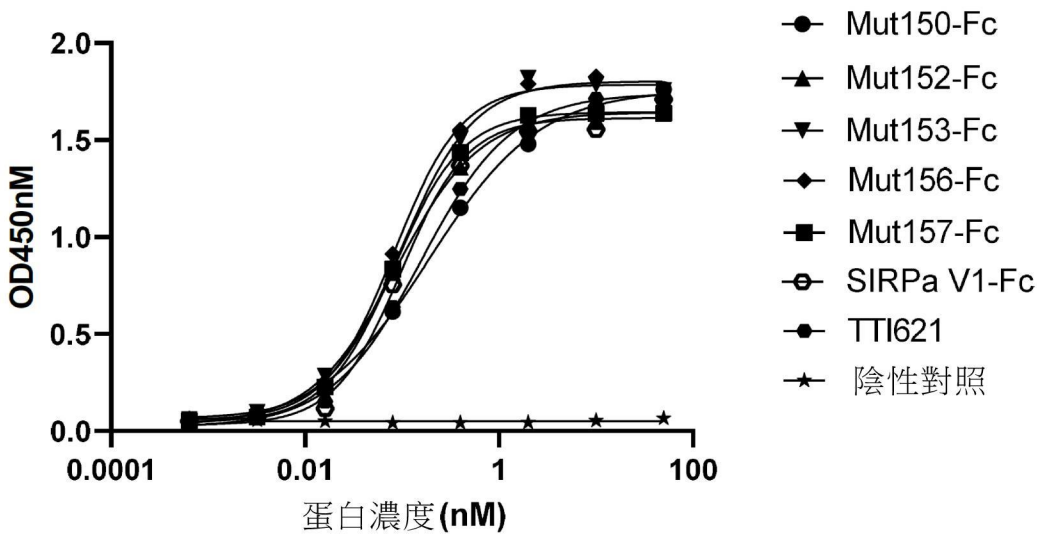
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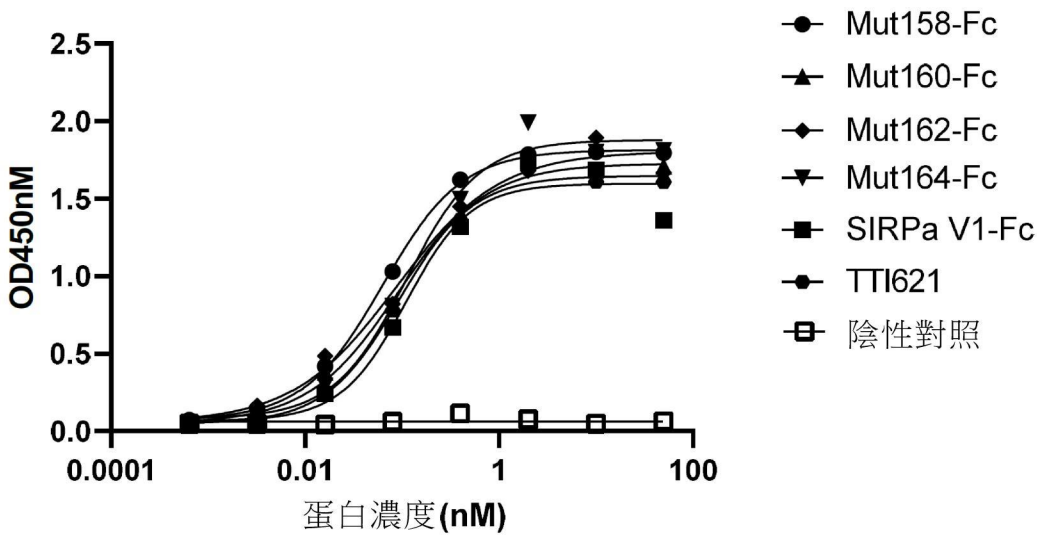
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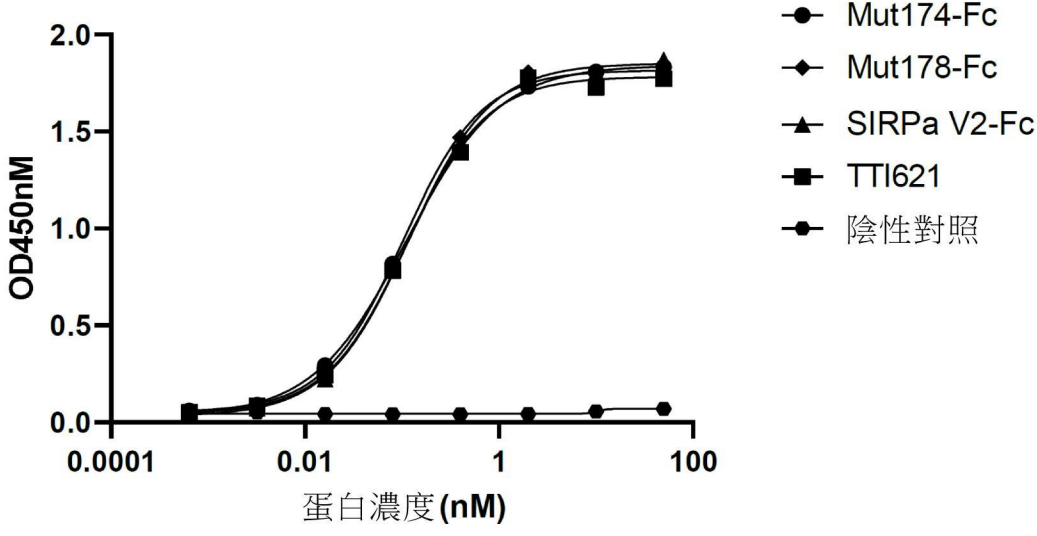
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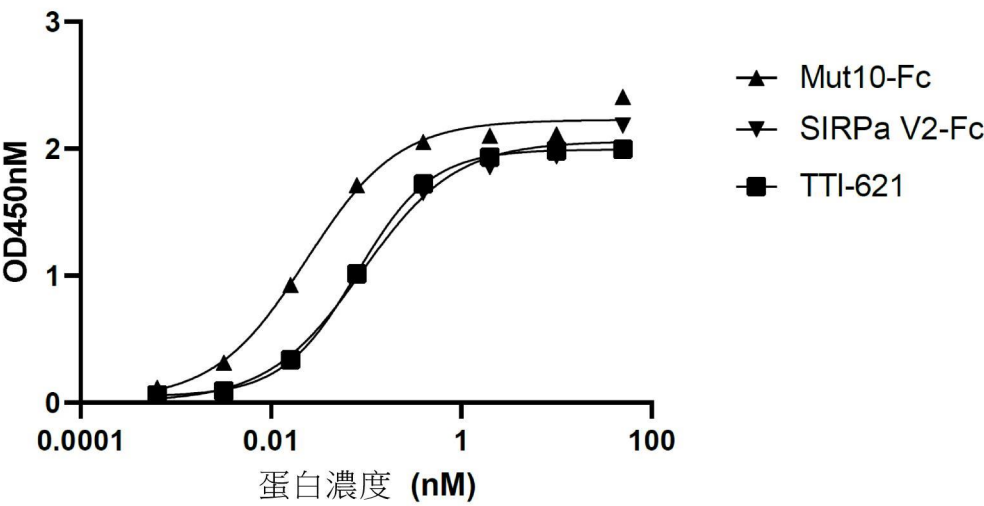
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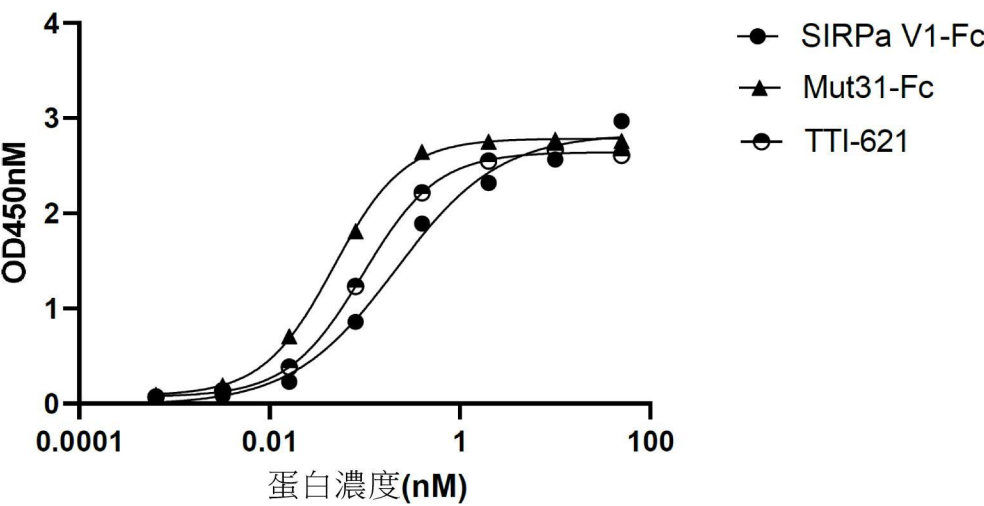
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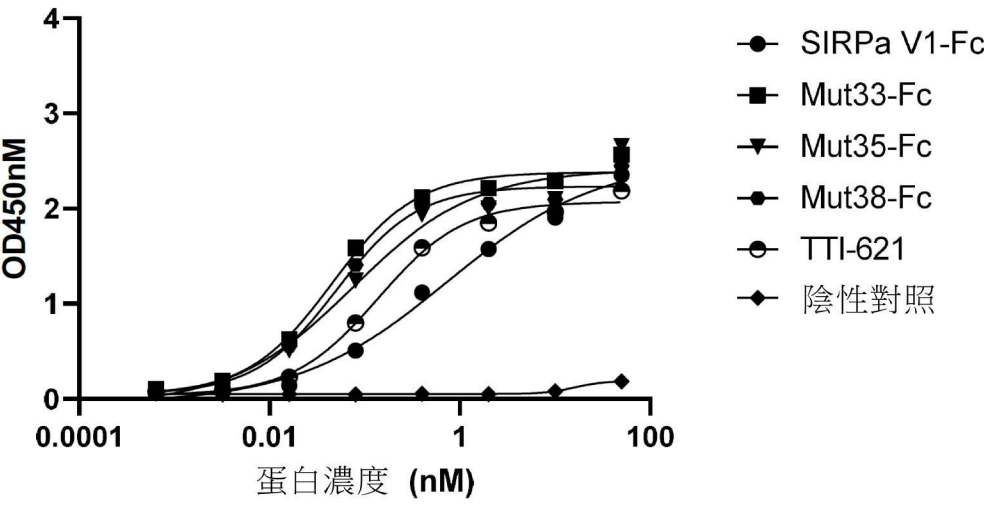
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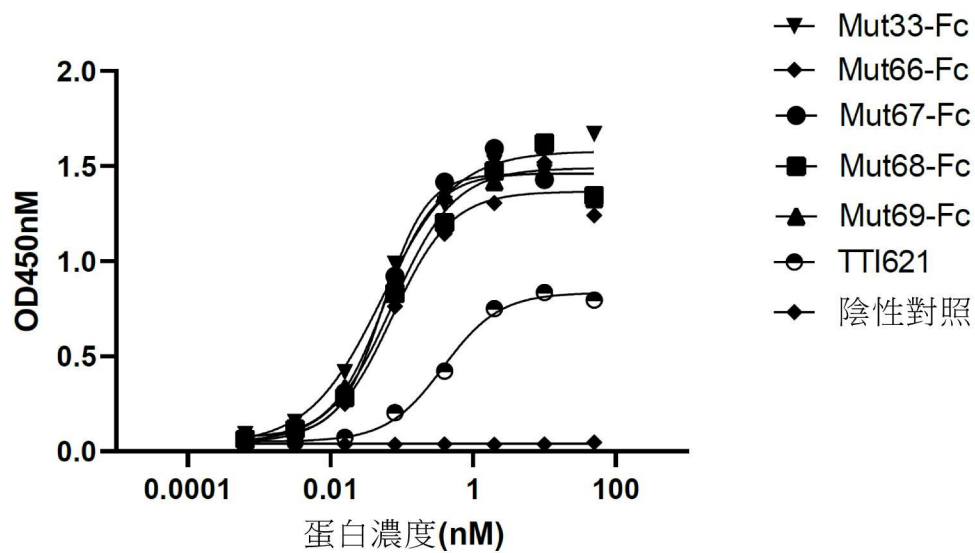
【圖2A】



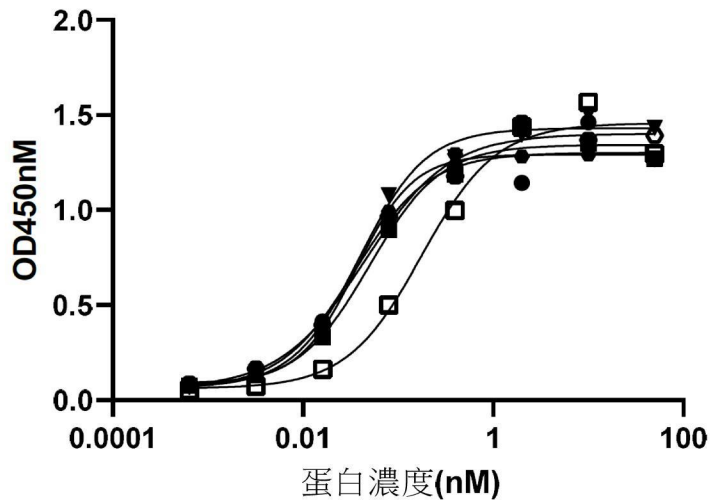
【圖2B】



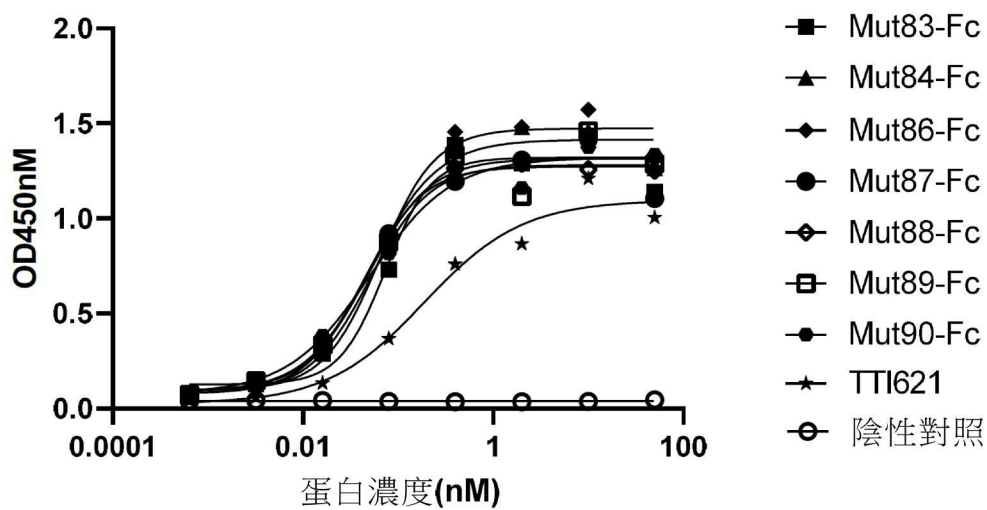
【圖2C】



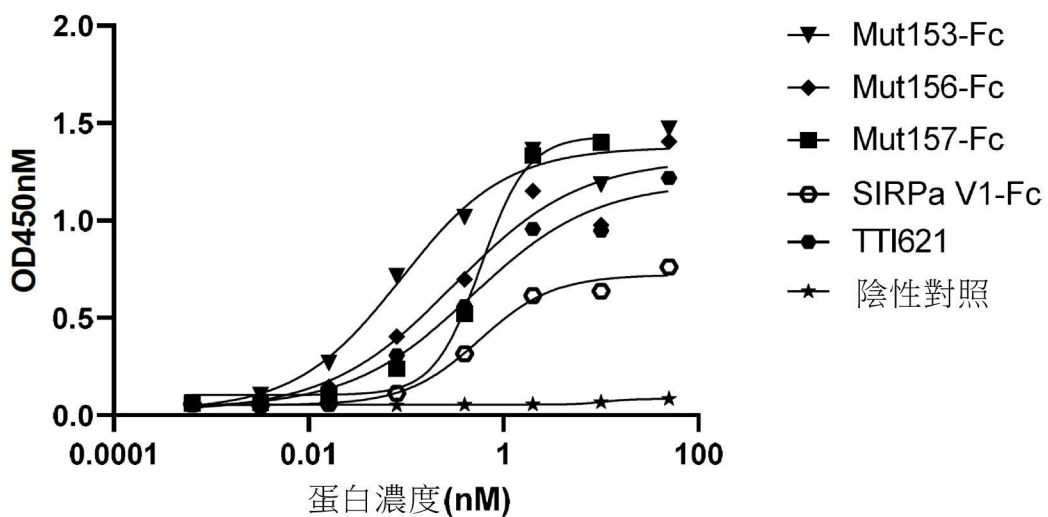
【圖2D】



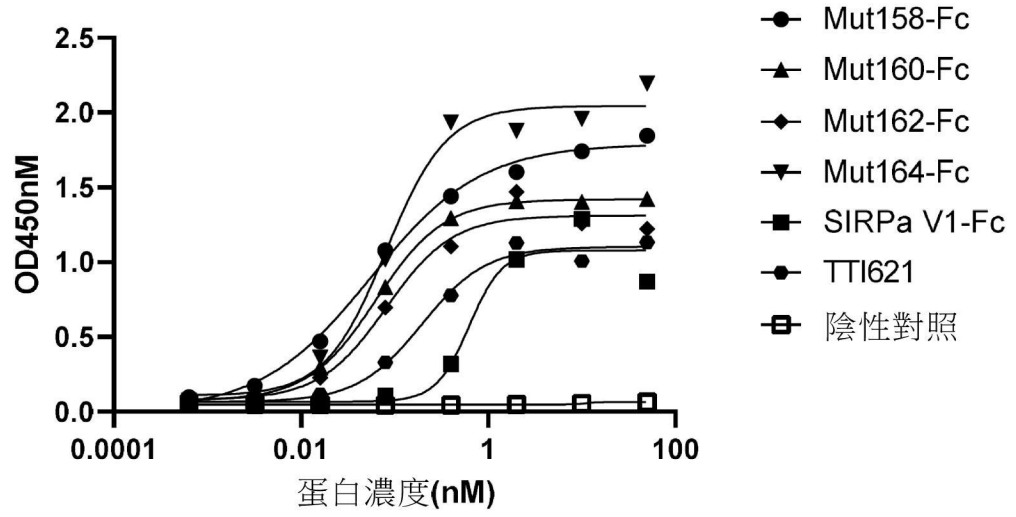
【圖2E】



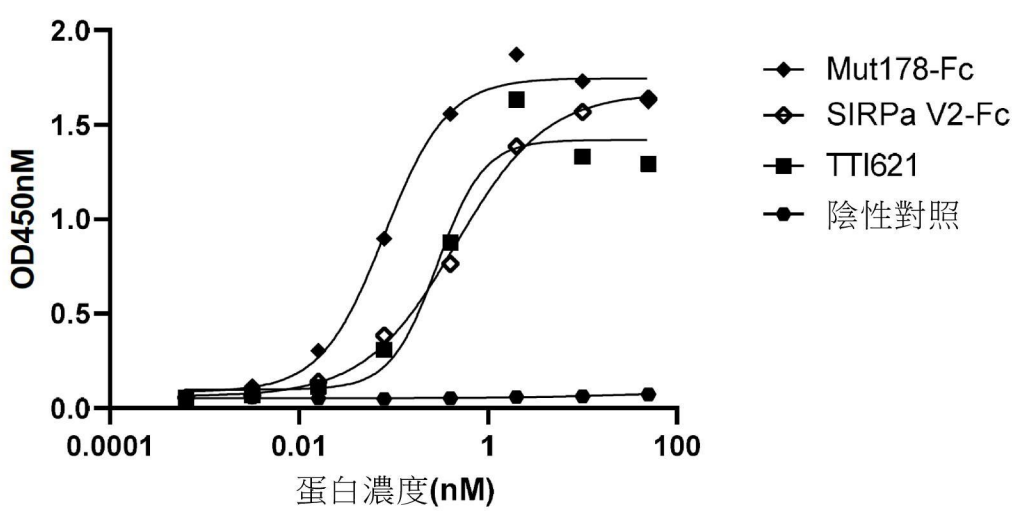
【圖2F】



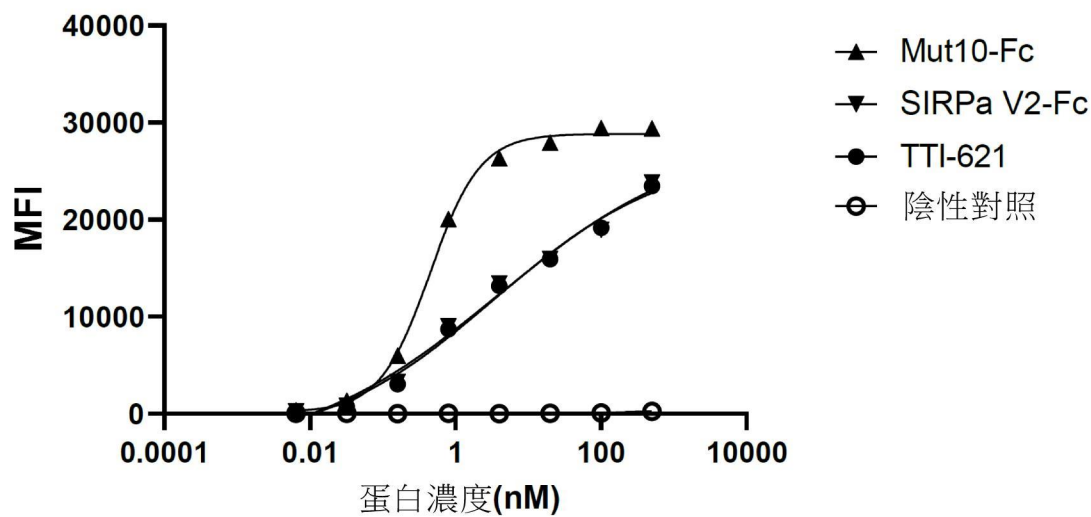
【圖2G】



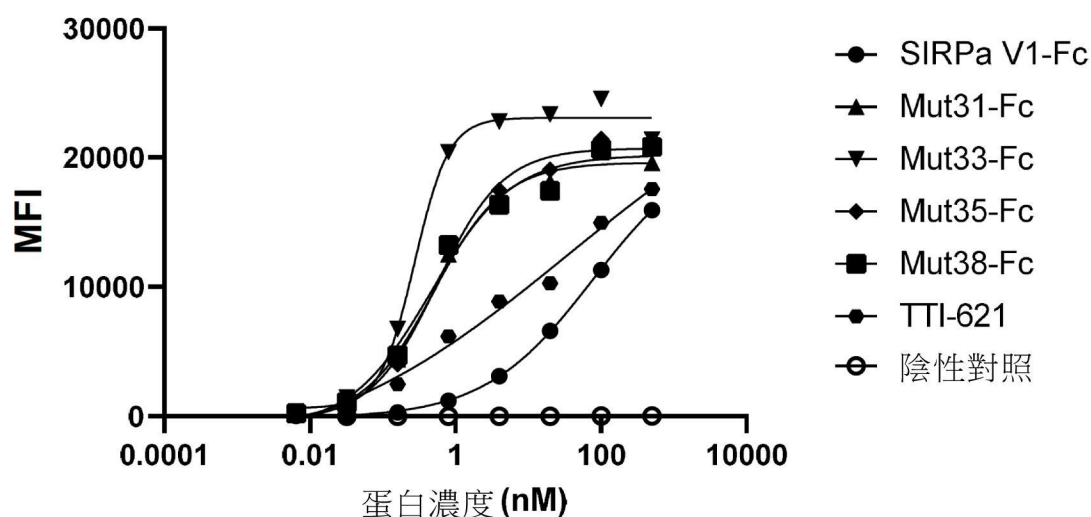
【圖2H】



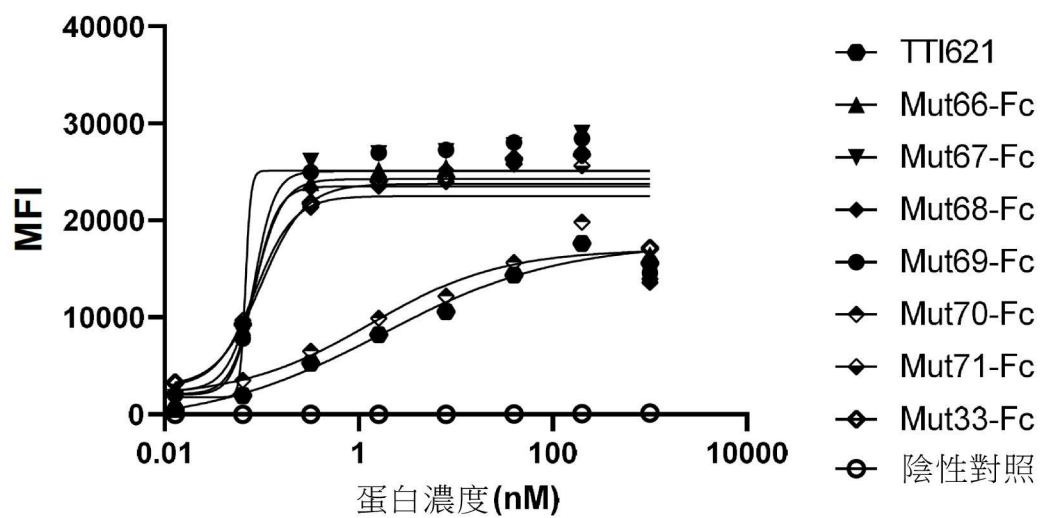
【圖2I】



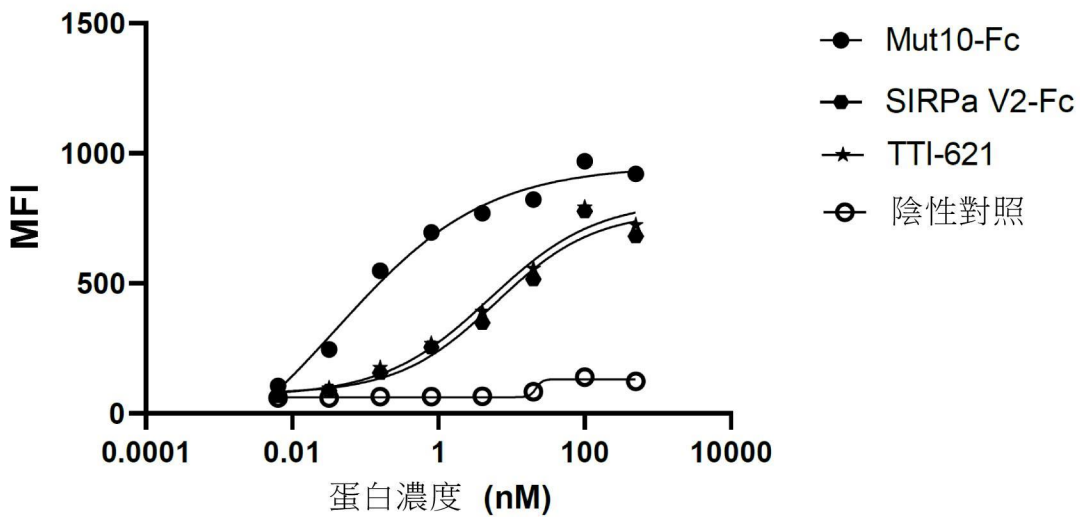
【圖3A】



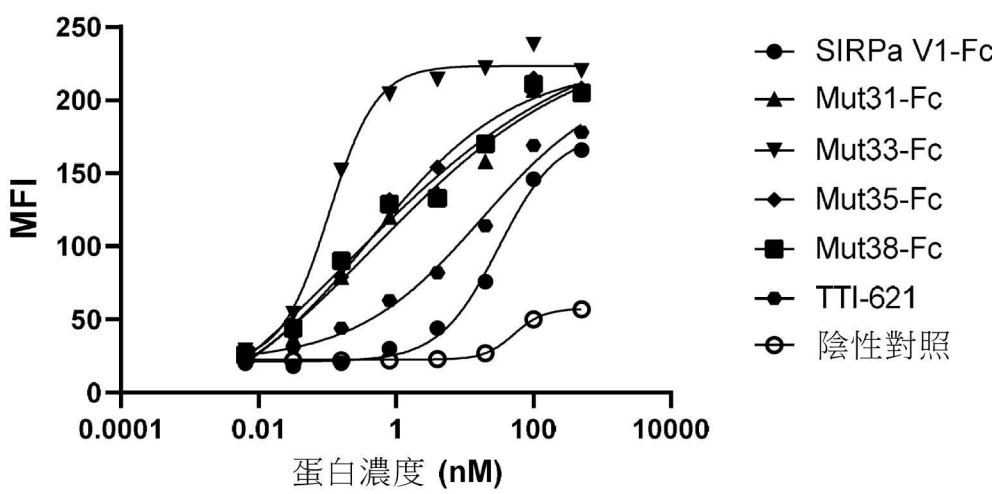
【圖3B】



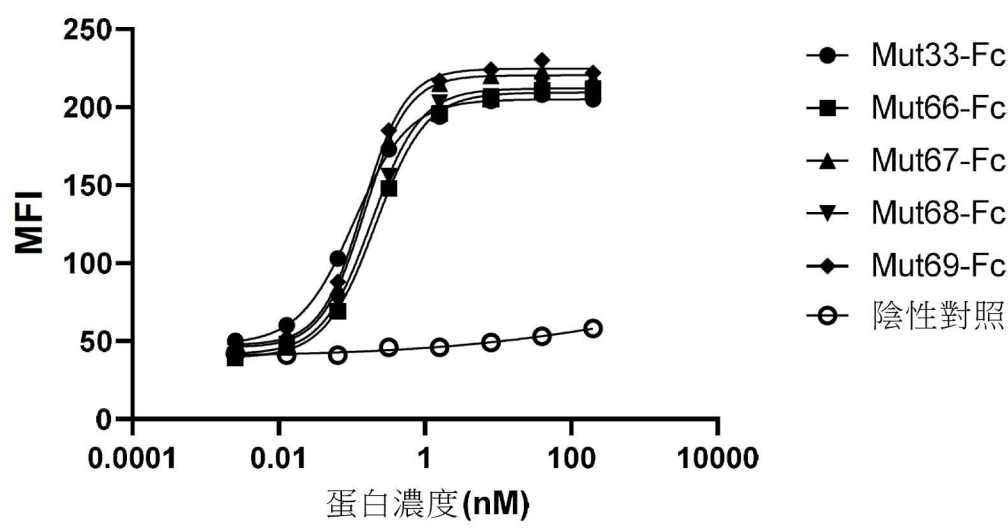
【圖3C】



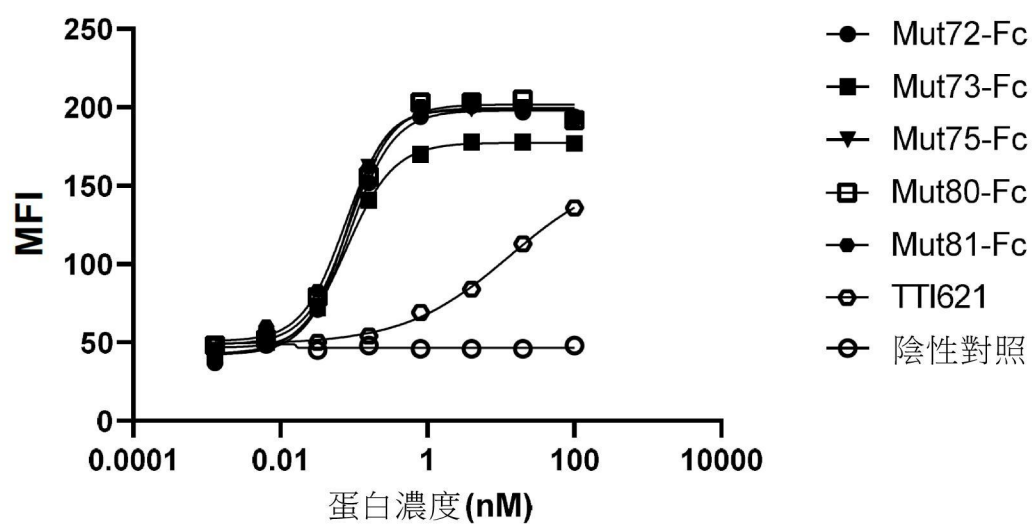
【圖4A】



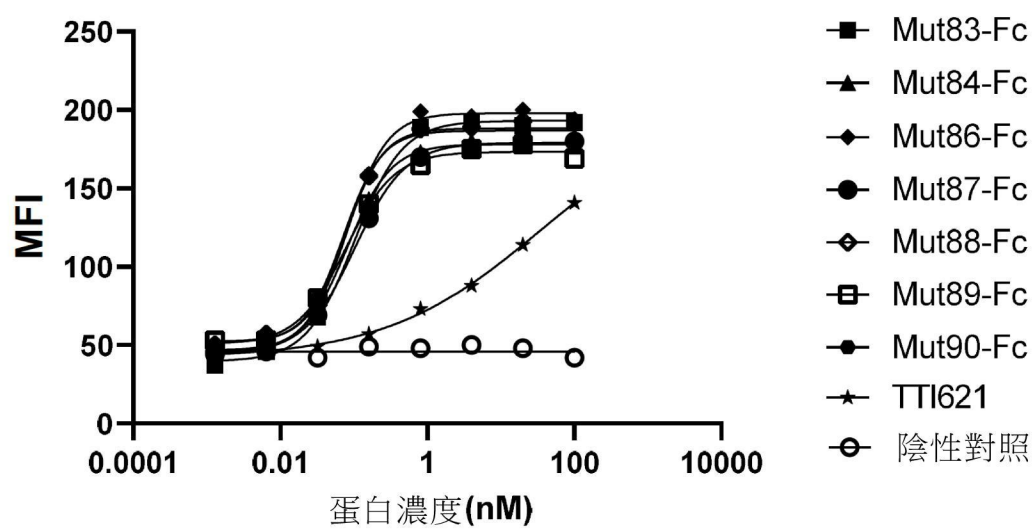
【圖4B】



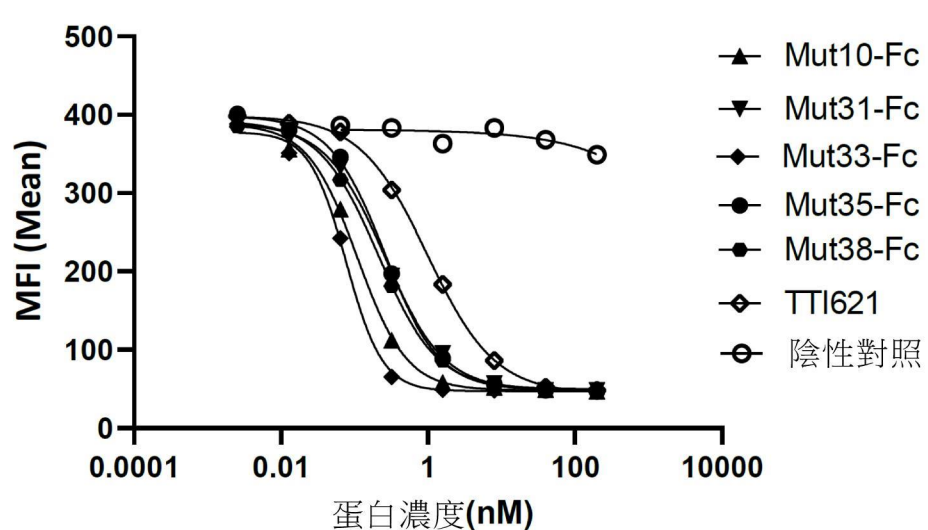
【圖4C】



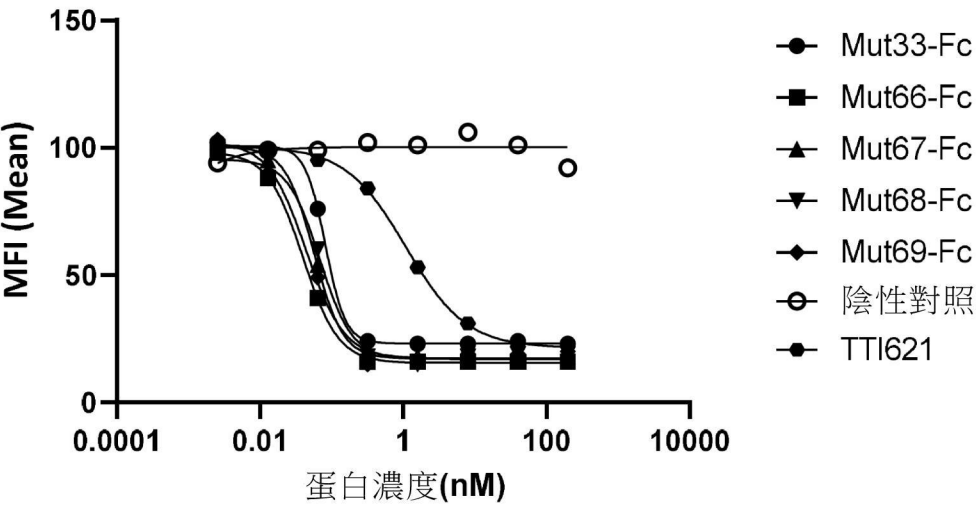
【圖4D】



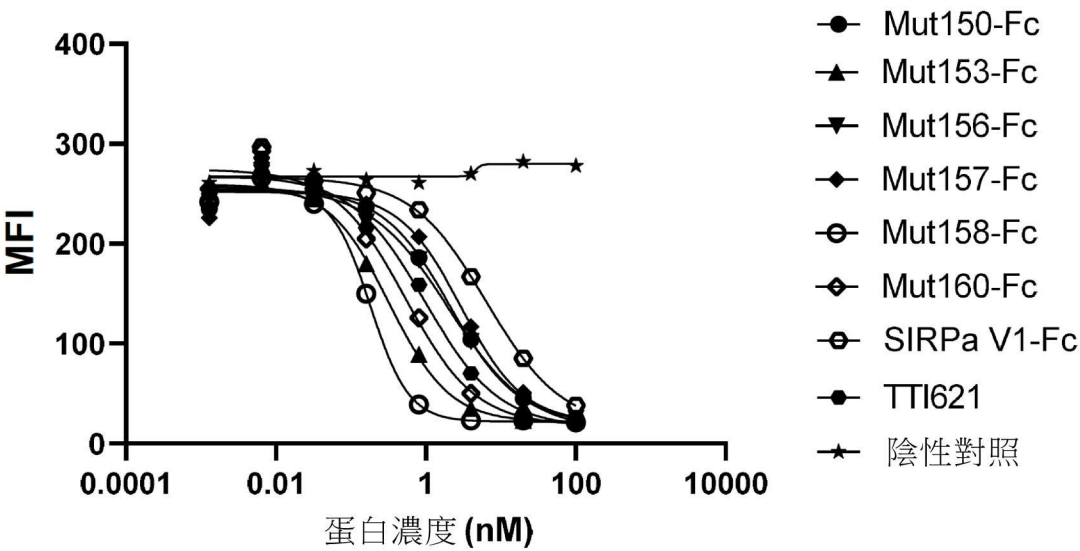
【圖4E】



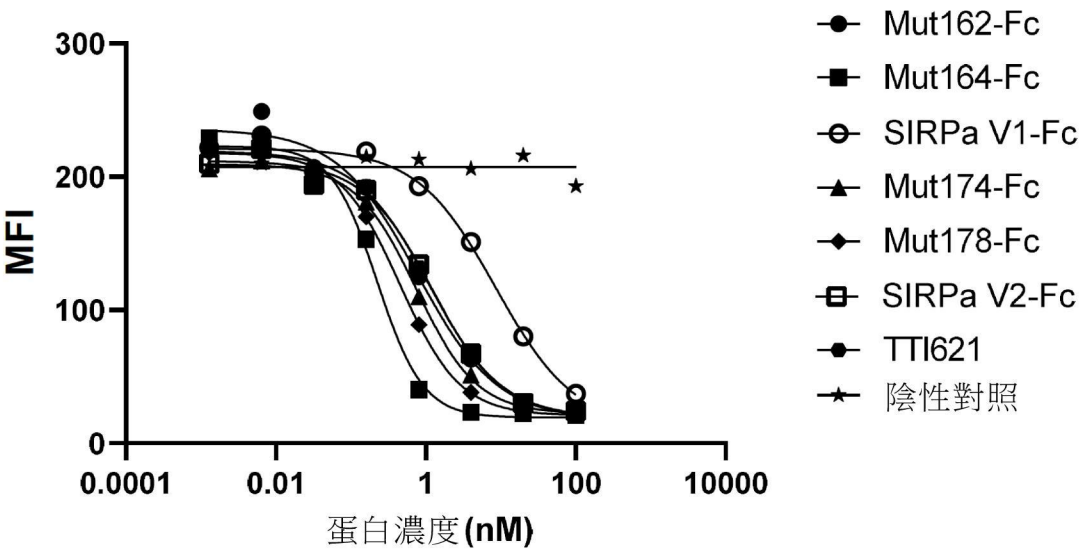
【圖5A】



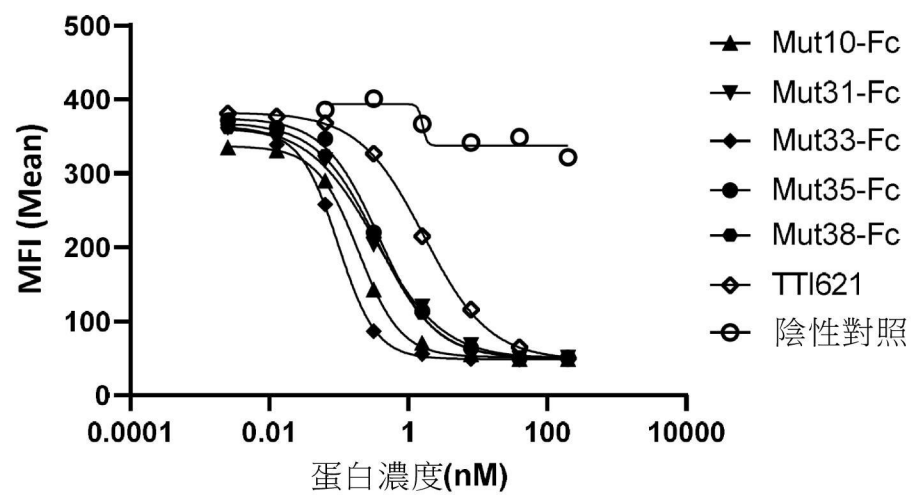
【圖5B】



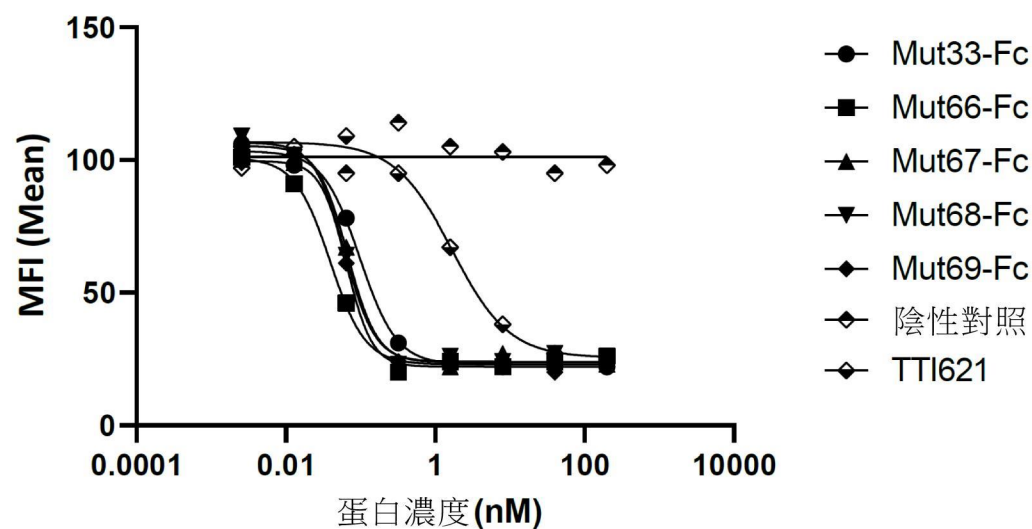
【圖5C】



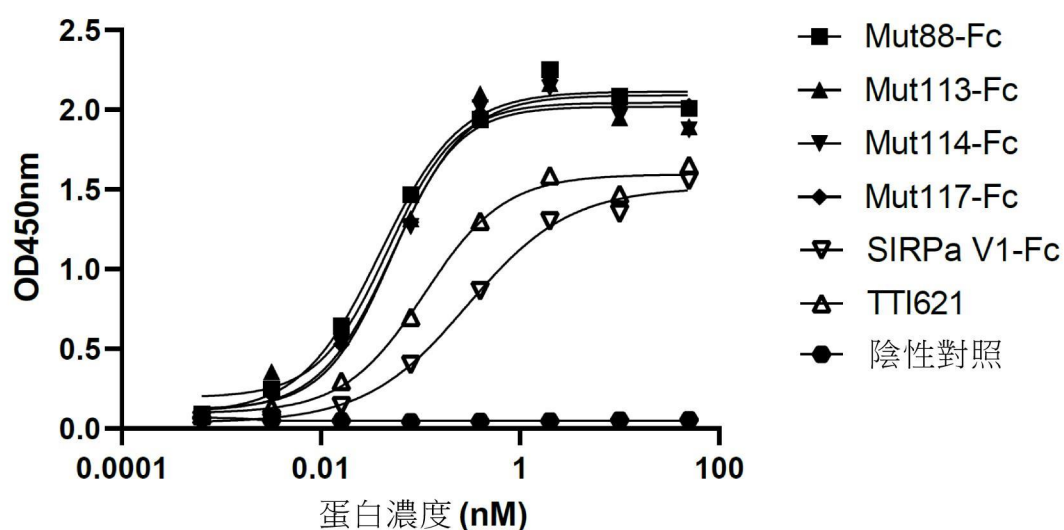
【圖5D】



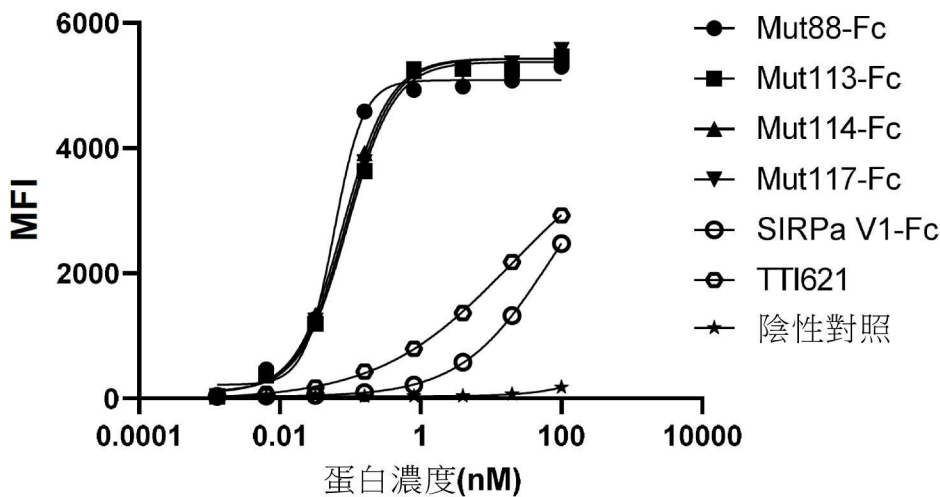
【圖6A】



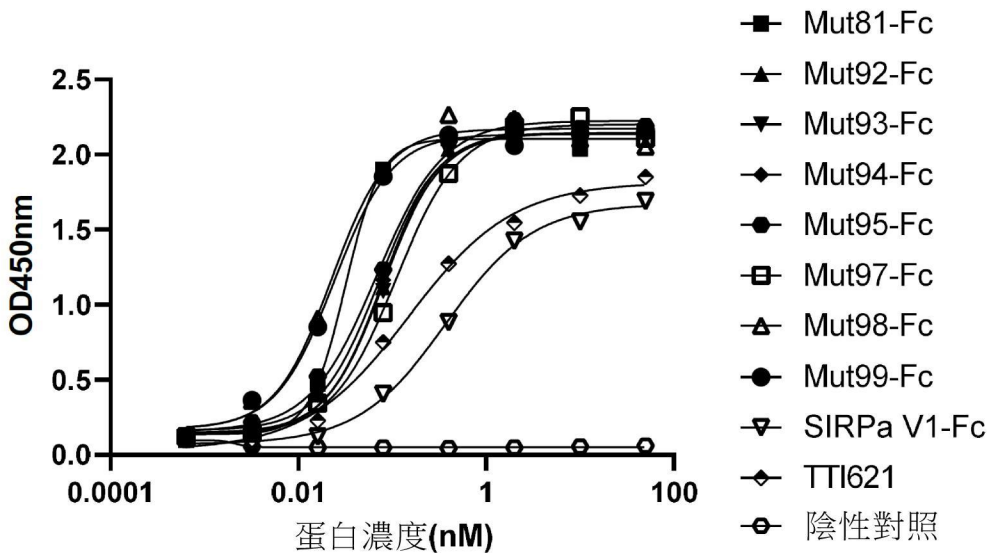
【圖6B】



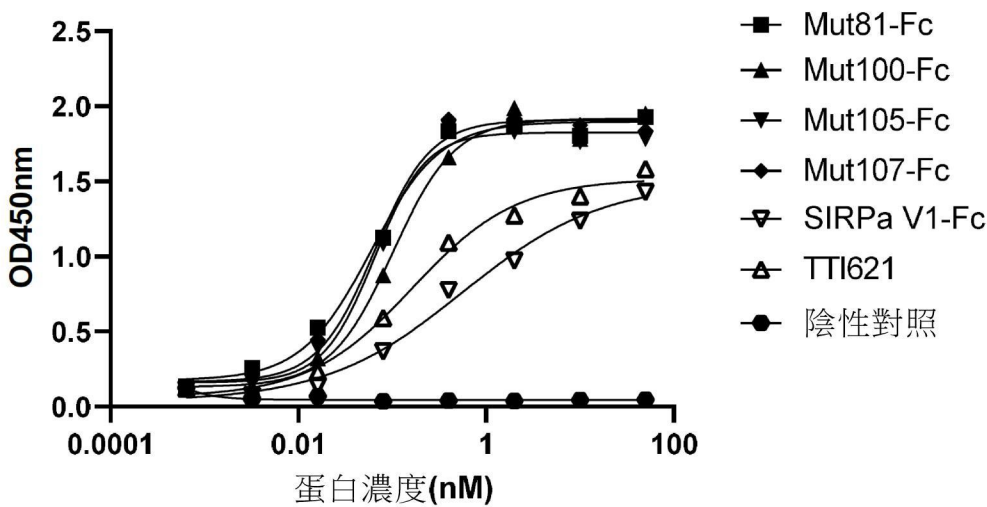
【圖7】



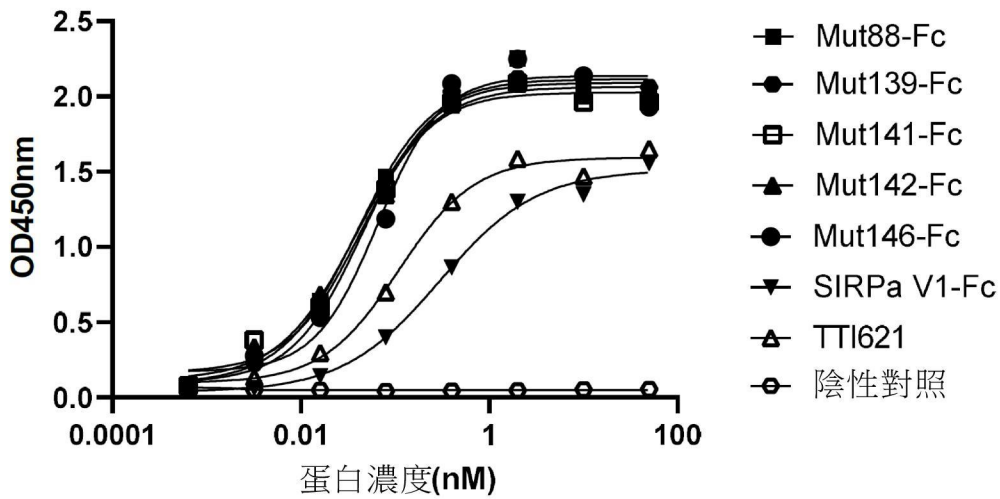
【圖8】



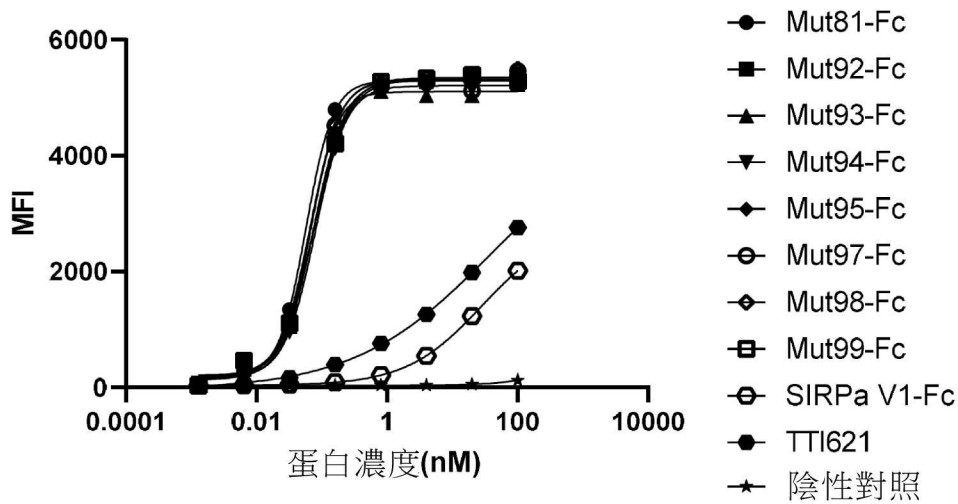
【圖9A】



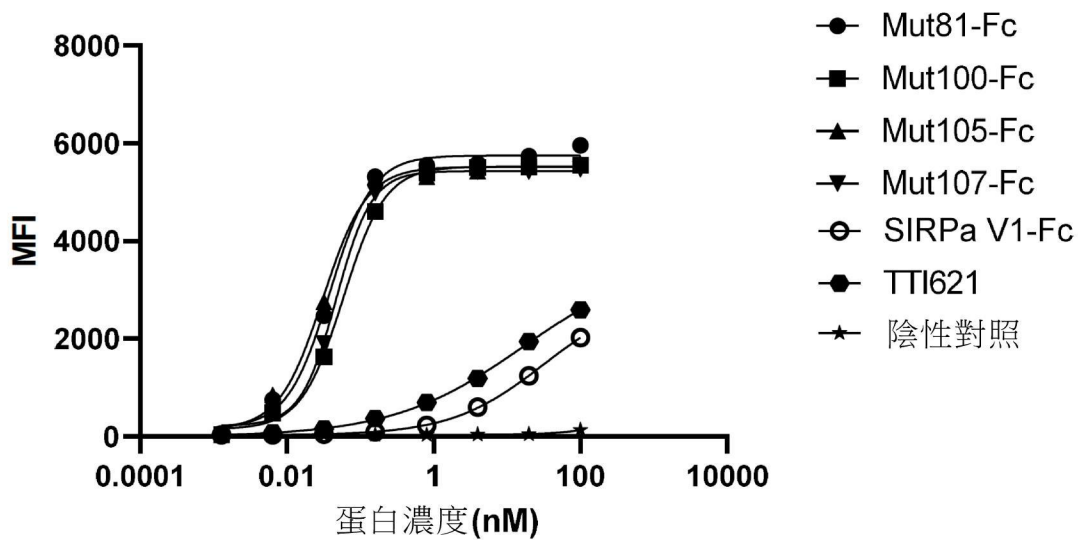
【圖9B】



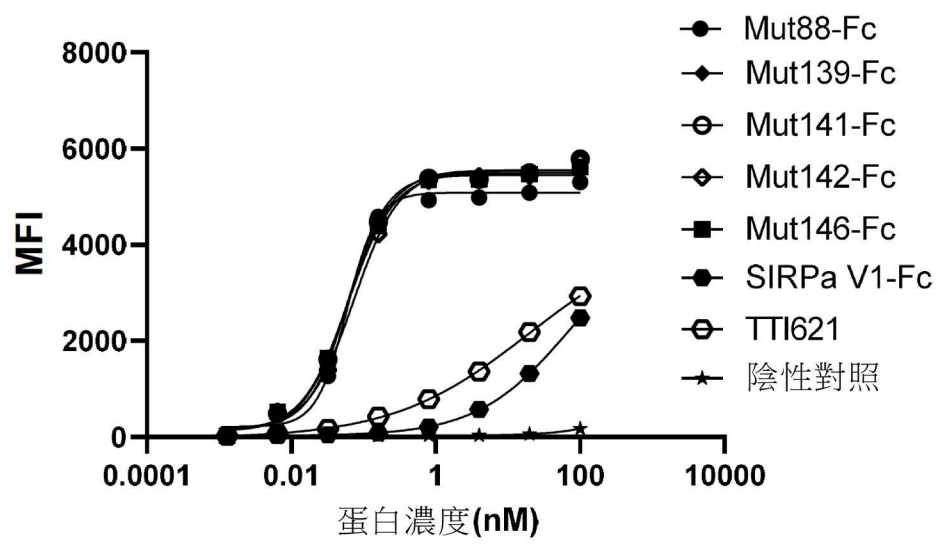
【圖9C】



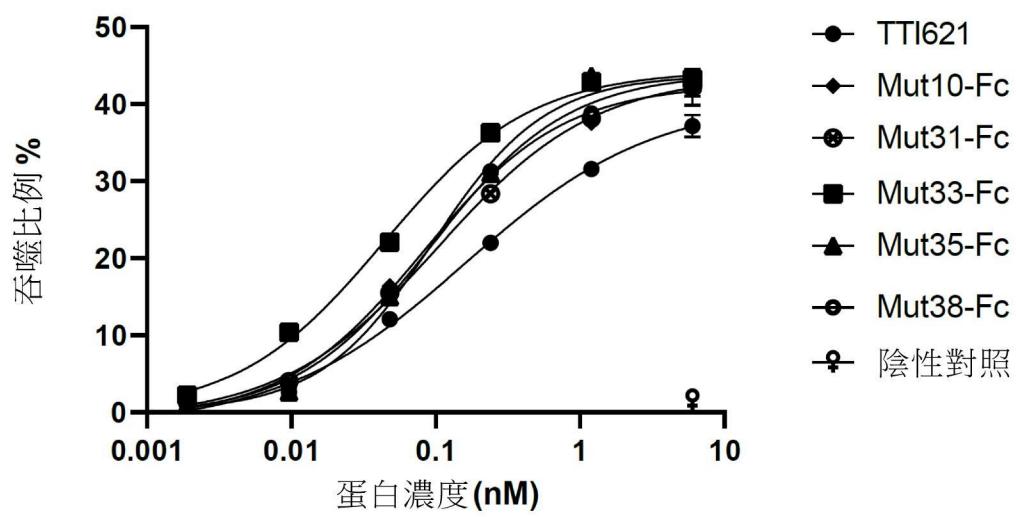
【圖10A】



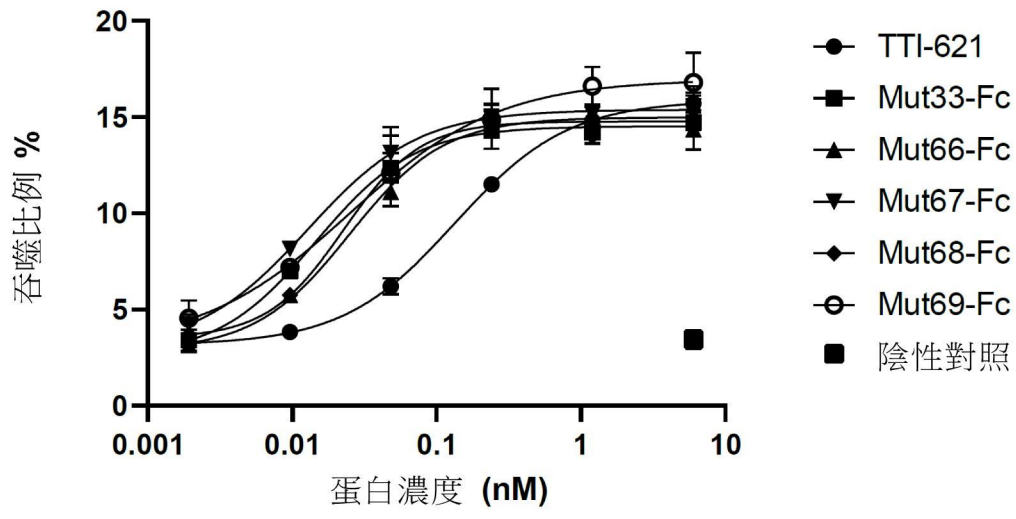
【圖10B】



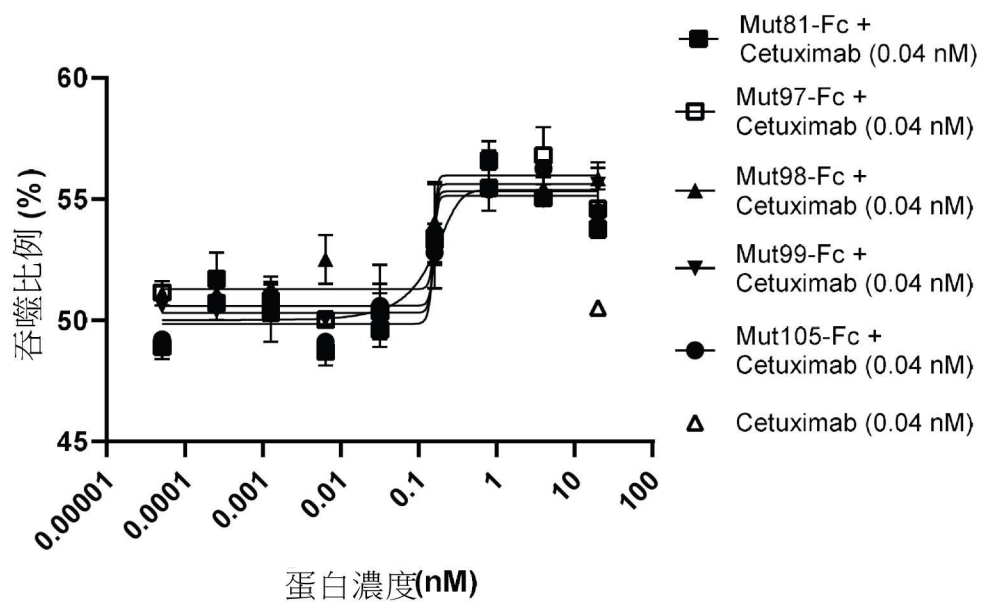
【圖10C】



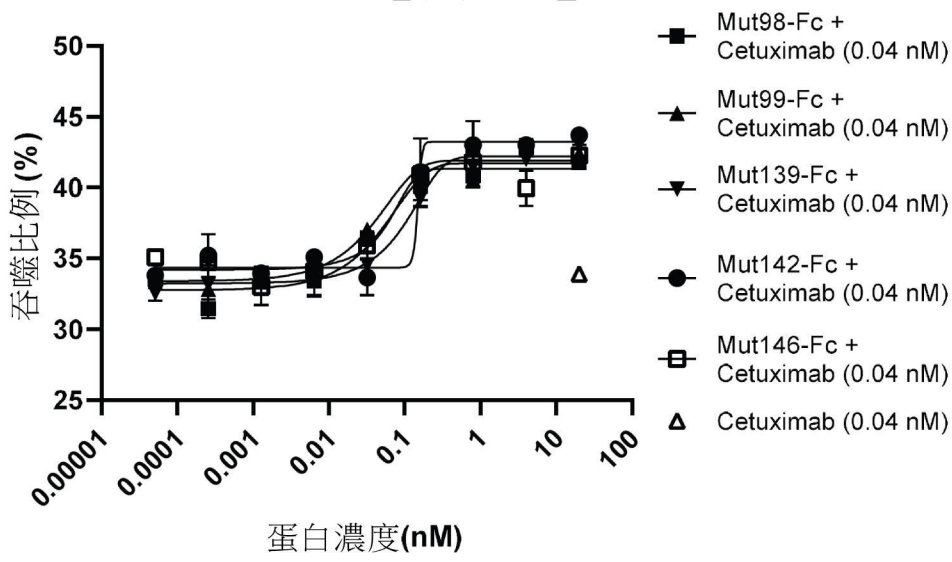
【圖11A】



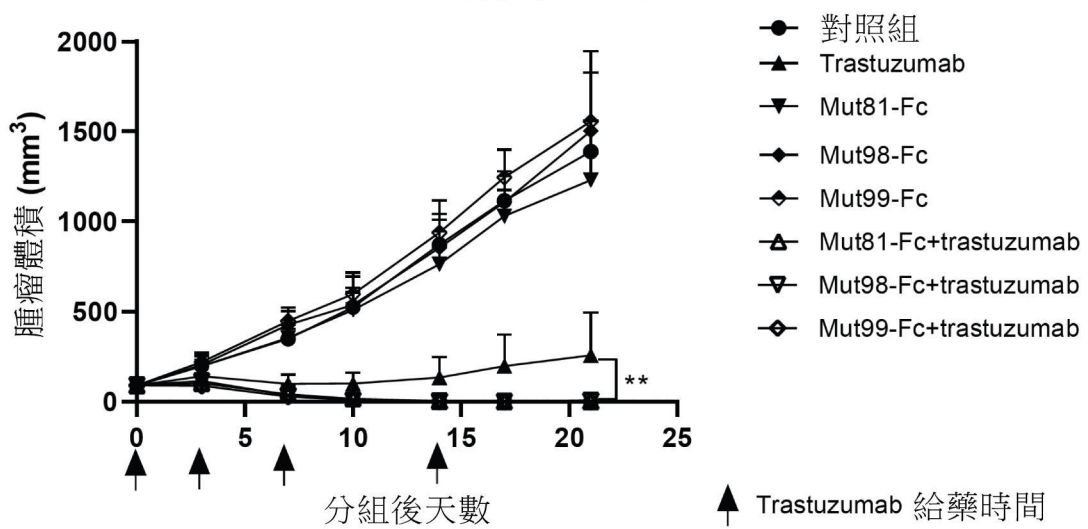
【圖11B】



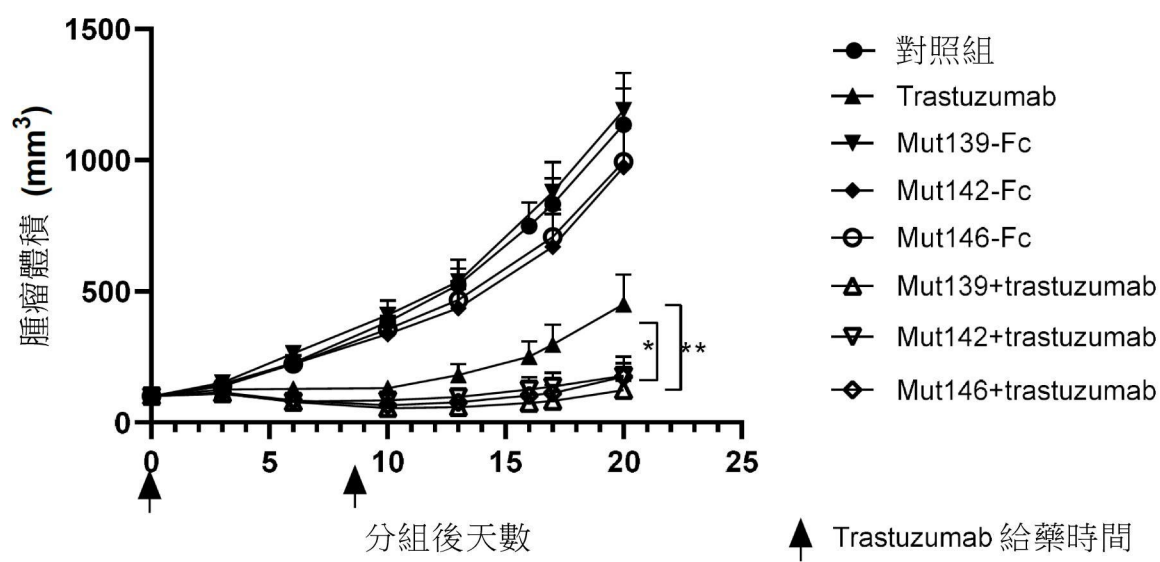
【圖12A】



【圖12B】



【圖13A】



【圖13B】