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(54)名稱

可經活化之細胞介素構築體和組合方法

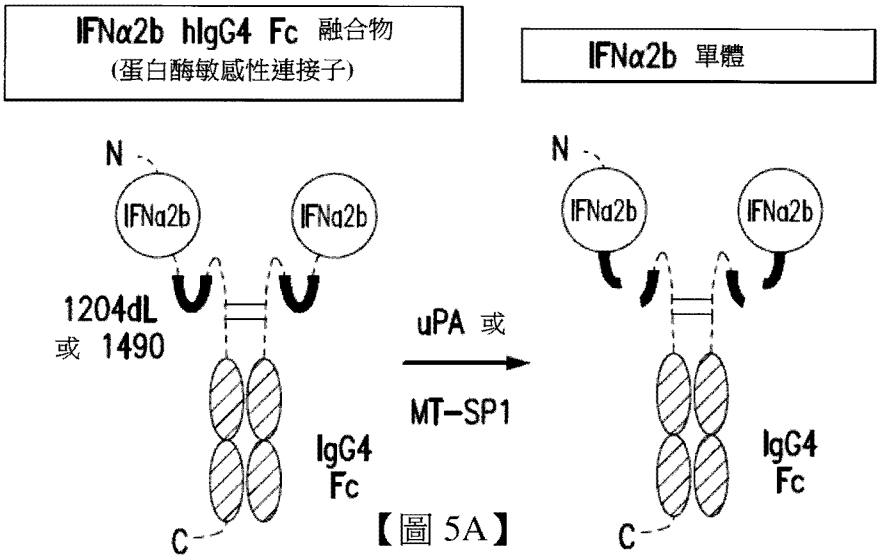
(57)摘要

本發明提供藉由投予可經活化之細胞介素構築體(ACC)和 PD-1/PD-L1 路徑抑制劑之組合以治療個體之方法，其中該 ACC 包括：第一單體構築體和第二單體構築體，該第一單體構築體包括可選擇之第一肽掩蔽物(PM1)、可選擇之第三可裂解部分(CM3)、第一成熟細胞介素蛋白(CP1)、第一可裂解部分(CM1)及第一二聚化結構域(DD1)，其中該 CM1 位於該 CP1 與該 DD1 之間，且該第二單體構築體包括可選擇之第二肽掩蔽物(PM2)、可選擇之第四可裂解部分(CM4)、第二成熟細胞介素蛋白(CP2)、第二可裂解部分(CM2)及第二二聚化結構域(DD2)，其中該 CM2 位於該 CP2 與該 DD2 之間；其中該 DD1 與該 DD2 彼此結合從而形成該第一單體構築體和該第二單體構築體之二聚體；且其中該 ACC 之特徵在於與該 CP1 和/或該 CP2 之至少一種活性的對照水準相比較，該 CP1 和/或該 CP2 之該至少一種活性降低。

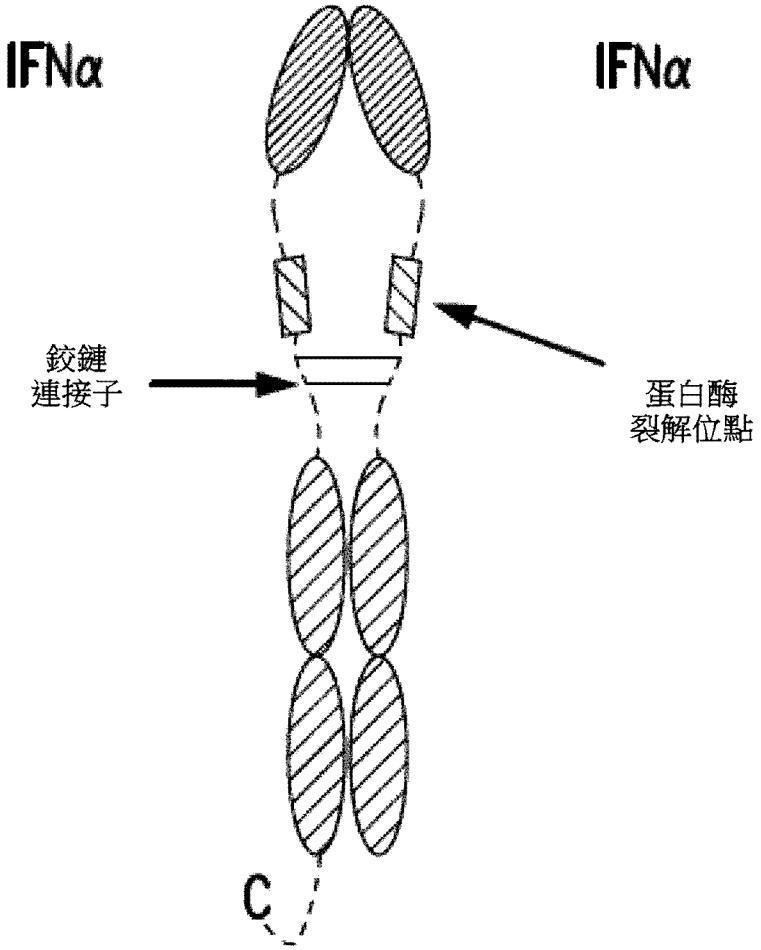
Provided herein are methods of treating a subject by administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor in which the ACC includes: a first monomer construct including an optional first peptide mask (PM1), an optional third cleavable moiety (CM3), a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1; and a second monomer construct including an optional second peptide mask (PM2), an optional forth cleavable moiety (CM4), a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2; wherein the DD1 and the DD2 bind to each other thereby forming a dimer of the first monomer construct and the second monomer construct; and where the ACC is

characterized by a reduction in at least one activity of the CP1 and/or CP2 as compared to a control level of the at least one activity of the CP1 and/or CP2.

指定代表圖：



【圖 5A】



【圖 5B】

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【發明摘要】

【中文發明名稱】

可經活化之細胞介素構築體和組合方法

【英文發明名稱】

ACTIVATABLE CYTOKINE CONSTRUCTS AND COMBINATION METHODS

【中文】

本發明提供藉由投予可經活化之細胞介素構築體(ACC)和PD-1/PD-L1路徑抑制劑之組合以治療個體之方法，其中該ACC包括：第一單體構築體和第二單體構築體，該第一單體構築體包括可選擇之第一肽掩蔽物(PM1)、可選擇之第三可裂解部分(CM3)、第一成熟細胞介素蛋白(CP1)、第一可裂解部分(CM1)及第一二聚化結構域(DD1)，其中該CM1位於該CP1與該DD1之間，且該第二單體構築體包括可選擇之第二肽掩蔽物(PM2)、可選擇之第四可裂解部分(CM4)、第二成熟細胞介素蛋白(CP2)、第二可裂解部分(CM2)及第二二聚化結構域(DD2)，其中該CM2位於該CP2與該DD2之間；其中該DD1與該DD2彼此結合從而形成該第一單體構築體和該第二單體構築體之二聚體；且其中該ACC之特徵在於與該CP1和/或該CP2之至少一種活性的對照水準相比較，該CP1和/或該CP2之該至少一種活性降低。

【英文】

Provided herein are methods of treating a subject by administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor in which the ACC includes: a first monomer construct including an optional first peptide mask (PM1), an optional third cleavable moiety (CM3), a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1; and a second monomer construct including an optional second peptide mask (PM2), an optional forth cleavable moiety (CM4), a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2; wherein the DD1 and the DD2 bind to each other thereby forming a dimer of the first monomer construct and the second monomer construct; and where the ACC is characterized by a reduction in at least one activity of the CP1 and/or CP2 as compared to a control level of the at least one activity of the CP1 and/or CP2.

【指定代表圖】圖5A,5B

【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】

可經活化之細胞介素構築體和組合方法

【英文發明名稱】

ACTIVATABLE CYTOKINE CONSTRUCTS AND COMBINATION METHODS

【技術領域】

【0001】本揭示關於生物技術之領域，更具體地關於可經活化之細胞介素構築體，其包括用於免疫腫瘤學療法之可經活化的細胞介素構築體。

[相關申請案之交叉引用]

【0002】本申請案主張2021年10月8日提交申請之美國臨時申請案號63/253,893和2022年4月7日提交申請之美國臨時申請案號63/328,525的權益。上述申請案之全文特此以引用方式全部併入本文。

[對電子序列表之引用]

【0003】創建日期：2022年10月3日；大小：907,197字節；且標題為“CYTX086PCT.xml”之電子序列表的全部內容以引用方式併入本文。

【先前技術】

【0004】基於抗體之療法已用於治療各種疾病並取得不同程度的成功，且在某些情況下，由於廣泛之標靶表現而導致之毒性會限制其治療效力。此外，基於抗體之療法亦顯現其他侷限性，諸如在投予後從循環中快速清除。聯合療法亦與基於抗體之療法一起使用，但通常受到來自各別活性藥物之毒性增加的限制。

【0005】細胞介素為天然存在之小蛋白質和糖蛋白家族，其係由大多數有核之細胞在回應病毒感染和/或其他抗原刺激時產生及分泌。干擾素為細胞介素之亞類別。干擾素目前分為三種主要類別：第I型干擾素、第II型干擾素和第III型干擾素。干擾素藉由與細胞表面上之特定膜受體結合而發揮其細胞活性。

【0006】干擾素療法具有許多臨床益處。例如，已知干擾素可上調免疫系統且亦具有抗病毒和抗增殖特性。這些生物學性能導致干擾素在臨床上作為用於治療病毒感染和惡性腫瘤之治療劑。此外，干擾素可用於募集患者之先天免疫系統以識別和攻擊癌細胞。因此，干擾素療法已廣泛用於癌症和抗病毒療法，包括用於治療肝炎、卡波西氏肉瘤、髮樣細胞白血病、慢性骨髓性白血病(CML)、濾泡性淋巴瘤、腎細胞癌(RCC)、黑色素瘤及其他疾病狀態。然而，該干擾素之全身投予伴隨著劑量依賴性毒性，包括強烈的流感樣症狀、神經系統症狀、肝毒性、骨髓抑制和心律不整，等。在一項黑色素瘤患者研究中，派姆單抗

(Pembrolizumab)和聚乙二醇化IFNa的組合導致60.5%之ORR。聯合治療亦與49%之G3/G4不良事件相關，這些不良事件需要減少聚乙二醇化IFNa之劑量(Davar et al. J. Clin. Oncol.,2018)。這些不良副作用限制該干擾素療法之劑量且有時會導致中斷或延遲干擾素治療。

【0007】介白素為另一亞類之細胞介素。介白素調節細胞生長、分化和運動。其在刺激免疫反應(諸如發炎)方面尤為重要。介白素已用於治療癌症、自體免疫性疾病及其他病症。例如介白素-2(IL2)被指示用於治療黑色素瘤、移植物抗宿主病(GVHD)、神經母細胞瘤、腎細胞癌(RCC)且亦被認為可用於治療下列病況：包括急性冠脈症候群、急性骨髓性症候群、異位性皮膚炎、自體免疫性肝病、基底細胞癌、膀胱癌、乳癌、念珠菌病、結腸直腸癌、皮膚T細胞淋巴瘤、子宮內膜異位瘤、HIV感染、缺血性心臟病、類風濕性關節炎、鼻咽腺癌、非小細胞肺癌(NSCLC)、卵巢癌、胰腺癌、全身性紅斑狼瘡、肺結核及其他病症。其他介白素(諸如IL-6、IL-7、IL-12和IL-21，等)為用於癌症和其他病症之潛在治療。介白素療法通常伴隨著不欲有之副作用，包括流感樣症狀、噁心、嘔吐、腹瀉、低血壓和心律失常，等。

【0008】在慢性刺激條件下，T細胞上調並維持抑制性受體PD-1之表現以負調節T細胞反應之品質和幅度。PD-1之主要配體PD-L1在許多腫瘤細胞上被上調，且經由其與腫瘤浸潤性T細胞上之PD-1結合而與抗腫瘤T細胞免

疫力之抑制相關。臨床試驗已確認抗體阻斷PD-1或PD-L1以恢復多種腫瘤類型患者之持久性腫瘤特異性免疫活性的能力。(Herbst et al, 2014；Lipson et al, 2015)。然而，PD-1/PD-L1單一療法有缺點，包括有大量無反應之患者和/或顯示復發、腫瘤耐藥性及與自體免疫反應相關之副作用的患者。

【0009】因此，對於提高細胞介素療法對合需標靶之特異性和選擇性的需求和渴望令人極感興趣。增加細胞介素治療劑對疾病部位之靶向性可減少基於全身機制之毒性並導致更廣泛之治療效用。對於改善聯合療法之治療效力亦存在需求，該治療係針對誘導具有特異性和選擇性之對抗各種標靶的免疫反應。

【發明內容】

【0010】本發明提供用於治療個體之組合、組成物、套組和方法，該方法藉由對個體投予可經活化之細胞介素構築體(ACC)和PD-1/PD-L1路徑抑制劑之組合來進行。於某些態樣中，該組合增加療法之功效。於某些態樣中，當對個體投予該組合時，該組合降低一或二種該組合組分之毒性。於某些態樣中，該組合減少或抑制腫瘤生長、增殖和/或轉移。於某些態樣中，該組合治療罹患癌症或感染之個體。於某些態樣中，相對於常規細胞介素療法和/或常規PD-1/PD-L1抑制劑療法，該組合增進或加強個體中之治療功效和/或治療指數。於某些態樣中，相對於常規細

胞介素療法和PD-1/PD-L1抑制劑聯合療法，該組合增進或加強個體中之治療功效和/或治療指數。於某些態樣中，相對於投予單獨ACC，該組合增進或加強治療功效和/或治療指數。

【0011】於一態樣中，該ACC可包括：(a)第一單體，其包含第一肽掩蔽物(PM1)、第一成熟細胞介素蛋白(CP1)、第一和第三可裂解部分(CM1和CM3)及第一二聚化結構域(DD1)，其中該CM1位於該CP1與該DD1之間且該CM3位於該PM1與該CP1之間；及(b)第二單體，其包含第二成熟細胞介素蛋白(CP2)、第二可裂解部分(CM2)及第二二聚化結構域(DD2)，其中該CM2位於該CP2與該DD2之間，其中：該CM1、該CM2和該CM3作為蛋白酶之受質；該DD1與該DD2彼此結合；且其中該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，該至少一種CP1和/或CP2活性降低。相對於健康組織，裂解該CM1、該CM2和該CM3之蛋白酶可能經患病組織(例如腫瘤組織)過度表現。該ACC可在該CM1、該CM2和/或該CM3裂解後經活化，使得該細胞介素可在患病組織中(例如在腫瘤微環境中)發揮其活性，而該細胞介素活性在健康組織之背景下減弱。因此，本發明提供之ACC可提供相對於傳統細胞介素治療劑降低之毒性，使細胞介素之有效劑量較高，和/或增加細胞介素之治療窗。

【0012】本發明提供可經活化之細胞介素構築體(ACC)，其包含第一單體構築體和第二單體構築體，其

中：(a)該第一單體構築體包含第一肽掩蔽物(PM1)、第一成熟細胞介素蛋白(CP1)、第一和第三可裂解部分(CM1和CM3)，及第一二聚化結構域(DD1)，其中該CM1位於該CP1與該DD1之間，且該CM3位於該PM1與該CP1之間；及(b)第二單體構築體，其包含第二成熟細胞介素蛋白(CP2)、第二可裂解部分(CM2)及第二二聚化結構域(DD2)，其中該CM2位於該CP2與該DD2之間；其中該DD1與該DD2彼此結合從而形成該第一單體構築體與該第二單體構築體之二聚體；且其中該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，該至少一種CP1和/或CP2活性水準降低。

【0013】於一些實施態樣中，該第二單體構築體進一步包含第二肽掩蔽物(PM2)和第四可裂解部分(CM4)，其中該CM4位於該PM2與該CP2之間。於一些實施態樣中，該第一單體構築體包含第一多肽，該第一多肽包含該PM1、該CM3、該CP1、該CM1及該DD1。於一些實施態樣中，該第二單體構築體包含第二多肽，該第二多肽包含該CP2、該CM2及該DD。於一些實施態樣中，該第二單體構築體包含第二多肽，該第二多肽包含該PM2、該CM4、該CP2、該CM2及該DD2。

【0014】於一些實施態樣中，該PM1包含選自由下列所組成之群組的序列：SEQ ID NO：97、298、292和299至336，且該CP1為干擾素；該PM1包含選自由下列所組成之群組的序列：SEQ ID NO：297、298、292和299至332，且

該CP1為干擾素α；該PM1包含選自由下列所組成之群組的序列：SEQ ID NO：299至328和330至332，且該CP1為干擾素β；該PM1包含選自由下列所組成之群組的序列：SEQ ID NO：299至328和333至336，且該CP1為干擾素γ；該PM1包含選自由下列所組成之群組的序列：SEQ ID NO：337至341，且該CP1為IL-12；該PM1包含選自由下列所組成之群組的序列：SEQ ID NO：342至349、436至444和445，且該CP1為IL-15；該PM1包含選自由下列所組成之群組的序列：SEQ ID NO：350至435和436至445，且該CP1為IL-2；或者該PM1包含選自由下列所組成之群組的序列：SEQ ID NO：445和446，且該CP1為IL-21。於一些實施態樣中，該PM2包含選自由下列所組成之群組的序列：SEQ ID NO：297、298、292和299至336，且該CP2為干擾素；該PM2包含選自由下列所組成之群組的序列：SEQ ID NO：297、298、292和299至364，且該CP2為干擾素α；該PM2包含選自由下列所組成之群組的序列：SEQ ID NO：299至328和330至332，且該CP2為干擾素β；該PM2包含選自由下列所組成之群組的序列：SEQ ID NO：299至328和333至336，且該CP2為干擾素γ；該PM2包含選自由下列所組成之群組的序列：SEQ ID NO：337至341，且該CP2為IL-12；該PM2包含選自由下列所組成之群組的序列：SEQ ID NO：342至349、436至444和445，且該CP2為IL-15；該PM2包含選自由下列所組成之群組的序列：SEQ ID NO：350至435、436至445，且該CP2為IL-2；或者

該PM2包含選自由下列所組成之群組的序列：SEQ ID NO：445和446，且該CP2為IL-21。於一些實施態樣中，該PM1包含選自由下列所組成之群組的胺基酸序列：SEQ ID NO：297、298、292和299至446。於一些實施態樣中，該PM2包含選自由下列所組成之群組的胺基酸序列：SEQ ID NO：297、298、292和299至446。

【0015】於一些實施態樣中，該DD1和該DD2為選自由下列所組成之群組的一對：一對Fc結構域；源自人IL-15受體之α鏈(IL15Rα)的sushi結構域和可溶性IL-15；barnase和barnstar；蛋白激酶A(PKA)和A激酶錨定蛋白(AKAP)；適配體/基於突變之RNase I片段之對接標籤構件；表位和單結構域抗體(sdAb)；表位和單鏈可變片段(scFv)；及基於突觸融合蛋白(syntaxin)、突觸結合蛋白(synaptotagmin)、突觸小蛋白(synaptobrevin)之交互作用的可溶性N-乙基馬來醯亞胺敏感性因子附著蛋白受體(SNARE)構件和SNAP25、抗原結合結構域和表位。

【0016】於一些實施態樣中，該DD1和該DD2為一對Fc結構域。於一些實施態樣中，該對Fc結構域為一對人Fc結構域。於一些實施態樣中，該人Fc結構域為人IgG1 Fc結構域、人IgG2 Fc結構域、人IgG3 Fc結構域或人IgG4 Fc結構域。於一些實施態樣中，該人Fc結構域為人IgG4 Fc結構域。於一些實施態樣中，該人Fc結構域各自包含與SEQ ID NO：3具有至少80%同一性之序列。於一些實施態樣中，該人Fc結構域各自包含與SEQ ID NO：3具有至少

90%、95%、96%、97%、98%或99%同一性之序列。於一些實施態樣中，該人Fc結構域包含SEQ ID NO：3。於一些實施態樣中，該DD1和該DD2分別包含SEQ ID NO：287和288。於一些實施態樣中，該DD1和該DD2係相同。於一些實施態樣中，該人Fc結構域包括消除糖基化和/或減少Fc-γ受體結合之突變。於一些實施態樣中，該人Fc結構域包含突變N297Q、N297A或N297G；於一些實施態樣中，該人Fc結構域在位置234和/或235包含突變，例如L235E或L234A和L235A(在IgG1中)，或F234A和L235A(在IgG4中)；於一些實施態樣中，該人Fc結構域為包含突變V234A、G237A、P238S、H268Q/A、V309L、A330S或P331S、或其組合(均根據EU編號)之IgG2 Fc結構域。

【0017】經工程處理之人Fc結構域的其他實例為本技藝之技術熟習人士所已知。其中至少一個胺基酸中之突變導致Fc功能降低之Ig重鏈恆定區胺基酸突變的實例包括，但不限於重鏈恆定區之胺基酸228、233、234、235、236、237、239、252、254、256、265、270、297、318、320、322、327、329、330和331(全部根據EU編號)中的突變。突變之胺基酸之組合的實例亦為本技藝所已知，諸如，但不限於胺基酸234、235和331中之突變的組合，諸如L234F、L235E和P331S，或胺基酸318、320和322中之突變的組合，諸如E318A、K320A和K322A。

【0018】經工程處理之Fc結構域的其他實例包括F243L/R292P/Y300L/V305I/P396 IgG1；S239D/I332E IgG1

；S239D/I332E/A330L IgG1；S298A/E333A/K334A；於一重鏈中，L234Y/L235Q/G236W/S239M/H268D/D270E/S298A IgG1，而於該相對之重鏈中，D270E/K326D、A330M/K334E IgG；G236A/S239D/I332E IgG1；K326W/E333S IgG1；S267E/H268F/S324T IgG1；E345R/E430G/S440Y IgG1；N297A或N297Q或N297G IgG1；L235E IgG1；L234A/L235A IgG1；F234A/L235A IgG4；H268Q/V309L/A330S/P331S IgG2；V234A/G237A/P238S/H268A/V309L/A330S/P331S IgG2；M252Y/S254T/T256E IgG1；M428L/N434S IgG1；S267E/L328F IgG1；N325S/L328F IgG1，及類似物。於一些實施態樣中，該經工程處理之Fc結構域包含一或多個選自由下列所組成之群組的取代：N297A IgG1、N297Q IgG1和S228P IgG4。

【0019】於一些實施態樣中，該DD1包含抗原結合結構域且該DD2包含對應之表位。於一些實施態樣中，該抗原結合結構域為抗His標籤抗原結合結構域且其中該DD2包含His標籤。於一些實施態樣中，該抗原結合結構域為單鏈可變片段(scFv)。於一些實施態樣中，該抗原結合結構域為單結構域抗體(sdAb)。於一些實施態樣中，該DD1和該DD2中至少一者包含選自由下列所組成之群組的二聚化結構域取代：非多肽聚合物和小分子。於一些實施態樣中，該DD1和該DD2包含彼此共價結合之非多肽聚合物。於一些實施態樣中，該非多肽聚合物為含硫聚乙二醇，且其中該DD1與該DD2係經由一或多個二硫鍵彼此共價結

合。於一些實施態樣中，該DD1和該DD2中至少一者包含小分子。於一些實施態樣中，該小分子為生物素。於一些實施態樣中，該DD1包含生物素且該DD2包含抗生物素蛋白。

【0020】於一些實施態樣中，該CP1和該CP2為成熟細胞介素。於一些實施態樣中，該CP1和該CP2之每一者包含成熟細胞介素序列且進一步包含信號肽。本文中信號肽亦稱為“信號序列”。於一些實施態樣中，該CP1和/或該CP2各自個別選自由下列所組成之群組：干擾素、介白素、GM-CSF、G-CSF、LIF、OSM、CD154、LT-β、TNF-α、TNF-β、4-1BBL、APRIL、CD70、CD153、CD178、GITRL、LIGHT、OX40L、TALL-1、TRAIL、TWEAK、TRANCE、TGF-β1、TGF-β1、TGF-β3、Epo、Tpo、Flt-3L、SCF、M-CSF和MSP，可選擇地其中該CP1和/或該CP2係獨立選自IL-2、IL-7、IL-8、IL-10、IL-12、IL-15、IL-21、IFN-α、IFNβ、IFNγ、GM-CSF、TGF-β、LIGHT、GITR-L、CD40L、CD27L、4-1BB-L、OX40和OX40L。於一些實施態樣中，該CP1和該CP2係相同。於一些實施態樣中，該CP1和該CP2係不同。於一些實施態樣中，該CP1和/或該CP2為干擾素。於一些實施態樣中，該CP1和該CP2二者均為干擾素。於一些實施態樣中，該CP1和該CP2係不同干擾素。於一些實施態樣中，該CP1和該CP2係相同干擾素。於一些實施態樣中，該CP1或該CP2其中一者為干擾素，且該CP1或該CP2中之另一者為干擾素以外的

細胞介素。於一些態樣中，該細胞介素之一或二者為單體細胞介素。於一些態樣中，該干擾素之一或二者為為單體干擾素。於一些態樣申，該CP1或該CP2其中一者為單體干擾素，而該CP1或該CP2中之另一者為不同細胞介素。於一些態樣中，該CP1和/或該CP2包括突變之細胞介素序列。於一些態樣中，該CP1和/或該CP2包括通用之細胞介素序列。於一些態樣中，該CP1和/或該CP2包括保留細胞介素活性之截短序列。

【0021】於一些實施態樣中，該干擾素為人野生型成熟干擾素。於一些實施態樣中，該干擾素可為第I型和第II型干擾素，例如包括，但不限於干擾素α、干擾素β、干擾素γ、干擾素ω和干擾素τ。於一些實施態樣中，該干擾素為干擾素α。於一些實施態樣中，該干擾素係選自由下列所組成之群組：干擾素α-2a、干擾素α-2b和干擾素α-n3。於一些實施態樣中，該干擾素為干擾素α-2b。於一些實施態樣中，該干擾素為突變之干擾素。於一些實施態樣中，該干擾素為突變之干擾素，其中內源蛋白酶裂解位點已藉由一或多個胺基酸之取代、缺失或插入而使其喪失功能。於一些實施態樣中，該干擾素為通用之細胞介素分子，例如具有為不同細胞介素亞型之雜合序列或嵌合型細胞介素序列或人源化細胞介素序列。於一些實施態樣中，該干擾素為通用之干擾素分子。於一些實施態樣中，該干擾素為通用之干擾素α，例如干擾素α1和干擾素α2a之雜合物。於一些實施態樣中，該CP1和/或該CP2包含與SEQ ID NO：1

具有至少80%同一性之序列。於一些實施態樣中，該CP1和/或該CP2包含與SEQ ID NO：1具有至少90%、95%、96%、97%、98%或99%同一性之序列。於一些實施態樣中，該CP1和/或該CP2包含SEQ ID NO：1之序列。於一些實施態樣中，該干擾素為干擾素β。於一些實施態樣中，該干擾素β係選自由干擾素β-1a和干擾素β-1b所組成之群組。於一些實施態樣中，該CP1和/或該CP2包含IFab結構域。於一些實施態樣中，該CP1和/或該CP2包含介白素。於一些實施態樣中，該介白素係選自由下列所組成之群組：IL-1α、IL-1β、IL-1RA、IL-18、IL-2、IL-4、IL-7、IL-9、IL-13、IL-15、IL-3、IL-5、IL-6、IL-11、IL-12、IL-10、IL-20、IL-14、IL-16和IL-17。

【0022】於一些實施態樣中，該CM1和/或CM2包含總共約3個胺基酸至約15個胺基酸。於一些實施態樣中，該CM1和該CM2包含不同蛋白酶之受質。於一些實施態樣中，其中該CM1和該CM2包含相同蛋白酶之受質。於一些實施態樣中，該蛋白酶係選自由下列所組成之群組：ADAM8、ADAM9、ADAM10、ADAM12、ADAM15、ADAM17/TACE、ADAMDEC1、ADAMTS1、ADAMTS4、ADAMTS5、BACE、腎素(Renin)、組織蛋白酶(Cathepsin)D、組織蛋白酶E、凋亡蛋白酶(Caspase)1、凋亡蛋白酶2、凋亡蛋白酶3、凋亡蛋白酶4、凋亡蛋白酶5、凋亡蛋白酶6、凋亡蛋白酶7、凋亡蛋白酶8、凋亡蛋白酶9、凋亡蛋白酶10、凋亡蛋白酶14、組織蛋白酶B、組織蛋

白酶C、組織蛋白酶K、組織蛋白酶L、組織蛋白酶S、組織蛋白酶V/L2、組織蛋白酶X/Z/P、Cruzipain、天冬醯胺內肽酶(Legumain)、OtubaiN2、KLK4、KLK5、KLK6、KLK7、KLK8、KLK10、KLK11、KLK13、KLK14、Meprin、腦啡肽酶(Neprilysin)、PSMA、BMP-1、基質金屬蛋白酶(例如MMP-1、MMP-2、MMP-3、MMP-7、MMP-9、MMP-10、MMP-11、MMP-12、MMP-13、MMP-14、MMP-15、MMP-16、MMP-17、MMP-19、MMP-20、MMP-23、MMP-24、MMP-26、MMP-27)、活化之蛋白C、組織蛋白酶A、組織蛋白酶G、凝乳酶(Chymase)、FVIIa、FIXa、FXa、FXIa、FXIIa、彈性蛋白酶、顆粒酶B、胍基苯甲酸酶、HtrA1、人嗜中性粒細胞裂解酶(lyase)、乳鐵蛋白、marapsin、NS3/4A、PACE4、纖溶酶、PSA、tPA、凝血酶、類胰蛋白酶(tryptase)、uPA、DESC1、DPP-4、FAP、Hepsin、馬曲肽酶(Matriptase)-2、MT-SP1/Matripase、TMPRSS2、TMPRSS3和TMPRSS4。於一些實施態樣中，該蛋白酶係選自：uPA、天冬醯胺內肽酶、MT-SP1、ADAM17、BMP-1、TMPRSS3、TMPRSS4、MMP-2、MMP-9、MMP-12、MMP-13和MMP-14。

【0023】合適之可裂解部分已揭示於WO 2010/081173、WO 2015/048329、WO 2015/116933、WO 2016/118629和WO 2020/118109中，彼等揭示內容全文以引用方式併入本文。

【0024】於一些實施態樣中，該CM1和/或該CM2包含

選自由下列所組成之群組的序列：LSGRSDNH(SEQ ID NO：5)、TGRGPSWV(SEQ ID NO：6)、PLTGRSGG(SEQ ID NO：7)、TARGPSFK(SEQ ID NO：8)、NTLSGRSENHSG(SEQ ID NO：9)、NTLSGRSGNHGS(SEQ ID NO：10)、TSTSGRSANPRG(SEQ ID NO：11)、TSGRSANP(SEQ ID NO：12)、VHMPLGFLGP(SEQ ID NO：13)、AVGLLAPP(SEQ ID NO：14)、AQNLLGMV(SEQ ID NO：15)、QNQALRMA(SEQ ID NO：16)、LAAPLGLL(SEQ ID NO：17)、STFPFGMF(SEQ ID NO：18)、ISSGLLSS(SEQ ID NO：19)、PAGLWLDP(SEQ ID NO：20)、VAGRSMRP(SEQ ID NO：21)、VVPEGRRS(SEQ ID NO：22)、ILPRSPAF(SEQ ID NO：23)、MVLGRSLL(SEQ ID NO：24)、QGRAITFI(SEQ ID NO：25)、SPRSIMLA(SEQ ID NO：26)、SMLRSMPL(SEQ ID NO：27)、ISSGLLSGRSDNH(SEQ ID NO：28)、AVGLLAPPGGLSGRSDNH(SEQ ID NO：29)、ISSGLLSSGGSGGSLSGRSDNH(SEQ ID NO：30)、LSGRSGNH(SEQ ID NO：31)、SGRSANPRG(SEQ ID NO：32)、LSGRSDDH(SEQ ID NO：33)、LSGRSDIH(SEQ ID NO：34)、LSGRSDQH(SEQ ID NO：35)、LSGRSDTH(SEQ ID NO：36)、LSGRSDYH(SEQ ID NO：37)、LSGRSDNP(SEQ ID NO：38)、LSGRSANP(SEQ ID NO：39)、LSGRSANI(SEQ ID NO：40)、LSGRSDNI(SEQ ID NO：41)、MIAPVAYR(SEQ ID NO：42)、RPSPMWAY (SEQ ID

NO：43)、WATPRPMR(SEQ ID NO：44)、FRLLDWQW(SEQ ID NO：45)、ISSGL(SEQ ID NO：46)、ISSGLLS(SEQ ID NO：47)、ISSGLL(SEQ ID NO：48)、ISSGLLSGRSANPRG(SEQ ID NO：49)、AVGLLAPPTSGRSANPRG(SEQ ID NO：50)、AVGLLAPPSGRSANPRG(SEQ ID NO：51)、ISSGLLSGRSDDH(SEQ ID NO：52)、ISSGLLSGRSDIH(SEQ ID NO：53)、ISSGLLSGRSDQH(SEQ ID NO：54)、ISSGLLSGRSDTH(SEQ ID NO：55)、ISSGLLSGRSDYH(SEQ ID NO：56)、ISSGLLSGRSDNP(SEQ ID NO：57)、ISSGLLSGRSANP(SEQ ID NO：58)、ISSGLLSGRSANI(SEQ ID NO：59)、AVGLLAPPGGLSGRSDDH(SEQ ID NO：60)、AVGLLAPPGGLSGRSDIH(SEQ ID NO：61)、AVGLLAPPGGLSGRSDQH(SEQ ID NO：62)、AVGLLAPPGGLSGRSDTH(SEQ ID NO：63)、AVGLLAPPGGLSGRSDYH(SEQ ID NO：64)、AVGLLAPPGGLSGRSDNP(SEQ ID NO：65)、AVGLLAPPGGLSGRSANP(SEQ ID NO：66)、AVGLLAPPGGLSGRSANI(SEQ ID NO：67)、ISSGLLSGRSDNI(SEQ ID NO：68)、AVGLLAPPGGLSGRSDNI(SEQ ID NO：69)、

GLSGRSDNHGGAVGLLAPP(SEQ ID NO：70)、GLSGRSDNHGGVHMPLGFLGP(SEQ ID NO：71)、LSGRSDNHGGVHMPLGFLGP(SEQ ID NO：72)、ISSGLSS(SEQ ID NO：73)、PVGYTSSL(SEQ ID NO：74)、DWLYWPGI(SEQ ID NO：75)、LKAAPRWA(SEQ ID NO：76)、GPSHLVLT(SEQ ID NO：77)、LPGGLSPW(SEQ ID NO：78)、MGLFSEAG(SEQ ID NO：79)、SPLPLRVP(SEQ ID NO：80)、RMHLRSLG(SEQ ID NO：81)、LLAPSHRA(SEQ ID NO：82)、GPRSFGL(SEQ ID NO：83)、GPRSFG(SEQ ID NO：84)、SARGPSRW(SEQ ID NO：85)、GGWHTGRN(SEQ ID NO：86)、HTGRSGAL(SEQ ID NO：87)、AARGPAIH(SEQ ID NO：88)、RGPAFNPM(SEQ ID NO：89)、SSRGPAYL(SEQ ID NO：90)、RGPATPIM(SEQ ID NO：91)、RGPA(SEQ ID NO：92)、GGQPSGMWGW(SEQ ID NO：93)、FPRPLGITGL(SEQ ID NO：94)、SPLTGRSG(SEQ ID NO：95)、SAGFSLPA(SEQ ID NO：96)、LAPLGLQRR(SEQ ID NO：97)、SGGPLGVR(SEQ ID NO：98)、PLGL(SEQ ID NO：99)和SGRSDNI(SEQ ID NO：100)。於一些實施態樣中，該CM包含選自由下列所組成之群組的序列：ISSGLLSGRSDNH(SEQ ID NO：28)、LSGRSDDH(SEQ ID NO：33)、ISSGLLSGRSDQH(SEQ ID NO：54)、SGRSDNI(SEQ ID NO：100)和ISSGLLSGRSDNI(SEQ ID NO：68)。於一些實施態樣中，該蛋白酶係由個體之腫瘤產生，例

如，該蛋白酶在腫瘤中之產量較在個體之健康組織中之產量更大。於一些實施態樣中，該個體已被診斷或鑑定為患有癌症。

【0025】於一些實施態樣中，該CP1與該CM1在該第一單體構築體中彼此直接鄰接。於一些實施態樣中，該CM1與該DD1在該第一單體構築體中彼此直接鄰接。於一些實施態樣中，該CP2與該CM2在該第二單體構築體中彼此直接鄰接。於一些實施態樣中，該CM2與該DD2在該第二單體構築體中彼此直接鄰接。於一些實施態樣中，該第一單體構築體包含與該CM1直接鄰接之該CP1和與該DD1直接鄰接之該CM1，其中該CM1包含選自由SEQ ID NO：5至100所組成之群組的序列。於一些實施態樣中，該第二單體構築體包含與該CM2直接鄰接之該CP2和與該DD2直接鄰接之該CM2，其中該CM2包含選自由SEQ ID NO：5至100所組成之群組的序列。於一些實施態樣中，該第一單體構築體包含與該CM直1接鄰接之該CP1和與該DD1直接鄰接之該CM1，其中該CM1包含長度不超過13、12、11、10、9、8、7、6、5或4個胺基酸之序列。於一些實施態樣中，該第二單體構築體包含與該CM2直接鄰接之該CP2和與該DD2直接鄰接之該CM2，其中該CM2包含長度不超過13、12、11、10、9、8、7、6、5或4個胺基酸之序列。於一些實施態樣中，該第一和第二單體構築體各自經配置使得該細胞介素(分別為該CM1和該CM2)直接鄰接長度不超過10、9、8、7、6、5或4個胺基酸之可裂解部分(分別為

該CM1和該CM2)，且該可裂解部分直接鄰接為人IgG之Fc區之二聚化結構域(分別為該DD1和該DD2)，其中該Fc區之N端為鉸鏈區中之第一個半胱胺酸殘基(從N端至C端方向閱讀)，其參與第二Fc結構域之二硫鍵鍵聯(例如根據EU編號人IgG1之半胱胺酸226)。於一些態樣中，該二聚化結構域為其中該上方鉸鏈殘基已被刪除之IgG Fc區。例如，該Fc為其中N端序列EPKSCDKTHT(SEQ ID NO：522)、ERK、ELKTPLGDTTHT(SEQ ID NO：523)或ESKYGPP(SEQ ID NO：524)已被刪除之變體。

【0026】於一些實施態樣中，該第一單體構築體包含至少一個連接子。於一些實施態樣中，該至少一個連接子為位在該PM1與該CM3之間的連接子L1和/或位在該CM3與該CP1之間的連接子L2。於一些實施態樣中，該第二單體構築體包含至少一個連接子。於一些實施態樣中，該至少一個連接子為位在該PM2與該CM4之間的連接子L3和/或位在CM4與該CP2之間的連接子L4。於一些實施態樣中，該第一單體構築體包含連接子L1且該第二單體構築體包含連接子L3。於一些實施態樣中，該L1和該L3係相同。於一些實施態樣中，該第一單體構築體包含連接子L2且該第二單體構築體包含連接子L4。於一些實施態樣中，該L2和該L4係相同。於一些實施態樣中，該第一單體構築體包含介於該CP1與該CM1之間的連接子和/或介於該CM1與該DD1之間的連接子。於一些實施態樣中，該第二單體構築體包含介於該CP2與該CM2之間的連接子和/或介於該CM2與該

DD2之間的連接子。於一些實施態樣中，各連接子之總長度為1個胺基酸至約15個胺基酸。於一些實施態樣中，各連接子之總長度為至少5個胺基酸。

【0027】於一些實施態樣中，該第一單體構築體包含至少一個連接子，其中各連接子係獨立選自由下列所組成之群組：GSSGGSGGSGG(SEQ ID NO：210)；GGGS(SEQ ID NO：2)；GGGSGGGS(SEQ ID NO：211)；GGGSGGGSGGGS(SEQ ID NO：212)；GGGGSGGGGSGGGGS(SEQ ID NO：213)；GGGGSGGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)；GGGGSGGGGS(SEQ ID NO：215)；GGGGS(SEQ ID NO：216)；GS；GGGGSGS(SEQ ID NO：217)；GGGGSGGGGSGGGGSGS(SEQ ID NO：218)；GGSLDPKGGGGS(SEQ ID NO：219)；PKSCDKTHTCPPCPAPELLG(SEQ ID NO：220)；SKYGPPCPPCPAPEFLG(SEQ ID NO：221)；GKSSGSGSESKS(SEQ ID NO：222)；GSTSGSGKSSEGKG(SEQ ID NO：223)；GSTSGSGKSSEGSGSTKG(SEQ ID NO：224)；GSTSGSGKPGSGEGSTKG(SEQ ID NO：225)；GSTSGSGKPGSSEGST(SEQ ID NO：226)；(GS)n、(GGS)n、(GSGGS)n(SEQ ID NO：227)、(GGGS)n(SEQ ID NO：228)、(GGGGS)n(SEQ ID NO：216)，其中各個n為至少1之整數；GGSG(SEQ ID NO：229)；GGSGG(SEQ ID

NO：230)；GSGSG(SEQ ID NO：231)；GSGGG(SEQ ID NO：232)；GGGSG(SEQ ID NO：233)；GSSSG(SEQ ID NO：234)；GGGGSGGGGSGGGGS(SEQ ID NO：213)；GGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)；GSTSGSGKPGSSEGST(SEQ ID NO：226)。於一些實施態樣中，該連接子包含GGGS(SEQ ID NO：2)之序列。

【0028】於一些實施態樣中，該第一單體構築體於N端至C端之方向包含該PM1、該CM3、該CP1、該CM1及直接或間接連接至該CM1之C-端之該DD1。於一些實施態樣中，該第一多肽於C端至N端之方向包含該PM1、該CM3、該CP1、該CM1及直接或間接連接至CM1之N端之該DD1。於一些實施態樣中，該第二多肽於N端至C端之方向包含該PM2、該CM4、該CP2、該CM2及直接或間接連接至該CM2之C端之該DD2。於一些實施態樣中，該第二多肽於C端至N端之方向包含該PM2、該CM4、該CP2、該CM2及直接或間接連接至該CM2之該DD2。

【0029】於一些實施態樣中，該第一單體構築體於N端至C端之方向包含該CP1、可選擇之連接子、該CM1、可選擇之連接子和該DD1，其中該DD1為IgG之Fc區，其中該Fc區之N端為在鉸鏈區中之第一個半胱胺酸殘基(於N端至C端之方向閱讀)，其參與與第二Fc結構域之二硫鍵鍵聯(例如根據EU編號之人IgG1或IgG4之半胱胺酸226)，且其中該CM1和插入該CP1與該DD1之N端半胱胺酸之間的任何連接子(該“連接區”或“LR”)的合併總長度不超過18、

17、16、15、14、13、12、11、10、9、8、7、6、5或4個胺基酸，較佳為不超過10個胺基酸，特佳為不超過7個胺基酸。於一些該等實施態樣中，該第一單體構築體於N端至C端之方向進一步包含該PM1、可選擇之連接子、該CM3及連接至該CP1之N端之可選擇的連接子。於一些實施態樣中，該第二單體構築體於N端至C端之方向包含該CP2、可選擇之連接子、該CM2、可選擇之連接子和該DD2，其中該DD2為IgG之Fc區，其中該Fc區之N端為鉸鏈區中之第一個半胱胺酸殘基(於N端至C端之方向閱讀)，其參與與第二Fc結構域之二硫鍵鍵聯(例如根據EU編號之人IgG1或IgG4之半胱胺酸226)，且其中該CM2和插入該CP2與該DD2之N端半胱胺酸之間的任何連接子(該“連接區”或“LR”)之合併總長度不超過18、17、16、15、14、13、12、11、10、9、8、7、6、5或4個胺基酸，較佳為不超過10個胺基酸，特佳為不超過7個胺基酸。於一些該等實施態樣中，該第二單體構築體於N端至C端之方向進一步包含該PM2、可選擇之連接子、該CM4及連接至該CP2之N端之可選擇的連接子。於一些態樣中，在肽掩蔽物與可裂解部分之間沒有連接子或間隔子。於一些態樣中，在細胞介素蛋白與可裂解部分之間沒有連接子或間隔子。於一些態樣中，在可裂解部分與二聚化結構域之間沒有連接子或間隔子。

【0030】於一些實施態樣中，該ACC為同源二聚體，其中該第一單體構築體和該第二單體構築體係相同且包含

SEQ ID NO：290之胺基酸序列。於一些實施態樣中，該第一單體構築體和該第二單體構築體各自包含與SEQ ID NO：290具有至少90%、95%、96%、97%、98%或99%同一性之胺基酸序列。於一些實施態樣中，該ACC為同源二聚體，其中該第一單體構築體和該第二單體構築體係相同且包含不具有N端間隔子序列(QSGQ)之SEQ ID NO：290的胺基酸序列。於一些實施態樣中，該第一單體構築體和該第二單體構築體於N端至C端之方向各自包含SEQ ID NO：292；可選擇之具有0至10個胺基酸之彈性連接子；該CM，其包含選自由下列所組成之群組的胺基酸序列：SEQ ID NO：41、SEQ ID NO：68和SEQ ID NO：100；可選擇之具有0至10個胺基酸之彈性連接子；SEQ ID NO：1；第二CM，其包含選自由下列所組成之群組的胺基酸序列：SEQ ID NO：41、SEQ ID NO：68和SEQ ID NO：100；及二聚化結構域。

【0031】於一些實施態樣中，該至少一種CP1和/CP2活性為如使用表面等離子共振所測定之該CP1和/或該CP2對其同源受體之結合親和力。例如，當該CP1或該CP2為干擾素時，該同源受體可為干擾素α/β受體(IFNAR)。於一些實施態樣中，該至少一種CP1和/CP2活性為淋巴瘤細胞之增殖水準。於一些實施態樣中，該至少一種CP1和/CP2活性為淋巴瘤細胞中JAK/STAT/ISGF3路徑活化之水準。於一些實施態樣中，該至少一種活性為淋巴瘤細胞中經分泌之鹼性磷酸酶(SEAP)產生水準。於一些實施態樣中，該

ACC之特徵在於與對照水準相比較，該CP1和/或該CP2活性中至少一者降低至少2倍。於一些實施態樣中，該ACC之特徵在於與對照水準相比較，該CP1和/或該CP2活性中至少一者降低至少5倍、10倍、20倍、50倍、100倍、200倍、300倍、400倍、500倍、600倍、700倍、800倍、900倍、1000倍、1100倍、1200倍、1300倍、1400倍、1500倍、1600倍、1700倍、1800倍、1900倍、2000倍、3000倍或4000倍。於一些實施態樣中，該ACC的特徵在於與對照水準相比較，該CP1和/或該CP2活性中至少一者降低至少5000倍。於一些實施態樣中，該CP1和/或該CP2活性中至少一者之對照水準為該ACC暴露於該蛋白酶後該ACC中之該CP1和/或該CP2的活性。於一些實施態樣中，該CP1和/或該CP2中至少一者之對照水準為對應之野生型成熟細胞介素之對應的CP1和/或CP2活性。

【0032】於一些實施態樣中，該ACC之特徵在於暴露於該蛋白酶後產生裂解產物，其中該裂解產物包含至少一種CP1和/或CP2活性。於一些實施態樣中，至少一種該CP1和/或該CP2活性為抗增殖活性。於一些實施態樣中，該對照水準為野生型成熟細胞介素之EC50值，且其中EC50(裂解產物)與EC50(對照水準)之比率小於約10、或小於約9、或小於約8、或小於約7、或小於約6、或小於約5、或小於約4、或小於約3、或小於約2、或小於約1.5、或等於約1。於一些實施態樣中，該裂解產物之EC50與野生型成熟細胞介素之EC50大致相同，此表明裂解後該CP1

和/或該CP2之活性完全恢復或幾乎完全恢復。

【0033】於一些態樣中，該ACC包括：(a)第一單體，其包含第一成熟細胞介素蛋白(CP1)、第一可裂解部分(CM1)及第一二聚化結構域(DD1)，其中該CM1位於該CP1與該DD1之間；(b)第二單體，其包含第二成熟細胞介素蛋白(CP2)、第二可裂解部分(CM2)及第二二聚化結構域(DD2)，其中該CM2位於該CP2與該DD2之間，其中：該CM1和該CM2係作為蛋白酶之受質；DD1和該DD2彼此結合；且其中該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，該CP1和/或該CP2活性中至少一者降低。相對於健康組織，患病組織(例如，腫瘤組織)中可能過度表現裂解該CM1和該CM2之蛋白酶。該ACC可在該CM1和/或該CM2裂解後被活化，使得該細胞介素可在患病組織中(例如在腫瘤微環境中)發揮其活性，而該細胞介素活性在健康組織之背景下會減弱。

【0034】本發明提供可經活化之細胞介素構築體(ACC)，該細胞介素構築體(ACC)包括第一單體構築體和第二單體構築體，其中：(a)該第一單體構築體包含第一成熟細胞介素蛋白(CP1)、第一可裂解部分(CM1)和第一二聚化結構域(DD1)，其中該CM1位於該CP1與該DD1之間；且(b)該第二單體構築體包含第二成熟細胞介素蛋白(CP2)、第二可裂解部分(CM2)及第二二聚化結構域(DD2)，其中該CM2位於該CP2與該DD2之間；其中該DD1與該DD2彼此結合從而形成該第一單體構築體與該第二單體構築體之二

聚體；且其中該ACC之特徵在於與至少一種該CP1和/或該CP2活性之對照水準相比較，該CP1和/或該CP2活性中至少一者之水準降低。

【0035】本發明提供可經活化之細胞介素構築體(ACC)，其包含：(a)第一單體，其包含第一成熟細胞介素蛋白(CP1)、第一二聚化結構域(DD1)；及(b)第二單體，其包含第二成熟細胞介素蛋白(CP2)、可裂解部分(CM)和第二二聚化結構域(DD2)，其中該CM位於該CP2與該DD2之間，其中：該CM作為蛋白酶之受質；該DD1與該DD2彼此結合；且其中該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，該CP1和/或該CP2活性中至少一者水準降低。

【0036】本發明提供可經活化之細胞介素構築體(ACC)，其包含：(a)第一單體，其包含第一成熟細胞介素蛋白(CP1)、可裂解部分(CM)和第一二聚化結構域(DD1)，其中該CM位於該CP1與該DD1之間；及(b)第二單體，其包含第二成熟細胞介素蛋白(CP2)和第二二聚化結構域(DD2)，其中：該CM作為蛋白酶之受質；該DD1與該DD2彼此結合；且其中該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，該CP1和/或該CP2活性中至少一者之水準降低。

【0037】本發明提供可經活化之細胞介素構築體(ACC)，其包含：(a)第一單體，其包含第一成熟細胞介素蛋白(CP1)和第一二聚化結構域(DD1)；及(b)第二單體，

其包含第二成熟細胞介素蛋白(CP2)和第二二聚化結構域(DD2)，其中該CP1、該CP2或該CP1和該CP2二者包括作為蛋白酶之受質的胺基酸序列；該DD1與該DD2彼此結合；且其中該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，該CP1和/或該CP2活性中至少一者之水準降低。

【0038】因此，本揭示之ACC不需要該CP1和CP2連接肽掩蔽物(例如親和力掩蔽部分)；該等肽掩蔽物為本揭示之某些ACC之可選擇的特徵。

【0039】於一些實施態樣中，該ACC係與PD-1/PD-L1路徑抑制劑聯合投予。本發明提供特異結合經編程之細胞死亡蛋白1(PD-1)(亦稱為CD279、SLEB2和/或hSLE1)的抑制劑，及特異結合經編程之死亡配體1(亦稱為分化簇274或B7同系物1和/或B7-H1)之抑制劑。術語“PD-1”或“PD-L1”之使用意圖涵蓋其任何變體，諸如(作為非限制性示例)PD1和/或PD-1和PDL1和/或PD-L1，本文中之所有變化可互換使用。

【0040】於一些實施態樣中，該與PD-1/PD-L1路徑抑制劑聯合投予之ACC包含該CP1和/或該CP2，該CP1和/或該CP2各自單獨選自由下列所組成之群組：干擾素、介白素、GM-CSF、G-CSF、LIF、OSM、CD154、LT-β、TNF-α、TNF-β、4-1BBL、APRIL、CD70、CD153、CD178、GITRL、LIGHT、OX40L、TALL-1、TRAIL、TWEAK、TRANCE、TGF-β1、TGF-β1、TGF-β3、Epo、Tpo、Flt-

3L、SCF、M-CSF和MSP，可選擇地其中該CP1和/或該CP2係獨立選自IL-2、IL-7、IL-8、IL-10、IL-12、IL-15、IL-21、IFN-α、IFN-β、IFN-γ、GM-CSF、TGF-β、LIGHT、GITR-L、CD40L、CD27L、4-1BB-L、OX40和OX40L。於較佳之實施態樣中，該CP1和/或該CP2各自單獨選自如上述之干擾素。於更佳之實施態樣中，與該PD-1/PD-L1路徑抑制劑聯合投予之該ACC包含各自為干擾素α-2b之CP1和CP2。

【0041】於一些實施態樣中，該PD-1/PD-L1路徑抑制劑為特異結合PD-1或PD-L1之抗體或其抗原結合片段。於一些實施態樣中，該結合PD-1或PD-L1之抗體或其抗原結合片段為單株抗體、結構域抗體、單鏈、Fab片段、$F(ab')_2$片段、scFv、scAb、dAb、單結構域重鏈抗體或單結構域輕鏈抗體。於一些實施態樣中，該等結合PD-1或PD-L1之抗體或其抗原結合片段為小鼠、其他嚙齒動物、嵌合型、人源化或全人類單株抗體。於一些實施態樣中，該抗體包括特異結合哺乳動物PD-1或PD-L1之經分離的抗體或其抗原結合片段(AB)，其中該AB具有一或多種選自由下列所組成之群組的特徵：(a)該AB抑制哺乳動物PD-1與哺乳動物PDL1結合。於一些實施態樣中，該PD-1/PD-L1路徑抑制劑為可經活化之抗體。

【0042】於一些實施態樣中，該抗體包括特異結合哺乳動物PD-1或PD-L1之經分離的抗體或其抗原結合片段(AB)，其中該AB具有一或多種選自由下列所組成之群組

的特徵：(a)該AB以小於5 nM之EC50值抑制哺乳動物PD-1與哺乳動物PDL1結合；(b)該AB以小於5 nM之EC50值抑制哺乳動物PD-2與哺乳動物PDL2結合；(c)該AB特異結合人PD-1和食蟹彌猴PD-1。

【0043】於一些實施態樣中，該抗體以下列解離常數與哺乳動物PD-1或PD-L1特異結合：0.01 nM至5 nM、0.05 nM至5 nM、0.1 nM至5 nM、0.2 nM至5 nM、0.3 nM至5 nM、0.4 nM至5 nM、0.5 nM至5 nM、0.75 nM至5 nM、1 nM至5 nM、2 nM至5 nM、0.01 nM至2 nM、0.05 nM至2 nM、0.1 nM至2 nM、0.2 nM至2 nM、0.3 nM至2 nM、0.4 nM至2 nM、0.5 nM至2 nM、0.75 nM至1 nM、1 nM至2 nM、0.01 nM至1 nM、0.05 nM至1 nM、0.1 nM至1 nM、0.2 nM至1 nM、0.3 nM至1 nM、0.4 nM至1 nM、0.5 nM至1 nM、0.75 nM至1 nM、0.01 nM至0.75 nM、0.05 nM至0.75 nM、0.1 nM至0.75 nM、0.2 nM至0.75 nM、0.3 nM至0.75 nM、0.4 nM至0.75 nM、0.5 nM至0.75 nM、0.01 nM至0.5 nM、0.05 nM至0.5 nM、0.1 nM至0.5 nM、0.2 nM至0.5 nM、0.3 nM至0.5 nM、0.4 nM至0.5 nM、0.01 nM至0.4 nM、0.05 nM至0.4 nM、0.1 nM至0.4 nM、0.2 nM至0.4 nM、0.3 nM至0.4 nM、0.01 nM至0.3 nM、0.05 nM至0.3 nM、0.1 nM至0.3 nM、0.2 nM至0.3 nM、0.01 nM至0.2 nM、0.05 nM至0.2 nM、0.1 nM至0.2 nM、0.01 nM至0.1 nM、0.05 nM至0.1 nM、或0.01 nM至0.05 nM。

【0044】於一些實施態樣中，該哺乳動物PD-1/PD-L1

係選自由下列所組成之群組：人類PD-1/PD-L1和食蟹彌猴PD-1/PD-L1。於一些實施態樣中，該哺乳動物PD-1/PD-L1為鼠PD-1/PD-L1。於一些實施態樣中，該抗體係以小於或等於1 nM之解離常數特異結合人PD-1/PD-L1或食蟹彌猴PD-1/PD-L1。於一些實施態樣中，該哺乳動物PD-1/PD-L1為人PD-1/PD-L1。

【0045】於一些實施態樣中，該抗體或其抗原結合片段以下列解離常數特異結合哺乳動物PD-1或PD-L1：小於或等於0.01 nM、小於或等於0.05 nM、小於或等於0.1 nM、小於或等於0.2 nM、小於或等於0.3 nM、小於或等於0.4 nM、小於或等於0.5 nM、小於或等於0.75 nM及小於或等於1 nM。

【0046】於一些實施態樣中，該抗體具有一或多種選自由下列所組成之群組的特徵：(a)該AB特異結合人PD-1或PD-L1及食蟹彌猴PD-1或PD-L1；(b)該AB抑制人PDL1和人PDL2與人PD-1結合；(c)該AB抑制食蟹彌猴PDL1和食蟹彌猴PDL2與食蟹彌猴PD-1結合；(d)該AB特異結合鼠PD-1；(e)該AB抑制鼠PDL1和鼠PDL2與鼠PD-1結合。

【0047】於一些實施態樣中，該抗體以下列EC50阻斷天然配體與哺乳動物PDL1結合之能力：0.1 nM至10 nM、0.1 nM至5 nM、0.1 nM至3 nM、0.1 nM至2 nM、0.1 nM至1 nM、0.1 nM至0.5 nM、0.1 nM至0.25 nM、0.25 nM至10 nM、0.25 nM至5 nM、0.25 nM至3 nM、0.25 nM至2 nM、0.25 nM至1 nM、0.25 nM至0.5 nM、0.5 nM至10

nM、0.5 nM至5 nM、0.5 nM至3 nM、0.5 nM至2 nM、0.5 nM至1 nM、1 nM至10 nM、1 nM至5 nM、1 nM至3 nM、1 nM至2 nM、2 nM至10 nM、2 nM至5 nM、2 nM至3 nM、3 nM至10 nM、3 nM至5 nM、或5 nM至10 nM。於一些實施態樣中，該天然配體為哺乳動物PDL1或哺乳動物PDL2。於一些實施態樣中，該天然配體係選自由下列所組成之群組：人PDL1、人PDL2、食蟹彌猴PDL1和食蟹彌猴PDL2。於一些實施態樣中，該天然配體為鼠PDL1或鼠PDL2。

【0048】於一些實施態樣中，該抗體以下列EC50阻斷天然配體與哺乳動物PDL1結合之能力：小於或等於0.1 nM、小於或等於0.25 nM、小於或等於0.5 nM、小於或等於1 nM、小於或等於2 nM、小於或等於3 nM、小於或等於4 nM、小於或等於5 nM、或小於或等於10 nM。

【0049】於一些實施態樣中，該抗PD-1抗體包括重鏈和輕鏈，該重鏈包含或源自選自由下列所組成之群組之胺基酸序列：SEQ ID NO：610至614及620至628，該輕鏈包含或源自選自由下列所組成之群組之胺基酸序列：SEQ ID NO：615至619及629至639。

【0050】於一些實施態樣中，該抗PD-1抗體包含重鏈胺基酸序列和輕鏈胺基酸序列，該重鏈胺基酸序列與選自由SEQ ID NO：610至614及620至628所組成之群組的胺基酸序列具有至少90%、91%、92%、93%、94%、95%、96%、97%、98%或99%同一性，該輕鏈胺基酸序列與選自

由SEQ ID NO：615至619及629至639所組成之群組的胺基酸序列具有至少90%、91%、92%、93%、94%、95%、96%、97%、98%或99%同一性。

【0051】於一些實施態樣中，該抗PD-1抗體包括：(a)可變重鏈互補決定區1(VH CDR1)，其包含選自由SEQ ID NO：487和642至645所組成之群組的胺基酸序列；(b)可變重鏈互補決定區2(VH CDR2)，其包含選自由SEQ ID NO：488和646至650所組成之群組的胺基酸序列；(c)可變重鏈互補決定區3(VH CDR3)，其包含選自由SEQ ID NO：489和652至655所組成之群組的胺基酸序列；(d)可變輕鏈互補決定區1(VL CDR1)，其包含選自由SEQ ID NO：656至663所組成之群組的胺基酸序列；(e)可變輕鏈互補決定區2(VL CDR2)，其包含選自由SEQ ID NO：491和664至666所組成之群組的胺基酸序列；及(f)可變輕鏈互補決定區3(VL CDR3)，其包含選自由SEQ ID NO：492和667至670所組成之群組的胺基酸序列。

【0052】於一些實施態樣中，該抗PD-1抗體包括可變重鏈互補決定區1(VH CDR1，本文中亦稱為CDRH1)序列、可變重鏈互補決定區2(VH CDR2，本文中亦稱為CDRH2)序列及可變重鏈互補決定區3(VH CDR3，本文中亦稱為CDRH3)序列，其中該VH CDR1序列包含GITFSNSG(SEQ ID NO：525)；該VH CDR2序列包含IWYDGSKR(SEQ ID NO：526)；且該VH CDR3序列包含TNDDY(SEQ ID NO：527)。

【0053】於一些實施態樣中，該抗PD-1抗體包括可變輕鏈互補決定區1(VL CDR1，本文中亦稱為CDRL1)序列、可變輕鏈互補決定區2(VL CDR2，本文中亦稱為CDRL2)序列及可變輕鏈互補決定區3(VL CDR3，本文中亦稱為CDRL3)序列，其中該VL CDR1序列包含QSVSSY(SEQ ID NO：528)；該VL CDR2序列包含DAS；且該VL CDR3序列包含QQSSNWPRT(SEQ ID NO：529)。

【0054】於一些實施態樣中，該抗PD-1抗體包括可變重鏈互補決定區1(VH CDR1，本文中亦稱為CDRH1)序列、可變重鏈互補決定區2(VH CDR2，本文中亦稱為CDRH2)序列及可變重鏈互補決定區3(VH CDR3，本文中亦稱為CDRH3)序列，其中該VH CDR1序列包含GYTFTNYY(SEQ ID NO：530)；該VH CDR2序列包含INPSNGGT(SEQ ID NO：531)；且該VH CDR3序列包含RRDYRFDMGFDY(SEQ ID NO：532)。

【0055】於一些實施態樣中，該抗PD-1抗體包括可變輕鏈互補決定區1(VL CDR1，本文中亦稱為CDRL1)序列、可變輕鏈互補決定區2(VL CDR2，本文中亦稱為CDRL2)序列及可變輕鏈互補決定區3(VL CDR3，本文中亦稱為CDRL3)序列，其中該VL CDR1序列包含KGVSTSGYSY(SEQ ID NO：533)；該VL CDR2序列包含LAS；且該VL CDR3序列包含QHSRDLPLT(SEQ ID NO：534)。

【0056】於一些實施態樣中，該抗PD-L1抗體包括重鏈和輕鏈，該重鏈包含或源自選自由SEQ ID NO：673至

694所組成之群組的胺基酸序列，該輕鏈包含或源自選自由SEQ ID NO：671或SEQ ID NO：672所組成之群組的胺基酸序列。

【0057】於一些實施態樣中，該抗PD-L1抗體包含與選自由SEQ ID NO：673至694所組成之群組的胺基酸序列具有至少90%、91%、92%、93%、94%、95%、96%、97%、98%或99%同一性之重鏈胺基酸序列，且包含與選自由SEQ ID NO：671或SEQ ID NO：672所組成之群組的胺基酸序列具有至少90%、91%、92%、93%、94%、95%、96%、97%、98%或99%同一性之輕鏈胺基酸序列。

【0058】於一些實施態樣中，該抗PD-L1抗體包含VH CDR1序列、VH CDR2序列、VH CDR3序列、VL CDR1序列、VL CDR2序列及VL CDR3序列之組合，其中至少一種CDR序列係選自由下列所組成之群組：包含RASQSISSYLN(SEQ ID NO：535)之VL CDR1序列；包含AASSLQS(SEQ ID NO：536)之VL CDR2序列；包含DNGYPST(SEQ ID NO：537)之VL CDR3序列；包含SYAMS(SEQ ID NO：538)之VH CDR1序列；包含SSIWRNGIVTVYADS(SEQ ID NO：539)之VH CDR2序列；及包含WSAAFDY(SEQ ID NO：540)之VH CDR3序列。

【0059】於一些實施態樣中，該PD-1/PD-L1路徑抑制劑係選自由下列所組成之群組：尼維魯單抗(nivolumab)、派姆單抗(pembrolizumab)、提利珠單抗(tislelizumab)、巴泰利珠單抗(spartalizumab)、卡利珠單抗(camrelizumab)、

賽特利單抗(cetrelimab)、賽普利單抗(cemiplimab)、巴西利單抗(Balstilimab)、多塔利單抗(Dostarlimab)、普戈利單抗(Prolgolimab)、沙山利單抗(Sasanlimab)、辛布利單抗(zimberelimab)、阿舒利珠單抗(Atezolizumab)、阿維魯單抗(Avelumab)、德維魯單抗(Durvalumab)、德布利單抗(adebrelimab)、洛普利單抗(Lodapolimab)、英佛利單抗(Envafolimab)、科貝利單抗(Cosibelimab)、布嘉利單抗(budigalimab)、薩本利單抗(ezabenlimab)、芬托利單抗(finotonlimab)、杰諾利單抗(geptanolimab)、洛普利單抗(lodapolimab)、潘普利單抗(penpulimab)、皮瓦利單抗(pimivalimab)、樸可利單抗(pucotenlimab)、思普利單抗(serplulimab)、西提利單抗(Sintilimab)、托巴利單抗(toripalimab)、哲瓦利單抗(zeluvalimab)、巴洛利單抗(iparomlimab)、諾辛利單抗(nofazinlimab)、魯洛利單抗(rulonilimab)、嘉維利單抗(garivulimab)、曼利單抗(manelimab)、歐普利單抗(opucolimab)、帕米單抗(pacmilimab)(CX-072)、舒多利單抗(sudubrilimab)、舒馬利單抗(sugemalimab)、索卡利單抗(socazolimab)及吉坦利單抗(tagitanlimab)。

【0060】於一些實施態樣中，該PD1/PD-L1路徑抑制劑包含帕米單抗(CX-072)(SEQ ID NO：485-HC、SEQ ID NO：496-LC)；CX-075(SEQ ID NO：485-HC、SEQ ID NO：497-LC)、CX-171(SEQ ID NO：504或505-HC、SEQ ID NO：506-LC)或CX-188(SEQ ID NO：483-HC、SEQ ID

NO：484-LC)。

【0061】本發明亦提供包括特異結合PD-1或PD-L1之抗體或其抗原結合片段之可經活化的抗體，該PD-1或PD-L1與掩蔽部分(MM)偶聯，而使該MM偶聯降低該抗體或其抗原結合片段與PD-1或PD-L1結合之能力。於一些實施態樣中，該MM經由可裂解部分(CM)偶聯，該可裂解部分包括作為蛋白酶之受質之序列。當該可裂解部分被蛋白酶裂解時，本揭示之可經活化的抗PD-1或抗PD-L1抗體被活化。例如，該蛋白酶係由接近該表現PD-1或PD-L1之T細胞的腫瘤產生。於一些實施態樣中，該蛋白酶係由與該表現PD-1或PD-L1之T細胞共定位的腫瘤產生。

【0062】本發明提供之可經活化的抗PD-1或抗PD-L1抗體(本文中亦稱為抗PD-1或抗PD-L1可經活化之抗體或PD-1和抗PD-L1可經活化之抗體)在循環中穩定，在預期之治療和/或診斷部位被活化，但在正常組織(例如健康組織或其他非治療和/或診斷目標之組織)中不會被活化，且當被活化時顯示出與PD-1或PD-L1之結合至少與該對應之未經修飾的抗體相當。

【0063】本發明亦提供治療、預防和/或延遲個體中與PD-1或PD-L1之異常表現和/或異常活性相關之症狀發生或進展、或減輕這些症狀的方法，該方法係使用單獨之可與PD-1或PD-L1結合的抗體或可經活化之抗體，或與可經活化之細胞介素(諸如可經活化之干擾素)組合之可與PD-1或PD-L1結合的抗體或可經活化之抗體(特別是結合並中

和，或以其他方式抑制至少一種PD-1或PD-L1之生物活性的可經活化之抗體)進行。

【0064】於一些實施態樣中，該可經活化之抗PD-1或抗PD-L1抗體包含在活化狀態下特異結合哺乳動物PD-1或PD-L1之可經活化的抗體，其中該可經活化之抗體包含：特異結合哺乳動物PD-1或抗PD-L1之抗體或其抗原結合片段(AB)；掩蔽部分(MM)，其當該可經活化之抗體處於未裂解狀態時抑制該AB與哺乳動物PD-1或PD-L1結合；及與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶之受質之多肽。

【0065】於一些實施態樣中，該可經活化之抗PD-1或抗PD-L1抗體包含可經活化的抗體，其在活化狀態下：(a)特異結合哺乳動物PD-1或PD-L1；及(b)特異阻斷PD-1之天然配體與哺乳動物PD-1結合，其中該可經活化之抗體包含：特異結合哺乳動物PD-1或PD-L1之抗體或其抗原結合片段(AB)；掩蔽部分(MM)，其當該可經活化之抗體處於未裂解狀態時抑制該AB與哺乳動物PD-1或PD-L1結合；及與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶之受質之多肽。

【0066】於一些實施態樣中，該處於未裂解狀態之可經活化的抗體以下列解離常數特異結合該哺乳動物PD-1或PD-L1：0.5 nM至1 nM、0.5 nM至2 nM、0.5 nM至5 nM、0.5 nM至10 nM、0.5 nM至15 nM、0.5 nM至20 nM、0.5 nM至25 nM、0.5 nM至50 nM、0.5 nM至75 nM、0.5 nM至100

nM、0.5 nM至150 nM、0.5 nM至200 nM、0.5 nM至300 nM、0.5 nM至400 nM、1 nM至2 nM、1 nM至5 nM、1 nM至10 nM、1 nM至15 nM、1 nM至20 nM、1 nM至25 nM、1 nM至50 nM、1 nM至75 nM、1 nM至100 nM、1 nM至150 nM、1 nM至200 nM、1 nM至300 nM、1 nM至400 nM、2 nM至5 nM、2 nM至10 nM、2 nM至15 nM、2 nM至20 nM、2 nM至25 nM、2 nM至50 nM、2 nM至75 nM、2 nM至100 nM、2 nM至150 nM、2 nM至200 nM、2 nM至300 nM、2 nM至400 nM、5 nM至10 nM、5 nM至15 nM、5 nM至20 nM、5 nM至25 nM、5 nM至50 nM、5 nM至75 nM、5 nM至100 nM、5 nM至150 nM、5 nM至200 nM、5 nM至300 nM、5 nM至400 nM、10 nM至15 nM、10 nM至20 nM、10 nM至25 nM、10 nM至5 0 nM、10 nM至75 nM、10 nM至100 nM、10 nM至150 nM、10 nM至200 nM、10 nM至300 nM、10 nM至400 nM、15 nM至20 nM、15 nM至25 nM、15 nM至50 nM、15 nM至75 nM、15 nM至100 nM、15 nM至150 nM、15 nM至200 nM、15 nM至300 nM、15 nM至400 nM、20 nM至25 nM、20 nM至50 nM、20 nM至75 nM、20 nM至100 nM、20 nM至150 nM、20 nM至200 nM、20 nM至300 nM、20 nM至400 nM、25 nM至50 nM、25 nM至75 nM、25 nM至100 nM、25 nM至150 nM、25 nM至200 nM、25 nM至300 nM、25 nM至400 nM、50 nM至75 nM、50 nM至100 nM、50 nM至150 nM、50 nM至200 nM、50 nM至300 nM、50 nM至400 nM、75 nM至100 nM、75 nM至150

nM、75 nM至200 nM、75 nM至300 nM、75 nM至400 nM、100 nM至150 nM、100 nM至200 nM、100 nM至300 nM、100 nM至400 nM、150 nM至200 nM、150 nM至300 nM、150 nM至400 nM、200 nM至300 nM、200 nM至400 nM、或300 nM至400 nM。

【0067】於一些實施態樣中，該處於活化狀態之可經活化的抗體係以下列解離常數特異結合哺乳動物PD-1或PD-L1：0.01 nM至5 nM、0.05 nM至5 nM、0.1 nM至5 nM、0.2 nM至5 nM、0.3 nM至5 nM、0.4 nM至5 nM、0.5 nM至5 nM、0.75 nM至5 nM、1 nM至5 nM、2 nM至5 nM、0.01 nM至2 nM、0.05 nM至2 nM、0.1 nM至2 nM、0.2 nM至2 nM、0.3 nM至2 nM、0.4 nM至2 nM、0.5 nM至2 nM、0.75 nM至1 nM、1 nM至2 nM、0.01 nM至1 nM、0.05 nM至1 nM、0.1 nM至1 nM、0.2 nM至1 nM、0.3 nM至1 nM、0.4 nM至1 nM、0.5 nM至1 nM、0.75 nM至1 nM、0.01 nM至0.75 nM、0.05 nM至0.75 nM、0.1 nM至0.75 nM、0.2 nM至0.75 nM、0.3 nM至0.75 nM、0.4 nM至0.75 nM、0.5 nM至0.75 nM、0.01 nM至0.5 nM、0.05 nM至0.5 nM、0.1 nM至0.5 nM、0.2 nM至0.5 nM、0.3 nM至0.5 nM、0.4 nM至0.5 nM、0.01 nM至0.4 nM、0.05 nM至0.4 nM、0.1 nM至0.4 nM、0.2 nM至0.4 nM、0.3 nM至0.4 nM、0.01 nM至0.3 nM、0.05 nM至0.3 nM、0.1 nM至0.3 nM、0.2 nM至0.3 nM、0.01 nM至0.2 nM、0.05 nM至0.2 nM、0.1 nM至0.2 nM、0.01 nM至0.1 nM、0.05 nM至0.1 nM或0.01 nM至0.05

nM。

【0068】於一些實施態樣中，該可經活化之抗體包含以下列解離常數特異結合哺乳動物PD-1或PD-L1之AB：0.01 nM至5 nM、0.05 nM至5 nM、0.1 nM至5 nM、0.2 nM至5 nM nM、0.3 nM至5 nM、0.4 nM至5 nM、0.5 nM至5 nM、0.75 nM至5 nM、1 nM至5 nM、2 nM至5 nM、0.01 nM至2 nM、0.05 nM至2 nM、0.1 nM至2 nM、0.2 nM至2 nM、0.3 nM至2 nM、0.4 nM至2 nM、0.5 nM至2 nM、0.75 nM至1 nM、1 nM至2 nM、0.01 nM至1 nM、0.05 nM至1 nM、0.1 nM至1 nM、0.2 nM至1 nM、0.3 nM至1 nM、0.4 nM至1 nM、0.5 nM至1 nM、0.75 nM至1 nM、0.01 nM至0.75 nM、0.05 nM至0.75 nM、0.1 nM至0.75 nM、0.2 nM至0.75 nM、0.3 nM至0.75 nM、0.4 nM至0.75 nM、0.5 nM至0.75 nM、0.01 nM至0.5 nM、0.05 nM至0.5 nM、0.1 nM至0.5 nM、0.2 nM至0.5 nM、0.3 nM至0.5 nM、0.4 nM至0.5 nM、0.01 nM至0.4 nM、0.05 nM至0.4 nM、0.1 nM至0.4 nM、0.2 nM至0.4 nM、0.3 nM至0.4 nM、0.01 nM至0.3 nM、0.05 nM至0.3 nM、0.1 nM至0.3 nM、0.2 nM至0.3 nM、0.01 nM至0.2 nM、0.05 nM至0.2 nM、0.1 nM至0.2 nM、0.01 nM至0.1 nM、0.05 nM至0.1 nM、或0.01 nM至0.05 nM。

【0069】於一些實施態樣中，該哺乳動物PD-1或PD-L1係選自由人PD-1或PD-L1和食蟹彌猴PD-1或PD所組成之群組。於一些實施態樣中，該AB係以小於或等於1 nM之

解離常數特異結合人PD-1或PD-L1或食蟹彌猴PD-1或PD-L1。於一些實施態樣中，該哺乳動物PD-1或PD-L1為人PD-1或PD-L1。於一些實施態樣中，該AB具有一或多種選自由下列所組成之群組的特徵：(a)該AB特異結合人PD-1或PD-L1及食蟹彌猴PD-1或PD-L1；(b)該AB抑制人PDL1和人PDL2與人PD-1結合；及(c)該AB抑制食蟹彌猴PDL1和食蟹彌猴PDL2與食蟹彌猴PD-1結合。

【0070】於一些實施態樣中，該哺乳動物PD-1或PD-L1為鼠PD-1或PD-L1。於一些實施態樣中，該可經活化之抗體包含特異結合鼠PD-1或PD-L1之AB或抑制小鼠PDL1和小鼠PDL2與鼠PD1結合之AB。

【0071】於一些實施態樣中，該處於未經裂解狀態之可經活化抗體係以下列解離常數與哺乳動物PD-1或PD-L1特異結合：大於或等於0.5 nM、大於或等於1 nM、大於或等於2 nM、大於或等於3 nM、大於或等於4 nM、大於或等於5 nM、大於或等於10 nM、大於或等於15 nM、大於或等於20 nM、大於或等於25 nM、大於或等於50 nM、大於或等於75 nM、大於或等於100 nM、大於或等於150 nM、大於或等於200 nM、大於或等於300 nM和/或大於或等於400 nM。

【0072】於一些實施態樣中，該處於活化狀態之可經活化的抗體係以下列解離常數與哺乳動物PD-1或PD-L1特異結合：小於或等於0.01 nM、小於或等於0.05 nM、小於或等於0.1 nM、小於或等於0.2 nM、小於或等於0.3 nM、

小於或等於0.4 nM、小於或等於0.5 nM、小於或等於0.75 nM，及小於或等於1 nM。

【0073】於一些實施態樣中，該可經活化之抗體包含以下列解離常數與哺乳動物PD-1或PD-L1特異結合之AB：小於或等於0.01 nM、小於或等於0.05 nM、小於或等於0.1 nM、小於或等於0.2 nM、小於或等於0.3 nM、小於或等於0.4 nM、小於或等於0.5 nM、小於或等於0.75 nM，及小於或等於1 nM。

【0074】於一些實施態樣中，該可經活化之抗體包含AB，該AB以下列EC_{50}阻斷天然配體與哺乳動物PDL1結合之能力：0.1 nM至10 nM、0.1 nM至5 nM、0.1 nM至3 nM、0.1 nM至2 nM、0.1 nM至1 nM、0.1 nM至0.5 nM、0.1 nM至0.25 nM、0.25 nM至10 nM、0.25 nM至5 nM、0.25 nM至3 nM、0.25 nM至2 nM、0.25 nM至1 nM、0.25 nM至0.5 nM、0.5 nM至10 nM、0.5 nM至5 nM、0.5 nM至3 nM、0.5 nM至2 nM、0.5 nM至1 nM、1 nM至10 nM、1 nM至5 nM、1 nM至3 nM、1 nM至2 nM、2 nM至10 nM、2 nM至5 nM、2 nM至3 nM、3 nM至10 nM、3 nM至5 nM、或 5 nM至10 nM。

【0075】於一些實施態樣中，該天然配體為哺乳動物PDL1或哺乳動物PDL2。於一些實施態樣中，該天然配體係選自由下列所組成之群組：人PDL1、人PDL2、食蟹彌猴PDL1和食蟹彌猴PDL2。

【0076】該處於經活化狀態之可經活化之抗體結合

PD-1或PD-L1，且包括(i)特異結合PD-1或PD-L1之抗體或其抗原結合片段(AB)；(ii)掩蔽部分(MM)，其當該可經活化之抗體處於未裂解狀態時抑制該AB與PD-1或PD-L1結合；及(iii)與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶的受質之多肽。

【0077】於一些實施態樣中，該處於未裂解狀態之可經活化之PD-1或PD-L1抗體於N端至C端之結構排列如下：MM-CM-AB或AB-CM-MM。

【0078】於一些實施態樣中，該可經活化之PD-1或PD-L1抗體在MM和CM之間包含連接肽。

【0079】於一些實施態樣中，該可經活化之PD-1或PD-L1抗體包含如本文所定義之CM。於一些實施態樣中，該可經活化之PD-1或PD-L1抗體在CM和AB之間包含連接肽。

【0080】於一些實施態樣中，該可經活化之PD-1或PD-L1抗體包含第一連接肽(LP1)和第二連接肽(LP2)，且其中該處於未裂解狀態之可經活化之抗體於N端至C端之結構排列如下：MM-LP1-CM-LP2-AB或AB-LP2-CM-LP1-MM。於一些實施態樣中，該二個連接肽不需要彼此相同。於一些實施態樣中，該LP1和該LP2各自為長度約1至20個胺基酸之肽。

【0081】於一些實施態樣中，該LP1和該LP2中至少一者包含選自由下列所組成之群組的胺基酸序列：$(GS)_n$、$(GGS)_n$、$(GSGGS)_n$(SEQ ID NO：227)和

$(GGGS)_n$(SEQ ID NO：228)，其中n為至少1之整數。

【0082】於一些實施態樣中，該LP1或該LP2中至少一者包含選自由下列所組成之群組的胺基酸序列：GGSG(SEQ ID NO：229)、GGSGG(SEQ ID NO：230)、GSGSG(SEQ ID NO：231)、GSGGG(SEQ ID NO：232)、GGGSG(SEQ ID NO：233)和GSSSG(SEQ ID NO：234)。

【0083】於一些實施態樣中，該LP1包含胺基酸序列GSSGGSGGSGGSG(SEQ ID NO：541)、GSSGGSGGSGG(SEQ ID NO：210)、GSSGGSGGSGGS(SEQ ID NO：542)、GSSGGSGGSGGSGGGS(SEQ ID NO：588)、GSSGGSGGSG(SEQ ID NO：543)、GSSGGSGGSGS(SEQ ID NO：544)、GGGSSGGS(SEQ ID NO：545)或GGGSSGG(SEQ ID NO：546)。

【0084】於一些實施態樣中，LP2包含胺基酸序列GSS、GGS、GGGS(SEQ ID NO：2)、GSSGT(SEQ ID NO：548)或GSSG(SEQ ID NO：549)。

【0085】於一些實施態樣中，該可經活化之抗體亦包括信號肽。於一些實施態樣中，該信號肽經由間隔子與該可經活化之抗體結合。於一些實施態樣中，該間隔子係在不存在信號肽之情況下與該可經活化之抗體結合。於一些實施態樣中，該間隔子與該可經活化之抗體的MM直接連接。於一些實施態樣中，該間隔子以於N端至C端的結構排列：間隔子-MM-CM-AB直接連接該可經活化之抗體的

MM。

【0086】於一些實施態樣中，該可經活化之抗PD-1抗體包括重鏈和輕鏈，該重鏈包含或源自選自由SEQ ID NO：610至614及620至628所組成之群組的胺基酸序列，該輕鏈包含或源自選自由SEQ ID NO：615至619及629至639所組成之群組的胺基酸序列。於一些態樣中，本揭示包括WO2017011580(其全文以引用整方式併入本文)中揭示之可經活化的抗PD-1抗體。

【0087】於一些實施態樣中，該可經活化之抗PD-1抗體包含掩蔽部分(MM)，該掩蔽部分(MM)包含選自由下列所組成之群組的胺基酸序列：AMSGCSWSAFCPYLA(SEQ ID NO：550)、DVNCAIWYSVCITVP(SEQ ID NO：551)、LVCPLYALSSGVCMG(SEQ ID NO：552)、SVNCRIWSAVCAGYE(SEQ ID NO：553)、MLVCSLQPTAMCERV(SEQ ID NO：554)、APRCYMFASYCKSQY(SEQ ID NO：555)、VGPCELTPKPVCNTY(SEQ ID NO：556)、ETCNQYERSSGLCFA(SEQ ID NO：557)、APRTCYTYQCSSFYT(SEQ ID NO：558)、GLCSWYLSSSGLCVD(SEQ ID NO：559)、VPWCQLTPRVMCMWA(SEQ ID NO：560)、NWLDCQFYSECSVYG(SEQ ID NO：561)、SCPLYVMSSFGGCWD(SEQ ID NO：562)、MSHCWMFSSSCDGVK(SEQ ID NO：563)、

VSYCTWLIEVICLRG(SEQ ID NO：564)、

VLCAAYALSSGICGG(SEQ ID NO：565)、

TTCNLYQQSSMFCNA(SEQ ID NO：566)、

APRCYMFASYCKSQY(SEQ ID NO：567)、

PCDQNPYFYPYVCHA(SEQ ID NO：568)、

SVCPMYALSSMLCGA(SEQ ID NO：569)、

LSVECYVFSRCSSLP(SEQ ID NO：570)、

FYCTYLVSLTCHPQ(SEQ ID NO：571)、

SMAGCQWSSFCVQRD(SEQ ID NO：572)、

IYSCYMFASRCTSDK(SEQ ID NO：573)、

SRCSVYEVSSGLCDW(SEQ ID NO：574)、

GMCSAYAYSSKLCTI(SEQ ID NO：575)、

MTTNTCNLLCQQFLT(SEQ ID NO：576)、

FQPCLMFASSCFTSK(SEQ ID NO：577)、

WNCHPAGVGPVFCEV(SEQ ID NO：578)、

ALCSMYLASSGLCNK(SEQ ID NO：579)、

NYLSCQFFQNCYETY(SEQ ID NO：580)、

GWCLFSDMWLGLCSA(SEQ ID NO：581)、

EFCARDWLPYQCSSF(SEQ ID NO：582)和

TSYCSIEHYPCNTHH(SEQ ID NO：583)。

【0088】於一些實施態樣中，該可經活化之抗PD-L1抗體包含與選自由SEQ ID NO：610至614及620至628所組成之群組的胺基酸序列具有至少90%、91%、92%、93%、94%、95%、96%、97%、98%或99%同一性之重鏈胺基酸

序列，且包含與選自由SEQ ID NO：615至619及629至639所組成之群組的胺基酸序列具有至少90%、91%、92%、93%、94%、95%、96%、97%、98%或99%同一性之輕鏈胺基酸序列。

【0089】於一些實施態樣中，該可經活化之抗PD-1抗體包括：(a)可變重鏈互補決定區1(VH CDR1)，其包含選自由SEQ ID NO：487及642至645所組成之群組的胺基酸序列；(b)可變重鏈互補決定區2(VH CDR2)，其包含選自由SEQ ID NO：488及646至650所組成之群組的胺基酸序列；(c)可變重鏈互補決定區3(VH CDR3)，其包含選自由SEQ ID NO：489及652至655所組成之群組的胺基酸序列；(d)可變輕鏈互補決定區1(VL CDR1)，其包含選自由SEQ ID NO：656至663所組成之群組的胺基酸序列；(e)可變輕鏈互補決定區2(VL CDR2)，其包含選自由SEQ ID NO：491及664至666所組成之群組的胺基酸序列；和(f)可變輕鏈互補決定區3(VL CDR3)，其包含選自由SEQ ID NO：683至687所組成之群組的胺基酸序列。

【0090】於一些實施態樣中，該可經活化之抗PD-1抗體包括可變重鏈互補決定區1(VH CDR1，本文亦稱為CDRH1)序列、可變重鏈互補決定區2(VH CDR2，本文亦稱為CDRH2)序列及可變重鏈互補決定區3(VH CDR3，本文亦稱為CDRH3)序列之組合，其中該VH CDR1序列包含GITFSNSG(SEQ ID NO：525)；該VH CDR2序列包含IWYDGSKR(SEQ ID NO：526)；且該VH CDR3序列包含

TNDDY(SEQ ID NO：527)。

【0091】於一些實施態樣中，該可經活化之抗PD-1抗體包括可變輕鏈互補決定區1(VL CDR1，本文亦稱為CDRL1)序列、可變輕鏈互補決定區2(VL CDR2，本文亦稱為CDRL2)序列及可變輕鏈互補決定區3(VL CDR3，本文亦稱為CDRL3)序列之組合，其中該VL CDR1序列包含QSVSSY(SEQ ID NO：528)；該VL CDR2序列包含DAS；且該VL CDR3序列包含QQSSNWPRT(SEQ ID NO：529)。

【0092】於一些實施態樣中，該可經活化之抗PD-1抗體包括可變重鏈互補決定區1(VH CDR1，本文亦稱為CDRH1)序列、可變重鏈互補決定區2(VH CDR2，本文亦稱為CDRH2)序列及可變重鏈互補決定區3(VH CDR3，本文亦稱為CDRH3)序列之組合，其中該VH CDR1序列包含GYTFTNYY(SEQ ID NO：530)；該VH CDR2序列包含INPSNGGT(SEQ ID NO：531)；且該VH CDR3序列包含RRDYRFDMGFDY(SEQ ID NO：532)。

【0093】於一些實施態樣中，該可經活化之抗PD-1抗體包括可變輕鏈互補決定區1(VL CDR1，本文亦稱為CDRL1)序列、可變輕鏈互補決定區2(VL CDR2，本文亦稱為CDRL2)序列及可變輕鏈互補決定區3(VL CDR3，本文亦稱為CDRL3)序列之組合，其中該VL CDR1序列包含KGVSTSGYSY(SEQ ID NO：533)；該VL CDR2序列包含LAS；且該VL CDR3序列包含QHSRDLPLT(SEQ ID NO：534)。

【0094】於一些實施態樣中，該可經活化之抗PD-L1抗體包含重鏈和輕鏈，該重鏈包含或源自選自由SEQ ID NO：673至694所組成之群組的胺基酸序列，且該輕鏈包含或源自選自由SEQ ID NO：671或SEQ ID NO：672所組成之群組的胺基酸序列。於一些態樣中，本揭示包括揭示於WO 2016/149201(其全文以引用方式併入本文)中之可經活化之抗PD-L1抗體。

【0095】於一些實施態樣中，該可經活化之抗PD-L1抗體包含與選自由SEQ ID NO：673至694所組成之群組的胺基酸序列具有至少90%、91%、92%、93%、94%、95%、96%、97%、98%或99%同一性之重鏈胺基酸序列且包含與選自由SEQ ID NO：671或SEQ ID NO：672所組成之群組的胺基酸序列具有至少90%、91%、92%、93%、94%、95%、96%、97%、98%或99%同一性之輕鏈胺基酸序列。

【0096】於一些實施態樣中，該可經活化之抗PD-L1抗體包含VH CDR1序列、VH CDR2序列、VH CDR3序列、VL CDR1序列、VL CDR2序列和VL CDR3序列之組合，其中至少一個CDR序列係選自由下列所組成之群組：VL CDR1序列，其包含RASQSISSYLN(SEQ ID NO：535)；VL CDR2序列，其包含AASSLQS(SEQ ID NO：536)；VL CDR3序列，其包含DNGYPST(SEQ ID NO：537)；VH CDR1序列，其包含SYAMS(SEQ ID NO：538)；VH CDR2序列，其包含SSIWRNGIVTVYADS(SEQ ID NO：539)；及

VH CDR3序列，其包含WSAAFDY(SEQ ID NO：540)。

【0097】於一些實施態樣中，該可經活化之抗PD-L1抗體包含掩蔽部分(MM)，該掩蔽部分(MM)包含選自由下列所組成之群組的胺基酸序列：YCEVSELFVLPWCMG(SEQ ID NO：584)、SCLMHPHYAHDYCYV(SEQ ID NO：585)、LCEVLMLLQHPWCMG(SEQ ID NO：586)、IACRHFMEQLPFCHH(SEQ ID NO：587)、FGPRCGEASTCVPYE(SEQ ID NO: 588)、LYCDSWGAGCLTRP(SEQ ID NO：589)、GIALCPSHFCQLPQT(SEQ ID NO：590)、DGPRCFVSGECSPIG(SEQ ID NO：591)、LCYKLDYDDRSYCHI(SEQ ID NO：592)、PCHPHPYDARPYCNV(SEQ ID NO：593)、PCYWHPFFAYRYCNT(SEQ ID NO：594)、VCYYMDWLGRNWCSS(SEQ ID NO：595)、LCDLFKLREFPYCMG(SEQ ID NO：596)、YLPCHFVPIGACNNK(SEQ ID NO：597)、FCHMGVVVPQCANY(SEQ ID NO：598)、ACHPHPYDARPYCNV(SEQ ID NO：599)、PCHPAPYDARPYCNV(SEQ ID NO：600)、PCHPHAYDARPYCNV(SEQ ID NO：601)、PCHPHPADARPYCNV(SEQ ID NO：602)、PCHPHPYAARPYCNV(SEQ ID NO：603)、PCHPHPYDAAPYCNV(SEQ ID NO：604)、

PCHPHPYDARPACNV(SEQ ID NO：605)、
PCHPHPYDARPYCAV(SEQ ID NO：606)、
PCHAHPYDARPYCNV(SEQ ID NO：607)、
PCHPHPYDARAYCNV(SEQ ID NO：608)。

【0098】本發明提供包含本文所描述之任一ACC之組成物。於一些實施態樣中，該組成物為醫藥組成物。本文亦提供包含至少一個本文所描述之任一組成物的劑量之套組。

【0099】本發明提供包含本文所描述之任一ACC及PD-1或PD-L1抗體之組成物。本發明提供包含本文所描述之任一ACC及可經活化的PD-1或PD-L1抗體之組成物。本文亦提供套組，該套組包含至少一個本文所描述之任一ACC的劑量和至少一個PD-1或PD-L1抗體或PD-1或PD-L1可經活化之抗體的劑量。

【0100】本發明提供治療有治療需要之個體的方法，其包含對個體投予治療有效量之本文所描述之任一ACC，加上或不加上PD1/PD-L1抑制劑，該PD1/PD-L1抑制劑係選自本文所描述之PD-1抗體、可經活化之PD-1抗體、PD-L1抗體、或可經活化之PD-L1抗體或任一組成物。於一些實施態樣中，該個體已被鑑定或診斷為患有癌症。於一些非限制性實施態樣中，該癌症為卡波西氏肉瘤、髮樣細胞白血病、慢性骨髓性白血病(CML)、濾泡性淋巴瘤、腎細胞癌(RCC)、黑色素瘤、神經母細胞瘤、基底細胞癌、膀胱癌、乳癌、結腸直腸癌、皮膚T細胞淋巴瘤、鼻咽腺

癌、非小細胞肺癌(NSCLC)、結腸癌、腎癌、卵巢癌、胰臟癌。於一些非限制性實施態樣中，該癌症為癌瘤。於一些非限制性實施態樣中，該癌症為肉瘤。於一些非限制性實施態樣中，該癌症為淋巴瘤。於一些非限制性實施態樣中，該淋巴瘤為伯基特氏淋巴瘤。

【0101】本發明提供編碼多肽之核酸，該多肽包含本文所描述之任一ACC之CP1和CM1。於一些實施態樣中，該多肽進一步包含本文所描述之任一該DD1。於一些實施態樣中，該多肽進一步包含本文所描述之該PM1和CM3中任一者。本文亦提供編碼多肽之核酸，該多肽包含本文所描述之任一該ACC的CP2和CM2。當該單體相同時，則本發明提供編碼二聚化以形成該ACC之單體的單一核酸。於一些實施態樣中，該多肽進一步包含本文所描述之任一該DD2。於一些實施態樣中，該多肽進一步包含本文所描述之該PM2和該CM4中任一者。於某些實施態樣中，該第一單體構築體和該第二單體構築體包含相同之該CP、該CM和該DD組分。於一些該等實施態樣中，該第一和第二單體構築體係由相同多肽(即，相同胺基酸序列)編碼。通常，當該第一和第二單體構築體包含相同胺基酸序列時，其係由相同核酸(即，該相同核酸序列)編碼。於一些該等實施態樣中，該第一和第二單體構築體係由該相同核酸編碼。本文亦提供包含本文所描述之任一核酸的載體。於一些實施態樣中，該載體為表現載體。本文亦提供包含本文所描述之任一核酸或本文所描述之任一載體的細胞。

【0102】本發明提供成對之核酸，該成對之核酸一起編碼包含本文所描述之任一ACC的第一單體構築體之該CP1和該CM1的多肽及包含本文所描述之任一ACC的第二單體構築體之該CP2和該CM2的多肽。本文亦提供成對之核酸，該成對之核酸一起編碼包含本文所描述之任一ACC的第一單體構築體之該PM1、該CM3、該CP1和該CM1的多肽及包含本文所描述之任一ACC的第二單體構築體之該PM2、該CM4、該CP2和該CM2的多肽。本文亦提供成對之載體，該成對之載體一起包含本文所描述之任何核酸對。於一些實施態樣中，該成對之載體為成對之表達載體。本文亦提供包含本文所描述之任何核酸對或本文所描述之任何載體對的細胞。於其他實施態樣中，本發明提供包含該載體對之載體。

【0103】本發明提供產生ACC之方法，其包含：在足以產生該ACC之條件下，在液體培養基中培養本文所描述之任一細胞；從該細胞或該液體培養基回收該ACC。於一些實施態樣中，該方法進一步包含：將該從細胞或液體培養基回收之該ACC分離出。於一些實施態樣中，該方法進一步包含：將該經分離之ACC配製成醫藥組成物。於其他實施態樣中，該方法進一步包含：將該經分離之ACC及該選自PD-1抗體、可經活化之PD-1抗體、PD-L1抗體或該可經活化之PD-L1抗體的PD1/PD-L1抑制劑配製成醫藥組成物。

【0104】本發明提供藉由本文所描述之任一方法產生

之ACC。本文亦提供包含本文所描述之任一ACC，具有或不具有該PD1/PD-L1抑制劑之組成物，該PD1/PD-L1抑制劑係選自該PD-1抗體、該可經活化之PD-1抗體、該PD-L1抗體或該可經活化之PD-L1抗體。本文亦提供本文所描述之任一組成物的組成物，其中該組成物為醫藥組成物。本文亦提供包含至少一個本文所描述之任一組成物之劑量的套組。

【0105】除非另有定義，本文所使用之所有技術和科學術語與本發明所屬技藝之一般技術人士所通常理解者具有相同含義。本文描述用於本發明之方法和材料；亦可使用本技藝已知之其他合適的方法和材料。該材料、方法和實施例僅用於說明而非用於限制。本文提及之所有出版物、專利申請案、專利案、序列、數據庫條目和其他參考文獻之全文均以引用方式併入本文。在與本文互相矛盾之情況下，以本專利說明書(包括定義)為準。

【0106】本發明之其他特性和優點將從下列詳細描述和附圖，及該申請專利範圍中顯明。

【0107】術語“一(a和an)”係指一或多個(即，至少一個)該冠詞之語法對象。舉例而言，“細胞”包含一或多個細胞。

【0108】如本文所使用之術語“約”和“近似”當用於修飾數值或範圍中具體指定之量時，表明該數值及與本技藝之技術熟習人士已知之該數值的合理偏差。例如在適當之情況下，±20%、±10%或±5%係在所全文述之值的預期含

義內。

【0109】本文中，濃度、量和其他數值數據可以範圍格式表達或呈現。應理解的是，使用該等範圍格式僅是為了方便和簡潔，因此應該被靈活地解釋為不僅包括該明確列舉為範圍限值之數值，且亦包括所有個別數值或包含在該範圍內之子範圍，如同各數值和子範圍皆被明確地敘述一樣。作為說明，“約0.01至2.0”之數值範圍應被解釋為不僅包括該明確列舉之約0.01至約2.0的值，且亦包括在該指明之範圍內之個別值和子範圍。因此，包括在此數值範圍內的為個別值，諸如0.5、0.7和1.5，及子範圍，諸如0.5至1.7、0.7至1.5及1.0至1.5，等。此外，不論所描述之範圍寬度或特徵該等解釋均應適用。此外，應注意的是，除非另有說明，所有百分比均以重量計。

【0110】在理解本揭示之範圍時，如本文所使用之術語“包括”或“包含”及其衍生詞意圖為開放式術語，其明確指明所陳述之特性、元素、組分、群組、整體和/或步驟的存在，但不排除存在其他未陳述之特性、元素、組分、群組、整體和/或步驟。前述內容亦適用於具有類似含義之字詞，諸如術語“包括”、“具有”及其衍生詞。如本文所使用之術語“由...組成”及其衍生詞意圖為封閉式術語，其具體指明所陳述之特性、元素、組分、群組、整體和/或步驟的存在，但排除存在其他未陳述之特性、元素、組分、群組、整體和/或步驟。如本文所使用之術語“基本上由.....組成”意圖具體指明所陳述之特性、元素、組分、

群組、整體和/或步驟，及那些不會對該特性、元素、組件、群組、整數和/或步驟之基本和新穎特徵產生實質影響者之存在。應理解的是，對這些過渡術語中之任一者(即“包含”、“由...組成”或“基本上由...組成”)的引用提供對置換未具體使用之任何其他過渡術語的直接支持。例如，將術語從“包含”修改為“基本上由.....組成”或“由.....組成”將因本定義而對本揭示全文中揭示之任何元素提供直接支持。基於該定義，本文揭示或藉由引用併入之任何元素可包括在所申請專利之發明中或從該申請專利之發明中排除。

【0111】為方便起見，如本文所使用之多個化合物、元素或步驟可呈現於共同列表中。然而，這些列表應被解釋為如同列表中之每一員都被個別識別為單獨且獨特之成員。因此，在沒有相反指示之情況下，該等列表中之任何個別成員不應僅根據其出現在共同群組中而被解釋為事實上等同於該同一列表中之任何其他成員。

【0112】此外，某些分子、構築體、組成物、元素、部分、賦形劑、病症、條件、性能、步驟等可能在一種具體之實施態樣或態樣之背景下或在本揭示之單獨段落或部分中討論。應理解的是，此僅是為了方便和簡潔，且任何此類揭示同樣適用且旨在與在本揭示和申請專利中之任何地方發現的任何其他實施態樣或態樣組合，這些實施態樣或態樣全部構成該在提交日期提交之該申請案和申請專利範圍。例如，相關於本揭示之構築體、組成物或方法描述

之構築體、分子、方法步驟、套組或組成物之列表意圖且確實對與本揭示之任何其他部分描述之構築體、組成物、配製劑和方法相關的實施態樣提供直接支持，即使那些方法步驟、活性劑、套組或組成物未在該實施態樣或態樣的上下文或章節中重新列出。

【0113】除非另外具體表明，否則“編碼蛋白質之核酸序列”包括為彼此之簡併版本且因此編碼相同胺基酸序列的所有核苷酸序列。

【0114】當相對於多肽一級胺基酸序列中之第二結構域或序列提及第一結構域或序列之位置時，術語“N端定位”係指該第一結構域或序列較該第二結構域或序列位於更靠近該多肽一級胺基酸序列之N端。於一些實施態樣中，該第一結構域或序列與第二結構域或序列之間可能存在額外之序列和/或結構域。

【0115】當相對於多肽一級胺基酸序列中之第二結構域或序列提及第一結構域或序列之位置時，術語“C端定位”係指該第一結構域或序列較該第二結構域或序列位於更靠近該多肽一級胺基酸序列之C端。於一些實施態樣中，該第一結構域或序列與第二結構域或序列之間可能存在額外之序列和/或結構域。

【0116】術語“外源性”係指自細胞、組織或生物體外部引入，或源自細胞、組織或生物體外部之任何物質，該物質非由該經引入該物質之相同細胞、組織或生物體產生或非源自該經引入該物質之相同細胞、組織或生物體。

【0117】術語“經轉導的”、“經轉染的”或“經轉化的”係指將外源核酸引入或轉移入細胞之過程。“經轉導的”、“經轉染的”或“經轉化的”細胞(例如哺乳動物細胞)為已經過外源核酸(例如載體)轉導、轉染或轉化之細胞，該外源核酸包括編碼本文描述之任一可經活化之細胞介素構築體的外源核酸。

【0118】術語“核酸”係指為單股或雙股形式之脫氧核糖核酸(DNA)或核糖核酸(RNA)或其組合。除非特別限制，該術語包含含有已知之天然核苷酸類似物的核酸，該等天然核苷酸類似物具有與該參考核苷酸相似之結合性能。除非另有說明，特定之核酸序列亦隱含互補序列以及明確指明之序列。於一些本文所描述之任何核酸的實施態樣中，該核酸為DNA。於一些本文所描述之任何核酸的實施態樣中，該核酸為RNA。

【0119】修飾可藉由本技藝已知之標準技術(諸如定點誘變及聚合酶鏈反應(PCR)介導之誘變)被引入核苷酸序列。保留式胺基酸取代為其中該胺基酸殘基被具有相似側鏈之胺基酸殘基取代的家族。本技藝已定義具有相似側鏈之胺基酸殘基家族。該等家族包括：具有酸性側鏈之胺基酸(例如天冬胺酸和麩胺酸)、具有鹼性側鏈之胺基酸(例如離胺酸、精胺酸及組胺酸)、非極性胺基酸(例如丙胺酸、纈胺酸、白胺酸、異白胺酸、脯胺酸、苯丙胺酸、甲硫胺酸和色胺酸)、不帶電荷之極性胺基酸(例如甘胺酸、天冬醯胺、麩胺醯胺、半胱胺酸、絲胺酸、蘇胺酸和酪胺

酸)、親水性胺基酸(例如精胺酸、天冬醯胺、天冬胺酸、麩胺醯胺、麩胺酸、組胺酸、離胺酸、絲胺酸和蘇胺酸)、疏水性胺基酸(例如丙胺酸、半胱胺酸、異白胺酸、白胺酸、甲硫胺酸、苯丙胺酸、脯胺酸、色胺酸、酪胺酸和纈胺酸)。其他胺基酸家族包括：脂族羥基胺基酸(例如絲胺酸和蘇胺酸)、醯胺家族(例如天冬醯胺和麩胺醯胺)、脂肪族(例如丙胺酸、纈胺酸、白胺酸和異白胺酸)及芳香族(例如苯丙胺酸、色胺酸和酪胺酸)。

【0120】如本文所使用之短語“特異結合”或“與...免疫反應”係指該可經活化之抗原結合蛋白複合物與合需之靶抗原的一或多個抗原決定簇反應但不與其他多肽反應，或以低得多的親和力結合，例如約或大於10^{-6} M。

【0121】術語“治療”係指改善病症之至少一種症狀。於一些實施態樣中，所治療之病症為癌症且改善至少一種癌症之症狀。

【圖式簡單說明】

【0122】[**圖1至4**]為示例性可經活化之細胞介素構築體的示意圖。

【0123】[**圖5A至5B**]描繪不具有肽掩蔽物之細胞介素構築體IFNα-2b-hIgG4 Fc(具有可裂解部分1204dL或可裂解部分1490)與蛋白酶(uPA或MT-SP1)之裂解反應，該裂解反應產生單體成熟IFNα-2b。

【0124】[**圖6A至6C**]顯示藉由蛋白酶uPa和MMP14將

細胞介素構築體(ProC440)活化。圖6B中之ProC440具有SEQ ID NO：286之序列。

【0125】[**圖7A至7B**]顯示在活體外使用IFN反應性HEK293細胞(**圖7A**)和Daudi細胞(**圖7B**)測試之細胞介素構築體(ProC440)的活性。

【0126】[**圖8**]顯示經掩蔽之細胞介素構築體ProC732的序列，該可選擇之信號序列以斜體表示，該掩蔽肽序列以雙下加線表示，該可裂解部分之序列以粗體表示，而成熟IFNα-2b之序列以下方劃線表示。

【0127】[**圖9**]顯示經掩蔽之細胞介素構築體ProC733的序列，該細胞介素與二聚化結構域之間不具有可裂解部分序列，該可選擇之信號序列以斜體表示，該掩蔽肽序列以雙下加線表示，該可裂解部分序列以粗體表示，而成熟IFNα-2b之序列以下方劃線表示。

【0128】[**圖10A**]顯示ProC440、ProC732和ProC733之示意圖。[**圖10B**]顯示使用IFN反應性HEK293細胞測試之細胞介素構築體(ProC440、ProC732和 ProC733)的活性。

【0129】[**圖11A**]顯示細胞介素構築體ProC286之結構示意圖，及在Daudi細胞凋亡分析中ProC286活性與Sylatron®(聚乙二醇化之干擾素α-2b)活性之比較。ProC286和Sylatron®顯示相似之活性水準，表明ProC286可作為Sylatron®對照替代，以評估IFNα-2b在倉鼠研究中之耐受性。[**圖11B**]描繪ProC291之結構示意圖及Daudi細胞凋亡分析中ProC291活性與Sylatron®活性之比較。

ProC291顯示出活性較Sylatron®和ProC286顯著降低。

【0130】[**圖12**]顯示IFNa-con(重組干擾素α，一種非天然存在之第I型干擾素)；ProC440之活性細胞介素裂解產物(ProC440+uPA)；Sylatron®(“PEG-IFNa2b”)；和ProC440之比活性，及在活體內劑量遞增研究(例如遞增劑量為0.08、0.4、2、10和15 mg/kg(“mpk”))中之預期的毒性劑量。

【0131】[**圖13A至13D**]顯示在敘利亞金倉鼠中進行之不同劑量的耐受性測試中動物對不同劑量之細胞介素構築體ProC286、ProC440和ProC732或對照組(人IgG4)反應時體重減輕的輪廓。圖13A顯示各測試之構築體在2 mg/kg(“2 mpk”)劑量下之數據；圖13B顯示在10 mg/kg劑量下之數據；且圖13C顯示在15 mg/kg劑量下之數據；圖13D顯示在經給予未經掩蔽之IFNa2b/Fc劑量的動物中，對應於增加之ALP之由INFa2b介導的毒性和IFNa2b單掩蔽物和雙重掩蔽物之增加的治療指數。

【0132】[**圖14**]顯示敘利亞金倉鼠在耐受性測試中對不同劑量(2 mpk、10 mpk和15 mpk)之細胞介素構築體ProC286、ProC440和ProC732或對照組(人IgG4)反應之臨床化學分析結果(鹼性磷酸酶、丙胺酸轉胺酶和天冬胺酸轉胺酶)。

【0133】[**圖15**]顯示敘利亞金倉鼠在耐受性測試中對不同劑量(2 mpk、10 mpk和15 mpk)之細胞介素構築體ProC286、ProC440和ProC732或對照組(人IgG4)反應之血

液學分析結果(網狀紅血球、嗜中性粒細胞和白血球(WBC)計數)。

【0134】[**圖16**]描繪從Daudi細胞凋亡分析測定之連接區(LR)長度對不具有肽掩蔽物之IFNα-2b-Fc融合蛋白之活性的影響。

【0135】[**圖17**]示意圖示說明不具有肽掩蔽物之細胞介素構築體，包括對連接區(LR)之描述。

【0136】[**圖18A**]顯示10、50和200μg之經掩蔽之可經活化的IFNa A/D(ProC1023)的抗腫瘤活性。[**圖18B**]顯示經掩蔽之IFNa A/D(ProC1023)相對於不可裂解之經掩蔽之IFNa A/D(ProC1549)在活體內的活化情形。[**圖18C**]顯示與單獨之經掩蔽的IFNa A/D(ProC1023)相比較及與單獨之PD-L1單株抗體(CX-171)相比較，該經掩蔽之IFNa A/D(ProC1023)與PD-L1單株抗體(CX-171)之組合的抗腫瘤活性。

【0137】[**圖19A至19B**]顯示與未經治療之對照小鼠(上方，圖19B)中的MC38腫瘤細胞挑戰相比較，先前使用可經活化之IFNa A/D(200微克之ProC1023)治療之小鼠(下方，圖19B)對MC38腫瘤細胞再挑戰反應時的免疫記憶。

【0138】[**圖20**]顯示與經掩蔽之IFN-a2b、未經掩蔽之IFN-a2b、單獨之Peg-IFN-a2b、單獨之PD-L1單株抗體和對照組相比較，Pro-IFN-a2b和PD-L1單株抗體在患者之PBMC(左)和患者之經分離的腫瘤細胞(右)中對患者組織中IFN-γ釋放的組合效果。

【0139】[**圖21**]顯示未經掩蔽之IFN-a2b以活化依賴方式誘導第I型干擾素特徵。

【0140】[**圖22**]顯示經雙重掩蔽之INF-a2b(ProC732)和對照分子在倉鼠中的藥代動力學。

【0141】[**圖23**]顯示與對照組相比較，20μg和200μg之經掩蔽的可經活化之IFNa A/D的抗腫瘤活性。

【0142】[**圖24A**]顯示在B16小鼠黑色素瘤細胞中之IFNa報告基因分析中ProC1023之活性與ProC859之活性的比較。[**圖24B和24C**]顯示在B16小鼠黑色素瘤細胞中之IFNa報告基因分析中，ProC1023活性與ProC1549活性的比較。

【0143】[**圖25**]顯示在活體外使用IFN反應性HEK293細胞測試之ProC1239和ProC732的活性。

【0144】[**圖26**]顯示在活體外使用IFN反應性HEK293細胞測試之處於未經裂解狀態和使用uPa或MTSP1蛋白酶活化後之ProC732、ProC1550和ProC1552的活性。

【0145】[**圖27**]顯示使用IFN反應性HEK293細胞測試之處於未經裂解狀態和蛋白酶活化後之重組IFNa2b、單體IFNa2b/Fc、經活化之同二聚體型IFNa2b/Fc和同二聚體型IFNa2b/Fc的活性。

【0146】[**圖28**]顯示在遞增劑量下之經單掩蔽之IFNa2b/Fc(上方)和聚乙二醇化之干擾素(下方)的抗腫瘤活性。

【0147】[**圖29**]描繪ACC ProC859通用干擾素之結構

(上方)、ACC ProC859在B16小鼠黑色素瘤細胞分析中之抗增殖作用和ACC ProC859在IFN反應性HEK293分析中之活性。

【0148】[**圖30**]顯示來自健康供體之PBMC群體中的CD14、CD3、PD-L1和IFNAR1陽性細胞以及骨髓細胞與患者PBMC和經分離之腫瘤的比較。

【0149】[**圖31**]顯示與未經處理的、經雙重掩蔽之IFN-a2b、單獨之sylatron和PD-L1單株抗體或單獨之經雙重掩蔽之IFN-a2b相比較，該經活化之IFN-a2b和PD-L1單株抗體對患者組織中之IFN-γ釋放的組合作用。

【0150】[**圖32**]顯示使用IFN反應性HEK293細胞在活體外測試之處於未經裂解狀態和蛋白酶活化後之經活化的和未經活化的經單掩蔽之IFNa2b及經活化的和未經活化之經雙重掩蔽的IFNa2b之活性。

【0151】[**圖33A**]顯示與10μg、50μg和200μg之經雙重掩蔽之不可活化的IFNa A/D相比較，該經雙重掩蔽之可經活化的IFNa A/D之抗腫瘤活性。

【0152】[**圖33B**]顯示與單獨之經雙重掩蔽之IFNa A/D或PD-L1單株抗體相比較，該經雙重掩蔽之IFNa A/D與PD-L1單株抗體之組合的抗腫瘤活性。

【0153】[**圖34A**]顯示與PBS對照組相比較，10、50和200μg之Pro IFNa A/D(ProC1023)的抗腫瘤活性。[**圖34B**]顯示與200μg之IFNa A/D NSUB(ProC1549)相比較，Pro IFNa A/D(ProC1023)之抗腫瘤活性。

【0154】[**圖35A**]顯示與200μg之PD-L1單株抗體(CX-171)相比較，10μg、50μg和200μg之Pro IFNa A/D (ProC1023)的抗腫瘤活性。[**圖35B**]顯示與PBS對照組相比較，50和200μg之IFNa A/D NSUB(ProC1549)的抗腫瘤活性。

【0155】[**圖36**]示意說明細胞介素構築體，包括該連接區(LR)和掩蔽物連接區(MLR)之描述。

【0156】[**圖37**]顯示植入CT26和B16之小鼠同源腫瘤移植模型隨時間之腫瘤體積變化和存活率。

【0157】[**圖38至38D**]顯示該經單掩蔽之Pb-IFN-a2b分子與人IFNAR2的結合。該配體被捕捉在經塗覆固定化抗人Fc(圖38A至38B)或抗組胺酸抗體(圖38C至38D)的晶片上。令濃度在25 nM至1.5625 μM之範圍內的IFN-a2b (ProC1640)流過配體捕捉晶片以產生多周期動力學傳感圖(圖38A和38C)。令濃度在250 nM至15.625 μM之範圍內的經掩蔽之Pb-IFN-a2b分子(ProC440-圖38D，ProC1976-圖38B)流過配體捕捉晶片以產生多周期動力學傳感圖。

【0158】[**圖39A**]顯示MMP恢復NSUB(ProC649)活性。[**圖39B**]顯示ProC732和ProC1299被uPA條件式活化。[**圖39C**]顯示與IFNaAD相比較之IFNa2b(SEQ ID NO：1)，而與ProC732相比較，ProC1301對活化有抗性。

【0159】[**圖40A至40D**]顯示經活化之Pb-IFN-a2b與干擾素α受體在活體外之結合。人IFNAR1、人IFNAR2、食蟹獼猴IFNAR1或食蟹獼猴IFNAR2蛋白被捕捉在塗覆固定

化之抗人Fc的晶片上。令濃度在25 nM至1.5625 μM之範圍內的經活化之IFN-a2b(ProC1640)流過配體捕捉晶片以產生多周期動力學傳感圖。

【0160】[**圖41A至41C**]顯示由腫瘤組織活化ProC732之分析(圖41A)和結果。將經螢光標記之ProC732在37℃下，在腫瘤組織切片上培育。然後透過能夠量化活性分子之毛細管電泳(圖41C)並使用HEK-blue IFNA報告基因模型(圖41B)分析回收之溶液。使用酶法上無活性樣品作為對照組織。

【0161】[**圖42A至42C**]顯示ProC732(圖42A)和重組IFN-a2b(圖42B)分子在與腫瘤組織一起培育後藉由HEK-blue IFNA報告基因模型分析之生物活性的變化。相對於0h值計算10 ng/mL之ProC732或1 ng/mL之重組IFN-a2b的生物活性之倍數變化。在沒有腫瘤組織之存在下培育24小時的ProC732和IFN-a2b蛋白之生物活性(圖42C)。每一條線連接一個在培育前和培育後24小時分析之個別樣品(濃度範圍100至0.01 ng/mL)。

【0162】[**圖43、44A和44B**]顯示經掩蔽之INF-a2b和對照分子在非人靈長類動物中之藥代動力學。使用經由皮下投予之單一劑量的0.03、0.3、3或15 mg/kg ProC732處理食蟹彌猴(每組N=2)。圖43顯示在指定時間點收集血漿樣品並分析總ProC732濃度之結果。圖44A顯示藉由MSD V-plex分析測量血清中之IP-10的濃度。圖44B顯示在投予後第1天和第7天之循環Pb-IFN-a2b和IP-10濃度相對於彼此作

圖。

【0163】[**圖45和46**]顯示基於濃度由ProC732非人靈長類動物誘導的基因表現輪廓變化(圖45)。以經由皮下投予之0.03、0.3、3或15mg/kg之單一ProC732劑量處理食蟹彌猴(每組N=2)。收穫來自經處理之動物的PBMC並藉由大量RNAseq進行分析。若讀數數量變化>3，則基因被稱為差別表現(圖46)。

【0164】[**圖47**]顯示ProC1023優先活化腫瘤組織中之免疫細胞。處理後六天收獲腫瘤和組織並藉由流式細胞術進行分析。門控設在存活之CD45+CD3+細胞。

【0165】[**圖48**]顯示在投予多個劑量後ProC732之耐受性良好。經由i.p.注射每週投予3次15、30或60 mg/kg Pb-IFN-a2b(ProC732)，或3.75、7.5或15 mg/kg之未經掩蔽的Fc-IFN-a2b(ProC286)融合蛋白來處理雄性敘利亞金倉鼠(N=5)。存活結果包括被發現死亡或體重減輕之動物>15%。

【0166】[**圖49**]顯示掩蔽ProC732可減弱非人靈長類動物中之細胞介素/趨化因子釋放。

【0167】[**圖50**]顯示經雙重掩蔽之Pb-IFN-a2b (ProC732)抑制具有免疫能力之嚙齒動物體內的腫瘤生長。經由皮下將1000萬個RPMI-1846倉鼠黑色素瘤細胞植入雄性敘利亞金倉鼠(N=16)中，並每週二次經由腹膜內投予5、10或20 mg/kg之Pb-IFN-a2b來處理之。

【0168】[**圖51**]顯示遞增劑量下之經雙重掩蔽之

IFNa2b/Fc和聚乙二醇化干擾素的抗腫瘤活性。經由皮下將1000萬個人淋巴瘤(Daudi)細胞植入Beige/SCID小鼠(每組n=8)中，且當平均腫瘤體積達到約200 mm^3時進行。每週一次i.v.投予指示劑量之Pb-IFN-a2b(ProC732)、未經掩蔽之Fc-IFN-a2b(ProC286)和Peg-IFN-a2b，共3週。

【0169】[**圖52**]顯示經雙重掩蔽之Pb-INF-a2b (ProC732)在Biege/SCID小鼠中之藥代動力學。以單次投予之指定劑量的Pb-IFN-a2b(ProC732)來處理Beige/SCID小鼠(每組n=15)。在投予後1、2、3、6、24、48、72、120小時、7和14天收集血漿以用於PK研究。藉由MSD分析來分析樣品。

【0170】[**圖53**]顯示Pb-IFN-a2b在非人靈長類動物中穩定。每週三次經由靜脈內途徑對食蟹彌猴(每組N=4，2隻雄性+2隻雌性)投予7.5、15、30或60 mg/kg之Pb-IFN-a2b(ProC732)以處理該食蟹彌猴。在衛星實驗中，每週使用30 mg/kg之Pb-IFN-a2b處理一組猴子(N=2，每種性別1隻)，共三週。藉由LC-MS測量Pb-IFN-a2b(ProC732)及其活化產物之血漿濃度。

【實施方式】

【0171】本發明提供可經活化之細胞介素構築體(ACC)，該細胞介素構築體顯示該對應之細胞介素中至少一種活性水準降低，但在暴露於活化條件後產生具有基本上恢復之活性的細胞介素產物。本發明之可經活化之細胞

介素構築體可設計成在暴露於患病組織時選擇性地活化，但在暴露於正常組織時則不。本發明進一步提供本文所描述之ACC結合選自下列之PD1/PD-L1抑制劑的組合療法或用途：該PD-1抗體、該可經活化之PD-1抗體、該PD-L1抗體或該可經活化之PD-L1抗體。因此，這些化合物具有賦予基於細胞介素之療法之益處的潛力，同時可能減少與某些基於細胞介素之療法相關的毒性。此外，該聯合療法可能賦予基於細胞介素之療法和抗PD1和/或抗PD-L1療法之益處，同時可能減少與不包含使用本發明揭示之ACC之各別單一療法和聯合療法相關的毒性。

【0172】本發明亦提供相關之中間體、組成物、套組、核酸和重組細胞及相關方法，包括本文所描述之任何可經活化之細胞介素構築體的使用方法和產生方法。

【0173】本發明者意外發現具有本文描述之特定元素和結構取向之ACC似乎可能有效提高族細胞介素於療法(特別是用於治療癌症)中之安全性和治療指數。雖然細胞介素為先天性和適應性免疫系統之調節劑，且在臨床前模型中具有廣泛之抗腫瘤活性，但其臨床成功受全身毒性和對標靶組織之不良全身暴露限制。本發明者意外發現發現具有本文所描述之特定元素和結構取向之ACC似乎降低與該細胞介素治療劑相關之全身毒性並改善對標靶組織之靶向和暴露。因此，本發明提供減少細胞介素治療劑之由標靶介導之藥物分佈(TMDD)的方法，該方法藉由對個體投予具有本文所描述之特定元素和結構取向之ACC來進行。

因此，本發明解決正常組織隔離大部分投予之細胞介素劑量的問題，該問題限制常規細胞介素治療劑在全身循環中到達靶組織(例如癌組織)之可用的劑量部分。本發明之細胞介素構築體將標靶結合定位於腫瘤組織，從而保持效力、降低副作用、實現新的標靶機會、改善經驗證之標靶的治療窗口、為不可下藥之標靶創建治療窗口並提供多種結合模式。

【0174】本揭示進一步提供聯合投予ACC與PD1/PD-L1抑制劑之方法，該PD1/PD-L1抑制劑選自該PD-1抗體、可經活化之PD-1抗體、PD-L1抗體或可經活化之PD-L1抗體。於一些實施態樣中，該ACC與PD1/PDL1抑制劑之組合可相對於常規細胞介素療法增加或增進治療功效和/或治療指數。於一些實施態樣中，該ACC和PD1/PDL1抑制劑之組合可相對於常規PD1/PDL1抑制劑聯合療法增加或增進療效和/或治療指數。於一些實施態樣中，該ACC和PD1/PDL1抑制劑之組合可相對於常規細胞介素和PD1/PDL1抑制劑聯合療法增加或增進治療功效和/或治療指數。再於其他實施態樣中，該ACC和PD1/PDL1抑制劑之組合可相對於單獨投予本發明之ACC增加或增進治療功效和/或治療指數。

【0175】本發明實現安全有效之全身遞送，從而避免常規全身性細胞介素療法之劑量依賴性毒性，且亦避免對腫瘤內注射之需要。本發明提供用於賦予局部抗病毒活性、免疫調節活性、抗增殖活性和促細胞凋亡活性之方

法。本發明者意外發現該第一和第二單體構築體之二聚化實現高度降低細胞介素活性，且意外發現藉由在該可經活化之構築體的另一端添加肽掩蔽物可以非常高之掩蔽效率來顯著降低細胞介素活性。參見，例如，圖10A-10B。

【0176】本申請者於2020年4月10日提交之美國臨時申請案第63/008,542號和2021年3月16日提交之美國臨時申請案第63/161,889號(其全文以引用方式併入本文)中描述某些不具有親和肽掩蔽物之可經活化的細胞介素構築體。

可經活化之細胞介素構築體和可經活化抗體

【0177】本發明之可經活化之細胞介素構築體(ACC)為包含第一單體構築體和第二單體構築體之二聚體複合物。該單體組分二聚化係由一對二聚化結構域促成。於一態樣中，各單體構築體包括細胞介素蛋白(CP)、一或多個可裂解部分(CM)、二聚化結構域(DD)和肽掩蔽物(PM)。本發明者意外發現，同時包含二聚化結構域和肽掩蔽物二者之ACC結構具有改善之掩蔽效率來使細胞介素之脫靶效果及不合需之活性和/或毒性副作用最小化或排除之。

【0178】於一特定之實施態樣中，本發明提供包括該第一單體構築體和該第二單體構築體之可經活化之細胞介素構築體(ACC)，其中：

(a)該第一單體構築體包含該第一肽掩蔽物(PM1)、該第一成熟細胞介素蛋白(CP1)、該第一和第三可裂解部分(CM1和CM2)及該第一二聚化結構域(DD1)，

其中該CM1位於該CP1與該DD1之間且該CM2位於該PM1與該CP1之間；且

(b)該第二單體構築體包含該第二成熟細胞介素蛋白(CP2)、該第二可裂解部分(CM3)和該第二二聚化結構域(DD2)，

其中該CM3位於該CP2與該DD2之間；

其中該DD1與該DD2彼此結合從而形成該第一單體構築體與該第二單體構築體之二聚體；且

其中該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，其CP1和/或CP2活性中至少一者之水準降低。於一些實施態樣中，該第二單體構築體進一步包含該第二肽掩蔽物(PM2)和位於該PM2與該CP2之間的該第四可裂解部分(CM4)。於一些實施態樣中，該第一單體構築體和該第二單體構築體係相同且彼此結合以形成同型二聚體。於其他實施態樣中，該第一和第二單體構築體之每一者中的該CP、該CM、該PM或該DD組分中至少一者不相同，且該第一和第二單體構築體彼此結合以形成異二聚體。

【0179】於另一特定實施態樣中，該ACC與特異結合該哺乳動物PD-1或PD-L1之經分離之抗體或其抗原結合片段(AB)一起用於聯合療法中。

【0180】於進一步之特定的實施態樣中，該ACC與在活化狀態下特異結合該哺乳動物PD-1或PD-L1之可經活化的抗PD-1或抗PD-L1抗體一起用於聯合療法中，其中該可

經活化之抗體包含：與該哺乳動物PD-1或抗PD-L1特異地結合之抗體或其抗原結合片段(AB)；掩蔽部分(MM)，其當該可經活化之抗體處於未裂解狀態時抑制該AB與哺乳動物PD-1或PD-L1結合；與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶的受質之多肽；及可選擇地第一連接肽(LP1)和/或第二連接肽(LP2)。

【0181】當相關於細胞介素構築體及可經活化之抗PD-1或抗PD-L1抗體使用時，術語“可經活化的”係指表現出一或多種活性之第一水準的細胞介素構築體或抗PD-1或抗PD-L1抗體，因此當暴露於引起一或多個可裂解部分裂解之條件時導致產生表現一或多種活性之第二水準的細胞介素構築體或抗PD-1或抗PD-L1抗體，其中該第二活性水準大於第一活性水準。活性之非限制性實例包括分別描述於本文中或本技藝已知之細胞介素、抗PD-1或抗PD-L1的任何示例性活性。

【0182】本文中術語“成熟細胞介素蛋白”係指缺乏信號序列之細胞介素蛋白。本文中信號序列亦稱為“信號肽”。細胞介素蛋白(CP)可為成熟的細胞介素蛋白或具有信號肽之細胞介素蛋白。因此，於一些態樣中，本揭示之ACC可包括成熟細胞介素蛋白序列。於一些態樣中，本揭示之ACC可包括成熟細胞介素蛋白序列，且另外包括信號序列。於一些態樣中，本揭示之ACC可包括本文揭示之序列，包括或缺乏本文描述之信號序列。於一些實施態樣中，該信號序列係選自由SEQ ID NO：468、SEQ ID NO：

469和SEQ ID NO：470所組成之群組。

【0183】本文中術語“可裂解部分”和“CM”可互換使用以指肽，該肽之胺基酸序列包含序列特異性蛋白酶之受質。適合作為CM之可裂解部分包括本技藝已知之任何蛋白酶受質。示例性可裂解部分更詳細地描述於下文中。

【0184】本文中，術語“肽掩蔽物”和“PM”可互換使用以指具有少於50個胺基酸之可減少或抑制細胞介素蛋白之一或多種活性的胺基酸序列。該PM可與細胞介素結合並限制該細胞介素與其受體交互作用。於一些實施態樣中，該PM之長度不超過40個胺基酸。於較佳之實施態樣中，該PM之長度不超過20個胺基酸。於一些實施態樣中，該PM之長度不超過19、18、17、16或15個胺基酸。於一些態樣中，該PM具有至少13個胺基酸(包括從13至49之任何數目)。於一些態樣中，該PM具有至少14個胺基酸(包括從14至49之任何數目)。於一些態樣中，該PM具有至少15個胺基酸(包括從15至49之任何數目)。於某些態樣中，該PM中之胺基酸的數目可計算成與該細胞介素蛋白結合之該等胺基酸。例如，該PM排除大的多肽。例如，該PM並非潛在相關肽。例如，該PM並非細胞介素。例如，該PM並非細胞介素受體。例如，該PM並非細胞介素受體之片段。於一些態樣中，該PM不具有與細胞介素受體具有至少85%同一性之胺基酸序列。例如，該PM並非白蛋白。例如，該PM不包括具有多於50個胺基酸之蛋白質或多肽。於一些態樣中，該PM不包括具有多於25個胺基酸之蛋白質或

多肽。於一些態樣中，該PM不包括具有多於20個胺基酸之蛋白質或多肽。於一些態樣中，該PM不包括具有多於15個胺基酸之蛋白質或多肽。於一些態樣中，該PM不包括形成彈性N端或C端尾區之胺基酸。

【0185】可經活化之大分子(即，尚未活化的)中之“掩蔽部分”或“MM”“掩蔽”或減少或以其他方式抑制該可經活化之大分子與其標靶和/或表位結合。於一些實施態樣中，該抗PD-1或抗PD-L1抗體與MM偶聯或以MM修飾時可藉由本技藝已知之抑制手段(例如，但不限於結構改變和競爭抗原結合結構域)來抑制該抗PD-1或抗PD-L1抗體特異結合其標靶和/或表位的能力。於一些實施態樣中，該抗PD-1或抗PD-L1抗體與MM偶聯或以MM修飾時可使結構變化起作用以降低或抑制該蛋白質特異結合其標靶和/或表位之能力。於一些實施態樣中，該抗PD-1或抗PD-L1抗體與MM偶聯或以MM修飾時可在空間上阻斷、降低或抑制該抗PD-1或抗PD-L1抗體與其標靶和/或表位特異結合之能力。於一些實施態樣中，該MM可為長度為約2至50個胺基酸之多肽。例如，該MM可為長度為2至40、2至30、2至20、2至10、5至15、10至20、15至25、20至30、25至35、30至40、35至45、40至50個胺基酸之多肽。例如，該MM可為長度為2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21 、22、23、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49或50

個胺基酸之多肽。於一些實施態樣中，該MM可為長度多於50個胺基酸(例如100、200、300、400、500、600、700、800或更多個胺基酸)之多肽。

【0186】本文中，術語“二聚化結構域”和“DD”可互換使用以指成對之二聚化結構域中的一員，其中該對之各成員能經由一或多種共價或非共價交互作用與另一成員結合。該第一DD和第二DD可為相同或不同。適合作為DD1和/或DD2之示例性DD更詳細地描述於下文中。

【0187】如本文所使用之術語“連接子”、“連接肽”、“LP”係指肽，其胺基酸序列並非蛋白酶之受質。示例性連接子和LP更詳細地描述於下文中。

【0188】如本文所使用之術語“連接區”或“LR”係指介於該細胞介素之C端與N-端鄰接該二聚化結構域之近端交互作用點的胺基酸殘基之間的胺基酸殘基延伸(即，該連接區不包括該細胞介素之C端胺基酸或該DD之N端胺基酸，該DD之N端胺基酸形成該對應之第二單體的DD之近端交互作用點)。例如，當該DD為一對Fc結構域時，該連接區為介於該細胞介素之C端與該Fc之第一個N端半胱胺酸殘基之間的胺基酸殘基延伸，該Fc之第一個N端半胱胺酸殘基參與與該第二Fc結構域的二硫鍵聯(例如根據EU編號之IgG1或IgG4 Fc結構域的半胱胺酸226)。當該二聚化結構域不是多肽時，則該連接區為在該細胞介素之C端之後直到最後一個胺基酸的胺基酸殘基延伸。例如，當該DD為生物素-鏈黴親和素對時，該含生物素單體之連接區為

介於該細胞介素之C端和該生物素分子之間的胺基酸殘基延伸，而該含鏈黴親和素單體之連接區為介於該細胞介素之C端和該鏈黴親和素分子之間的胺基酸殘基延伸。

【0189】如本文所使用之術語“掩蔽連接區”或“MLR”係指介於該PM和該CP之間的胺基酸殘基延伸。如圖36所示，該MLR從該CP之N端跨越至該PM之C端。因此，該MLR可包括一個PM、一個PM和一個連接子，或一個PM和二個連接子。於一些態樣中，該MLR跨越15至22個胺基酸。於一些態樣中，該MLR跨越16至21個胺基酸。於一些態樣中，該MLR跨越17至20個胺基酸。於一些態樣中，該MLR跨越18至20個胺基酸。於一些態樣中，該MLR跨越15、16、17、18、18、20、21或22個胺基酸。

【0190】如本文所使用之術語“掩蔽效率”係指該未經裂解之ACC、可經活化之抗PD-1或可經活化之抗PD-L1抗體的活性(例如EC50)除以對照細胞介素、抗PD-1或抗PD-L1抗體之活性，其中該對照細胞介素、抗PD-1或抗PD-L1抗體可為該ACC之裂解產物、可經活化之抗PD-1或可經活化之抗PD-L1或者作為該ACC之CP之該細胞介素、抗PD-1或抗PD-L1、可經活化之抗PD-1或可經活化之抗PD-L1抗體。具有至少一種降低之該CP1和/或該CP2活性水準的ACC具有大於10掩蔽效率。於一些實施態樣中，本文所描述之該ACC、可經活化之抗PD-1或可經活化之抗PD-L1抗體具有大於10、大於100、大於1000或大於5000之掩蔽效率。

【0191】如本文所使用之術語“間隔子”在本文中係指被併入該成熟ACC之游離端的胺基酸殘基或肽，例如介於該信號肽與該成熟ACC之N端之間。於一些態樣中，該間隔子(或“頭部(header)”)可含有麩胺醯胺(Q)殘基。於一些態樣中，該間隔子中之殘基將胺基肽酶和/或外肽酶作用最小化以防止N端胺基酸裂解。說明性和非限制性間隔子胺基酸序列可包含下列示例性胺基酸序列之任一者或由下列示例性胺基酸序列之任一者組成：QGQSGS(SEQ ID NO：471)；GQSGS(SEQ ID NO：472)；QSGS(SEQ ID NO：473)；SGS; GS; S; QGQSGQG(SEQ ID NO：474)；GQSGQG(SEQ ID NO：475)；QSGQG(SEQ ID NO：476)；SGQG(SEQ ID NO：477)；GQG；QG；G；QGQSGQ(SEQ ID NO：478)；GQSGQ(SEQ ID NO：479)；QSGQ(SEQ ID NO：480)；QGQSG(SEQ ID NO：481)；QGQS(SEQ ID NO：482)；SGQ；GQ；和Q。於一些實施態樣中，該間隔子序列可省略。

【0192】如本文所使用之多肽，諸如細胞介素或Fc結構域，可為野生型多肽(例如天然存在之多肽)或野生型多肽之變體。變體可為藉由對野生型多肽之一或多個胺基酸進行取代、插入、缺失和/或添加來修飾的多肽，惟其該變體保留該野生型多肽之基本功能或活性。於一些實例中，與野生型多肽相比較，該變體可能具有已改變(例如增加或減少的)之功能或活性。於一些態樣中，該變體可為該野生型多肽之功能片段。術語“功能片段”意指該多肽

(例如細胞介素)之序列可包括較全長多肽序列更少之胺基酸，但包括足夠之多肽鏈長度以賦予活性(例如細胞介素活性)。

【0193】該第一和第二單體構築體可進一步包含另外之元素，諸如，例如一或多個連接子，等。該另外之元素更詳細地描述於下文中。該第一和第二單體構築體之每一者中之該CP、該CM、該PM和該DD組分之組織可依各單體構築體之相同順序排列。與該對應之該CP2、該CM2、該PM2和該DD2相比較(例如就該CP、該CM和該PM組分(及其中該DD組分為多肽之實施態樣中的DD組分)之分子量、大小、胺基酸序列，等而言)，該CP1、該CM1、該PM1和該DD1組分可相同或不同。因此，該所產生之二聚體可能具有對稱或不對稱之單體構築體組分。

【0194】於一些實施態樣中，該第一單體構築體於該CP和該CM組分之N端至C端包含該PM1、該CM3、該CP1、該CM1，及直接或間接(藉由連接子)連接至該CM1之N端的該DD1。於其他實施態樣中，該第一單體構築體從該CP和該CM組分之C端至N端包含該PM1、該CM3、該CP1、該CM1，及直接或間接(藉由連接子)連接至該CM1之N端的該DD1。於一些實施態樣中，該第二單體構築體於該CP和該CM組分之N端至C端包含該PM2、該CM4、該CP2、該PM2、該CM2，及直接或間接(藉由連接子)連接至該CM2之C端的該DD2。於其他實施態樣中，該第二單體構築體於該CP和該CM組分之C端至N端包含該PM2、該

CM4、該CP2、該PM2、該CM2，及直接或間接(藉由連接子)連接至該CM2之N端的該DD2。於一實例中，該第一單體構築體包含第一多肽，該第一多肽包含該PM1、該CM3、該CP1、該CM1及該DD1。於一實例中，該第二單體構築體包含第二多肽，該第二多肽包含該CP2、該CM2和該DD2。於另一實例中，該第二單體構築體包含第二多肽，該第二多肽包含該PM2、該CM4、該CP2、該CM2和該DD2。

【0195】於一些實施態樣中，該CP和該DD組分係藉由不能被蛋白酶裂解之連接子連接。例如，該CP和該DD組分可藉由不可裂解之受質序列(NSUB)連接。於一些實施態樣中，該第一和第二單體構築體其中一者在該CP和該DD之間包含NSUB，而另一者在該CP和該DD之間包含該CM。於一些態樣中，該連接子可為包括甘胺酸和絲胺酸殘基，但不易被蛋白酶裂解之胺基酸受質序列。不可裂解之連接子序列之實例包括那些描述於美國專利案10,611,845B2號(其全文以引用方式併入本文)中者。在該等情況下，該CP和/或該DD可能具有蛋白酶之裂解位點。

【0196】本發明中ACC之實例可由下式表示(為單體1/單體2之形式，於各單體之N端至C端)

PM1-CM3-CP1-CM1-DD1/PM2-CM4-CP2-CM2-DD2

PM1-CM3-CP1-CM1-DD1/CP2-CM2-DD2

DD1-CM1-CP1-CM3-PM1/DD2-CM2-CP2-CM4-PM2

DD1-CM1-CP1-CM3-PM1/DD2-CM2-CP2

【0197】ACC可在組分之間包含一或多個連接子。例如，該ACC可在該PM和該CP之間和/或該CP和該DD之間包含一或多個連接子。因此，如本文所使用，且除非另有說明，介於該ACC組分之間的各連接號(-)代表直接鍵聯或經由一或多個連接子之鍵聯。

【0198】於一些態樣中，當該ACC具有N-PM-CM1-CP-CM2-DD-C之取向時，則於該ACC之N端至該細胞介素之N端胺基酸的整個胺基酸跨度長度為17至71個胺基酸。於一些態樣中，當該ACC具有N-DD-CM1-CP-CM2-PM-C之取向時，則於該ACC之C端至該細胞介素之C端胺基酸的整個胺基酸跨度長度為17至71個胺基酸。

【0199】於某些實施態樣中，該第一和第二單體構築體之取向使得該二聚體之各成員中的組分係以相同順序從該CP和該CM組分之N端至C端組織。圖1中提供說明性ACC之示意圖。參考圖1，該ACC於N端至C端包含：(1)第一單體構築體110，其具有PM1 119、CM3 117、CP1115、CM1 113和DD1 111，及；(2)第二單體構築體120，其可選擇地具有PM2 129和CM4 127、CP2125、CM2 123和DD2 121；及(3)將第一單體構築體110與第二單體構築體120結合之一或多個共價鍵或非共價鍵(←→)。該ACC可進一步在組分之間包含一個或多個可選擇之連接子112、114、116、118、122、124、126和128。於一實示例中，DD1 111和DD2 121相同。於另一實例中，DD1 111和DD2 121不相同。

【0200】圖2提供另一說明性ACC之示意圖，其組分以該ACC之相反方向組織。參考圖2，該ACC從CP和CM組分之N端至C端包含：(1)第一單體構築體210，其具有DD1 211、CM1 213、CP1 215、CM3 217和PM1 219；(2)第二單體構築體220，其具有DD2 221、CM2 223、CP2 225，及可選擇之CM4 227和PM2 229；(3)將第一單體構築體210與第二單體構築體220結合之一或多個共價鍵或非共價鍵(←→)。該ACC可進一步在組分之間包含一或多個可選擇之連接子212、214、216、218、222、224、226和228。於一實例中，DD1 211和DD2 221相同。於另一實例中，DD1 211和DD2 221不同。

【0201】圖3中提供另一個說明性ACC之示意圖。參考圖3，該ACC於N端至C端包含：(1)第一單體構築體310，其具有該PM1 319、該CM3 317、該CP1 315、該CM1 313、該DD1 311；(2)第二單體構築體320，其具有該CP2 325、該CM2 323和該DD2 321，及可選擇之該PM2 329和該CM4 327。該DD1 311和該DD2 321為結合伴侶，例如配體/受體對或抗原/抗原結合肽對，使得該DD1和該DD2以共價或非共價方式結合在一起。該ACC可在組分之間進一步包含一或多個可選擇之連接子312、314、316、318、322、324、326和328。於一實例中，該DD1 311和該DD2 321係相同。於另一實例中，該DD1 311和該DD2 321係不同。

【0202】於替換之態樣中，描繪成該CP1 315和該CP2

325的二個部分其中一者為缺乏細胞介素活性之截短的細胞介素蛋白。例如，該CP1或該CP2可為截短之干擾素α2b，其具有野生型干擾素α2b的前151個胺基酸。於替換之態樣中，描繪成該CP1 315和該CP2 325的二個部分其中一者為缺乏細胞介素活性之突變的細胞介素蛋白。例如，該CP1或該CP2可為具有L130P突變之截短的干擾素α2b(例如SEQ ID NO：298)。於替換之態樣中，描繪成該CP1 315和該CP2 325的二個部分其中一者為缺乏細胞介素活性之多肽序列，例如信號部分和/或殘段(stub)序列。於替換之態樣中，描繪成該CP1 315和該CP2 325的二個部分中之第一個部分為多肽序列，其以高親和力與該描繪成CP1 315和CP2 325的二個部分中之第二個部分結合，且使該第二個部分之細胞介素活性與該第二部分之對照水準相比較下降低。

【0203】圖4提供另一說明性ACC之示意圖，其組件以相反方向組織。參考圖4，該ACC於N端至C端包含該CP和該CM組分：1)第一單體構築體410，其具有該DD1 411、該CM1 413、該CP1 415、該CM3 417和該PM1 419；及(2)第二單體構築體420，其具有該DD2 421、該CM2 423、該CP2425及可選擇之該CM4 427和該PM2 429。該DD1411和該DD2 421為結合配偶體，例如配體/受體對或抗原/抗原結合肽對，使得該DD1和該DD2以共價或非共價方式結合在一起。該ACC可在組分之間進一步包含一或多個可選擇之連接子412、414、416、418、422、424、426

和428。於一實例中，該DD1 411和該該DD2 421係相同。於另一實例中，該DD1 411和該DD2 421係不同。

【0204】於本揭示之某些態樣中，圖中描繪之該PM1和該PM2可不存在於與抗PD1或抗PD-L1抗體組合使用之該ACC中。

【0205】該ACC結構被發現在降低該成熟細胞介素蛋白組分之活性方面非常有效，其方式不會導致活化後細胞介素活性顯著受損。該ACC中之CP活性可被該ACC之結構(例如二聚體結構)和該ACC中之肽掩蔽物二者降低。於一些實施態樣中，本文所描述之ACC之活化條件係暴露於一或多種可使CP與DD和PM二者解離之蛋白酶。例如，該一或多種蛋白酶可裂解介於該CP與該PM之間的CM以及介於該CP與該DD之間的CM。如實施例中所示，該ACC之活化導致細胞介素活性實質恢復。結果表明該細胞介素組分之構象在該ACC之背景下未被不可逆地改變。重要的是，本發明者已發現本結構(利用二聚化結構域和對該細胞介素蛋白具有特異結合親和力之一或多種肽掩蔽物)似乎導致優於使用單獨之肽掩蔽物或單獨之二聚化結構域所得之掩蔽效果。

【0206】該ACC可採用多種不同之成熟細胞介素蛋白、可裂解部分、肽掩蔽物及二聚化結構域中之任一者分別作為該CP1、CP2、CM1、CM2、CM3、CM4、PM1、PM2、DD1和DD2。例如，本技藝已知之多種不同的成熟細胞介素蛋白或其序列和/或截短變體中之任一者可能適

合作為該ACC之CP1和CP2組分中任一者或二者。該成熟細胞介素蛋白CP1和CP2可為相同或不同。於某些特定之實施態樣中，該CP1和該CP2係相同。於其他實施態樣中，該CP1和該CP2係不同。該ACC可在該CP1和/或該CP2之N和/或C端的任一端或二端包含額外之胺基酸殘基。

【0207】於一些實施態樣中，該CP1和/或該CP2可各自獨立地包含選自下列群組之成熟細胞介素蛋白：干擾素(諸如，例如干擾素α、干擾素β、干擾素γ、干擾素τ和干擾素ω)、介白素(諸如，例如IL-1α、IL-1β、IL-1RA、IL-18、IL-2、IL-4、IL-7、IL-9、IL-13、IL-15、IL-3、IL-5、GM-CSF、IL-6、IL-11、IL-21)、G-CSF、IL-12、LIF、OSM、IL-10、IL-20、IL-14、IL-16、IL-17、CD154、LT-β、TNF-α、TNF-β、4-1BBL、APRIL、CD27、CD70、CD153、CD178、GITRL、LIGHT、OX40L、OX40、TALL-1、TRAIL、TWEAK、TRANCE、TGF-β1、TGF-β2、TGF-β3、EPOo、TPO、Flt-3L、SCF、M-CSF和MSP，等，及其序列和截短變體。特別地，用於聯合使用之ACC可含有IL-2、IL-7、IL-8、IL-10、IL-12、IL-15、IL-21、IFN-α、IFN-β、IFN-γ、GM-CSF、TGF-β、LIGHT、GITR-L、CD40L、CD27L、4-1BB-L、OX40、OX40L。例如，該等蛋白質之序列包括表23中者，而該等序列之額外實例可從ncbi.nlm.nih.gov/protein獲得。適合用於本發明之ACC的截短變體包括保留細胞介素活性之任何N或C端截短之細胞介素。用於本發明中之示例性截

短變體包括本技藝已知之任何截短之細胞介素多肽(參見，例如Slutzki et al., *J. Mol. Biol.* 360:1019-1030, 2006和US 2009/0025106)以及N和/或C端被截短1至約40個胺基酸、1至約35個胺基酸、1至約30個胺基酸、1至約25個胺基酸、1至約20個胺基酸、1至約15個胺基酸、1至約10個胺基酸、1至約8個胺基酸、1至約6個胺基酸、1至約4個胺基酸之保留細胞介素活性的細胞介素多肽。於一些前述實施態樣中，該經截短之CP為N端經截短之CP。於其他實施態樣中，該經截短之CP為C端經截短之CP。於某些實施態樣中，該經截短之CP為C端和N端經截短之CP。

【0208】於一些實施態樣中，該CP1和/或該CP2各自獨立地包含與選自由下列所組成之群組的細胞介素參考序列具有至少80%同一性(例如，至少82%、至少84%、至少86%、至少88%、至少90%、至少92%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性)的胺基酸序列：SEQ ID NO：101、SEQ ID NO：102、SEQ ID NO：103、SEQ ID NO：104、SEQ ID NO：105、SEQ ID NO：106、SEQ ID NO：107、SEQ ID NO：108、SEQ ID NO：109、SEQ ID NO：110、SEQ ID NO：111、SEQ ID NO：112、SEQ ID NO：113、SEQ ID NO：114、SEQ ID NO：115、SEQ ID NO：116 、SEQ ID NO：117、SEQ ID NO：118、SEQ ID NO：119、SEQ ID NO：12、SEQ ID NO：121、SEQ ID NO：122、SEQ ID NO：123、SEQ ID NO：124、SEQ ID NO：125、SEQ ID NO：

126、SEQ ID NO：127、SEQ ID NO：128、SEQ ID NO：129、SEQ ID NO：130、SEQ ID NO：131、SEQ ID NO：132、SEQ ID NO：133、SEQ ID NO：134、SEQ ID NO：135、SEQ ID NO：136、SEQ ID NO：137、SEQ ID NO：138、SE Q ID NO：139、SEQ ID NO：140、SEQ ID NO：141、SEQ ID NO：142、SEQ ID NO：143、SEQ ID NO：144、SEQ ID NO：145、SEQ ID NO：146、SEQ ID NO：NO：147、SEQ ID NO：148、SEQ ID NO：149、SEQ ID NO：150、SEQ ID NO：151、SEQ ID NO：152、SEQ ID NO：153、SEQ ID NO：154、SEQ ID NO：155、SEQ ID NO：156、SEQ ID NO：157、SEQ ID NO：158、SEQ ID NO：159、SEQ ID NO：160、SEQ ID NO：161、SEQ ID NO：162、SEQ ID NO：163、SEQ ID NO：164、SEQ ID NO：165、SEQ ID NO：166、SEQ ID NO：167、SEQ ID NO：168、SEQ ID NO：169、SEQ ID NO：170、SEQ ID NO：171、SEQ ID NO：172、SEQ ID NO：173、SEQ ID NO：174、SEQ ID NO：175、SEQ ID NO：176、SEQ ID NO：177、SEQ ID NO：178、SEQ ID NO：179、SEQ ID NO：180、SEQ ID NO：181、SEQ ID NO：182、SEQ ID NO：183、SEQ ID NO：184、SEQ ID NO：185、SEQ ID NO：186、SEQ ID NO：187、SEQ ID NO：188、SEQ ID NO：189、SEQ ID NO：190、SEQ ID NO：191、SEQ ID NO：192、SEQ ID NO：193、SEQ ID NO：194、SEQ ID NO：195、SEQ ID NO：196、SEQ ID NO：NO：197、

SEQ ID NO：198、SEQ ID NO：199、SEQ ID NO：200、SEQ ID NO：201、SEQ ID NO：202、SEQ ID NO：203、SEQ ID NO：204、SEQ ID NO：205、SEQ ID NO：206、SEQ ID NO：207、SEQ ID NO：208和SEQ ID NO：209。序列同一性之百分比係指當使用序列比對程式(例如BLAST程式套組，其可在NCBI網站網路上公開取得)比對時介於二或更多個肽序列之間的胺基酸序列同一性之水準。亦參見Altschul et al., J. Mol. Biol. 215:403-10, 1990。於一些態樣中，該ACC包括作為CP1或CP2之干擾素α2b突變體，例如相對於SEQ ID NO：1在位置L130處具有突變(例如L130P突變)之干擾素α2b分子(例如SEQ ID NO：298)。於一些態樣中，該ACC包括在位置I24、F64、I60、I63、F64、W76、I116、L117、F123或L128或其組合處具有突變之干擾素α2b突變體。例如，該干擾素α2b突變體可包括突變I116至T、N或R；L128至N、H或R；I24至P或Q；L117H；或L128T，或彼等之組合。於一些態樣中，該干擾素α2b突變體可包括突變I24Q、I60T、F64A、W76H、I116R和L128N或其亞群。於一些態樣中，該ACC包括缺乏細胞介素活性之經截短的干擾素α2b分子作為該CP1和CP2其中一者。例如該經截短之干擾素α2b可由干擾素α2b之151個或更少個胺基酸組成，例如該野生型干擾素α2b序列中於N至C端之任一胺基酸：1至151、1至150、1至149、1至148、…、1至10、1至9、1至8、1至7、1至6、或2至151、3至151、4至151、5至150、6至149、7至148、

8至147或胺基酸或其突變體之任何間插序列。

【0209】於某些具體之實施態樣中，該CP1和/或該CP2包含干擾素。適合在本發明之構築體中作為CP1和/或CP2之干擾素包括，例如干擾素α、干擾素β、干擾素γ、干擾素ω和干擾素τ。於一些實施態樣中，當該干擾素為干擾素α時，其可為干擾素α-2a、干擾素α-2b或干擾素α-n3。干擾素α之進一步實例包括干擾素α-1、干擾素α-4、干擾素α-5、干擾素α-6、干擾素α-7、干擾素α-8、干擾素α-10、干擾素α-13、干擾素α-14、干擾素α-16、干擾素α-17和干擾素α-21。於一些實施態樣中，該干擾素為重組或純化之干擾素α。於某些實施態樣中，當該干擾素為干擾素β時，其係選自由干擾素β-1a和干擾素β-1b所組成之群組。於一些實施態樣中，該CP1和/或該CP2包含IFab結構域，其為在干擾素α或干擾素β中發現之保留的蛋白結構域。該IFab結構域負責細胞介素釋放和干擾素之抗病毒功能。示例性IFab序列提供於SEQ ID No：449至458中。於一實例中，該CP1和該CP2為不同干擾素。於另一實例中，該CP1和該CP2為相同干擾素。

【0210】於一些實施態樣中，該CP1和/或該CP2表現干擾素活性且包括與選自由下列所組成之群組之干擾素α參考序列具有至少80%同一性、至少82%同一性、至少84%同一性、至少86%同一性、至少88%同一性、至少90%同一性、至少92%同一性、至少94%同一性、至少96%同一性、至少98%同一性、或至少99%同一性、或100%同一

性的胺基酸序列：SEQ ID NO：1、SEQ ID NO：101、SEQ ID NO：102、SEQ ID NO：103、SEQ ID NO：104和SEQ ID NO：105。於某些具體之實施態樣中，該干擾素α參考序列為SEQ ID NO：1(人干擾素α-2b)。於一些實施態樣中，該CP1和/或該CP2包含成熟α干擾素，該成熟α干擾素具有選自由下列所組成之群組的胺基酸序列：SEQ ID NO：1、SEQ ID NO：101、SEQ ID NO：102、SEQ ID NO：103、SEQ ID NO：104和SEQ ID NO：105。於某些實施態樣中，該CP1和/或該CP2包含具有SEQ ID NO：1之胺基酸序列的成熟人α干擾素。於一些上述實施態樣中，該CP1和該CP2包含相同胺基酸序列。

【0211】於其他實施態樣中，該CP1和/或該CP2表現出干擾素活性且包括與選自由下列所組成之群組之干擾素β參考序列具有至少80%同一性、至少82%同一性、至少84%同一性、至少86%同一性、至少88%同一性、至少90%同一性、至少92%同一性、至少94%同一性、至少96%同一性、至少98%同一性、或至少99%同一性、或100%同一性的胺基酸序列：SEQ ID NO：106、SEQ ID NO：107、SEQ ID NO：108和SEQ ID NO：109。於某些實施態樣中，該干擾素β參考序列為選自由下列所組成之群組的人干擾素β參考序列：SEQ ID NO：106和SEQ ID NO：107。於一些實施態樣中，該CP1和/或該CP2包含成熟β干擾素，該成熟β干擾素具有選自由下列所組成之群組的胺基酸序列：SEQ ID NO：106、SEQ ID NO：107、SEQ ID NO：

108和SEQ ID NO：109。於一些上述之實施態樣中，該CP1和該CP2包含相同之胺基酸序列。

【0212】於一些實施態樣中，該CP1和/或該CP2顯現干擾素活性且包括與對應於SEQ ID NO：110(人干擾素ω)之干擾素ω參考序列具有至少80%同一性、至少82%同一性、至少84%同一性、至少86%同一性、至少88%同一性、至少90%同一性、至少92%同一性、至少94%同一性、至少96%同一性、至少98%同一性、或至少99%同一性、或100%同一性的胺基酸序列。於某些具體之實施態樣中，該CP1和/或該CP2包含成熟人ω干擾素，該成熟人ω干擾素具有SEQ ID NO：110之胺基酸序列。於一些上述之實施態樣中，該CP1和該CP2包含相同之胺基酸序列。

【0213】於一些實施態樣中，該CP1和/或該CP2顯現介白素活性且包括與選自由下列所組成之群組之介白素參考序列具有至少80%同一性、至少82%、至少84%、至少86%、至少88%、至少90%、至少92%、至少94%、至少96%、至少97%、至少98%、或至少99%同一性、或100%同一性的胺基酸序列：SEQ ID NO：111、SEQ ID NO：112、SEQ ID NO：113、SEQ ID NO：114、SEQ ID NO：115、SEQ ID NO：116、SEQ ID NO：NO：117、SEQ ID NO：118、SEQ ID NO：119、SEQ ID NO：12、SEQ ID NO：121、SEQ ID NO：122、SEQ ID NO：123、SEQ ID NO：124、SEQ ID NO：125、SEQ ID NO：126、SEQ ID NO：127、SEQ ID NO：128、SEQ ID NO：129、SEQ ID

NO：130、SEQ ID NO：131、SEQ ID NO：132、SEQ ID NO：133、SEQ ID NO：134、SEQ ID NO：135、SEQ ID NO：136、SEQ ID NO：137、SEQ ID NO：138、SEQ ID NO：139、SEQ ID NO：140、SEQ ID NO：143、SEQ ID NO：NO：144、SEQ ID NO：145、SEQ ID NO：146、SEQ ID NO：151、SEQ ID NO：152、SEQ ID NO:153、SEQ ID NO：154、SEQ ID NO：155、SEQ ID NO：156、SEQ ID NO：157、SEQ ID NO：158、SEQ ID NO：159和SEQ ID NO：160。於一些實施態樣中，該CP1和/或該CP2包含成熟介白素，該成熟介白素具有選自由下列所組成之群組的胺基酸序列：SEQ ID NO：111、SEQ ID NO：112、SEQ ID NO：113、SEQ ID NO：114、SEQ ID NO：NO：115、SEQ ID NO：116、SEQ ID NO：117、SEQ ID NO：118、SEQ ID NO：119、SEQ ID NO：12、SEQ ID NO：121、SEQ ID NO：122、SEQ ID NO：123、SEQ ID NO：124、SEQ ID NO：125、SEQ ID NO：126、SEQ ID NO：127、SEQ ID NO：128、SEQ ID NO：129、SEQ ID NO：130、SEQ ID NO：131、SEQ ID NO：132、SEQ ID NO：133、SEQ ID NO：134、SEQ ID NO：135、SEQ ID NO：136、SEQ ID NO：137、SEQ ID NO：138、SEQ ID NO：139、SEQ ID NO：NO：140、SEQ ID NO：143、SEQ ID NO：144、SEQ ID NO：145、SEQ ID NO：146、SEQ ID NO：151、SEQ ID NO：152、SEQ ID NO：153、SEQ ID NO：154、SEQ ID NO：155、SEQ ID NO：156、

SEQ ID NO：157、SEQ ID NO：158、SEQ ID NO：159和SEQ ID NO：160。於一些上述之實施態樣中，該CP1和該CP2包含相同之胺基酸序列。

【0214】於一些實施態樣中，該CP1和/或該CP2顯現介白素活性且包括與選自由下列所組成之群組之介白素參考序列具有至少80%同一性、至少82%、至少84%、至少86%、至少88%、至少90%、至少92%、至少94%、至少96%、至少97%、至少98%、或至少99%同一性的胺基酸序列：SEQ ID NO：111(人IL-1α)、SEQ ID NO：113(人IL-1β)、SEQ ID NO：115(人IL-1RA)、SEQ ID NO：117(人IL-18)、SEQ ID NO：119(人IL-2)、SEQ ID NO：121(人IL-4)、SEQ ID NO：123(人IL-7)、SEQ ID NO：125(人IL-9)、SEQ ID NO：127(人IL-13)、SEQ ID NO：129(人IL-15)、SEQ ID NO：131(人IL-3)、SEQ ID NO：133(人IL-5)、SEQ ID NO：137(人IL-6)、SEQ ID NO：139(人IL-11)、SEQ ID NO：143(人IL-12α)、SEQ ID NO：144(人IL-12β)、SEQ ID NO：151(人IL-10)、SEQ ID NO：153(人IL-20)、SEQ ID NO：155(人IL-14)、SEQ ID NO：157(人IL-16)和SEQ ID NO：159(人IL-17)。於某些該等實施態樣的中，該CP1和/或該CP2包含選自由下列所組成之群組的胺基酸序列：SEQ ID NO：111(人IL-1α)、SEQ ID NO：113(人IL-1β)、SEQ ID NO：115(人IL-1RA)、SEQ ID NO：117(人IL-18)、SEQ ID NO：119(人IL-2)、SEQ ID NO：121(人IL-4)、SEQ ID NO：123(人IL-7)、SEQ ID

NO：125(人IL-9)、SEQ ID NO：127(人IL-13)、SEQ ID NO：129(人IL-15)、SEQ ID NO：131(人IL-3)、SEQ ID NO：133(人IL-5)、SEQ ID NO：137(人IL-6)、SEQ ID NO：139(人IL-11)、SEQ ID NO：143(人IL-12α)、SEQ ID NO：NO：144(人IL-12β)、SEQ ID NO：151(人IL-10)、SEQ ID NO：153(人IL-20)、SEQ ID NO：155(人IL-14)、SEQ ID NO：157(人IL-16)和SEQ ID NO：159(人IL-17)。於一些上述之實施態樣中，該CP1和該CP2包含相同之胺基酸序列。

【0215】採用之細胞介素蛋白序列中之胺基酸的數量可能根據所使用之特定細胞介素蛋白而有所不同。於一些實施態樣中，該CP1和/或該CP2包括總共約10個胺基酸至約700個胺基酸、約10個胺基酸至約650個胺基酸、約10個胺基酸至約600個胺基酸、約10個胺基酸至約550個胺基酸、約10個胺基酸至約500個胺基酸、約10個胺基酸至約450個胺基酸、約10個胺基酸至約400個胺基酸、約10個胺基酸至約350個胺基酸、約10個胺基酸至約300個胺基酸、約10個胺基酸至約250個胺基酸、約10個胺基酸至約200個胺基酸、約10個胺基酸至約150個胺基酸、約10個胺基酸至約100個胺基酸、約10個胺基酸至約80個胺基酸、約10個胺基酸至約60個胺基酸、約10個胺基酸至約40個胺基酸、約10個胺基酸至約20個胺基酸、約20個胺基酸至約700個胺基酸、約20個胺基酸至約650個胺基酸、約20個胺基酸至約600個胺基酸、約20個胺基酸至約550個胺基酸、

約20個胺基酸至約500個胺基酸、約20個胺基酸至約450個胺基酸、約20個胺基酸至約400個胺基酸、約20個胺基酸至約350個胺基酸、約20個胺基酸至約300個胺基酸、約20個胺基酸至約250個胺基酸、約20個胺基酸至約200個胺基酸、約20個胺基酸至約150個胺基酸、約20個胺基酸至約100個胺基酸、約20個胺基酸至約80個胺基酸、約20個胺基酸至約60個胺基酸、約20個胺基酸至約40個胺基酸、約40個胺基酸至約700個胺基酸、約40個胺基酸至約650個胺基酸、約40個胺基酸至約600個胺基酸、約40個胺基酸至約550個胺基酸、約40個胺基酸至約500個胺基酸、約40個胺基酸至約450個胺基酸、約40個胺基酸至約400個胺基酸、約40個胺基酸至約350個胺基酸、約40個胺基酸至約300個胺基酸、約40個胺基酸至約250個胺基酸、約40個胺基酸至約200個胺基酸、約40個胺基酸至約150個胺基酸、約40個胺基酸至約100個胺基酸、約40個胺基酸胺基酸至約80個胺基酸、約40個胺基酸至約60個胺基酸、約60個胺基酸至約700個胺基酸、約60個胺基酸至約650個胺基酸、約60個胺基酸至約600個胺基酸、約60個胺基酸至約550個胺基酸、約60個胺基酸至約500個胺基酸、約60個胺基酸至約450個胺基酸、約60個胺基酸至約400個胺基酸、約60個胺基酸至約350個胺基酸、約60個胺基酸至約300個胺基酸、約60個胺基酸至約250個胺基酸、約60個胺基酸至約200個胺基酸、約60個胺基酸至約150個胺基酸、約60個胺基酸至約100個胺基酸、約60個胺基酸胺基酸至約80個胺

基酸、約80個胺基酸至約700個胺基酸、約80個胺基酸至約650個胺基酸、約80個胺基酸至約600個胺基酸、約80個胺基酸至約550個胺基酸、約80個胺基酸至約500個胺基酸、約80個胺基酸至約450個胺基酸、約80個胺基酸至約400個胺基酸、約80個胺基酸至約350個胺基酸、約80個胺基酸至約300個胺基酸、約80個胺基酸至約250個胺基酸、約80個胺基酸至約200個胺基酸、約80個胺基酸至約150個胺基酸、約80個胺基酸至約100個胺基酸、約100個胺基酸至約700個胺基酸、約100個胺基酸至約650個胺基酸、約100個胺基酸至約600個胺基酸、約100個胺基酸至約550個胺基酸、約100個胺基酸至約500個胺基酸、約100個胺基酸至約450個胺基酸、約100個胺基酸至約400個胺基酸、約100個胺基酸至約350個胺基酸、約100個胺基酸至約300個胺基酸、約100個胺基酸至約250個胺基酸、約100個胺基酸至約200個胺基酸、約100個胺基酸至約150個胺基酸、約150個胺基酸至約700個胺基酸、約150個胺基酸至約650個胺基酸、約150個胺基酸至約600個胺基酸、約150個胺基酸至約550個胺基酸、約150個胺基酸至約500個胺基酸、約150個胺基酸至約450個胺基酸、約150個胺基酸至約400個胺基酸、約150個胺基酸至約350個胺基酸、約150個胺基酸至約300個胺基酸、約150個胺基酸至約250個胺基酸、約150個胺基酸至約200個胺基酸、約200個胺基酸至約700個胺基酸、約200個胺基酸至約650個胺基酸、約200個胺基酸至約600個胺基酸、約200個胺基酸至約550

個胺基酸、約200個胺基酸至約500個胺基酸、約200個胺基酸至約450個胺基酸、約200個胺基酸至約400個胺基酸、約200個胺基酸至約350個胺基酸、約200個胺基酸至約300個胺基酸、約200個胺基酸至約250個胺基酸、約250個胺基酸至約700個胺基酸、約250個胺基酸至約650個胺基酸、約250個胺基酸至約600個胺基酸、約250個胺基酸至約550個胺基酸、約250個胺基酸至約500個胺基酸、約250個胺基酸至約450個胺基酸、約250個胺基酸至約400個胺基酸、約250個胺基酸至約350個胺基酸、約250個胺基酸至約300個胺基酸、約300個胺基酸至約700個胺基酸、約300個胺基酸至約650個胺基酸、約300個胺基酸至約600個胺基酸、約300個胺基酸至約550個胺基酸、約300個胺基酸至約500個胺基酸、約300個胺基酸至約450個胺基酸、約300個胺基酸至約400個胺基酸、約300個胺基酸至約350個胺基酸、約350個胺基酸至約700個胺基酸、約350個胺基酸至約650個胺基酸、約350個胺基酸至約600個胺基酸、約350個胺基酸至約550個胺基酸、約350個胺基酸至約500個胺基酸、約350個胺基酸至約450個胺基酸、約350個胺基酸至約400個胺基酸、約400個胺基酸至約700個胺基酸、約400個胺基酸至約650個胺基酸、約400個胺基酸至約600個胺基酸、約400個胺基酸至約550個胺基酸、約400個胺基酸至約500個胺基酸、約400個胺基酸至約450個胺基酸、約450個胺基酸至約700個胺基酸、約450個胺基酸至約650個胺基酸、約450個胺基酸至約600個胺基

酸、約450個胺基酸至約550個胺基酸、約450個胺基酸至約500個胺基酸、約500個胺基酸至約700個胺基酸、約500個胺基酸至約650個胺基酸、約500個胺基酸至約600個胺基酸、約500個胺基酸至約550個胺基酸、約550個胺基酸至約700個胺基酸、約550個胺基酸至約650個胺基酸、約550個胺基酸至約600個胺基酸、約600個胺基酸至約700個胺基酸、約600個胺基酸至約650個胺基酸、或約650個胺基酸至約700個胺基酸。於一些實施態樣中，該CP1和/或該CP2為成熟野生型人細胞介素蛋白。

【0216】該ACC之各單體構築體可採用多種不同之二聚化結構域中任一者。合適之DD包括聚合型(例如合成之聚合物、多肽、多核苷酸，等)和小分子(分子量小於約1000道耳吞，且有時小於約800道耳吞之非聚合部分)類型之部分。該DD對可為本技藝已知之彼此結合的任何一對部分。

【0217】例如，於一些實施態樣中，該DD1和該DD2為選自下列群組的一對成員：源自人IL-15受體之α鏈(IL15Rα)的sushi結構域和可溶性IL-15；barnase和barnstar；蛋白激酶A(PKA)和A激酶錨定蛋白(AKAP)；適配體/基於突變之RNase I片段之對接標籤構件；一對抗原結合結構域(例如一對單結構域抗體)；可溶性N-乙基馬來醯亞胺敏感因子附接蛋白受體(SNARE)；基於突觸融合蛋白(syntaxin)、突觸結合蛋白(synaptotagmin)、突觸小蛋白(synaptobrevin)之交互作用的構件和SNAP25；單結構域抗

體(sdAb)和對應之表位；抗原結合結構域(例如單鏈抗體，諸如單鏈可變片段(scFv)、單結構域抗體，等)和對應之表位；捲曲螺旋多肽結構(例如Fos-Jun捲曲螺旋結構、酸/鹼捲曲螺旋螺旋體、Glu-Lys捲曲螺旋螺旋體、白胺酸拉鏈結構)、小分子結合對，諸如生物素和親和素或鏈黴親和素、胺/醛、凝集素/碳水化合物；一對可彼此結合之聚合物，諸如，例如一對含硫或含硫醇聚合物(例如一對Fc結構域、一對硫醇化之人血清白蛋白多肽，等)；及類似物。

【0218】於一些實施態樣中，該DD1和該DD2為非多肽聚合物。該非多肽聚合物可彼此共價結合。於一些實施態樣中，該非多肽聚合物可為含硫聚合物，例如含硫聚乙二醇。於該等情況下，該DD1和該DD2可經由一或多個二硫鍵彼此共價結合。

【0219】當該成對之DD1和DD2為一對表位和抗原結合結構域的成員時，該表位可為天然或非天然發生之表位。示例性非天然發生之表位包括，例如非天然發生之肽，諸如，例如多聚-His肽(例如His標籤，等)。

【0220】於某些特定之實施態樣中，該DD1和該DD2為一對Fc結構域。如本文所使用之“Fc結構域”係指免疫球蛋白之單一重鏈的連續胺基酸序列。成對之Fc結構域結合在一起以形成免疫球蛋白之Fc區。

【0221】於一些實施態樣中，該對Fc結構域為一對人Fc結構域(例如一對野生型人Fc結構域)。於一些實施態樣

中，該人Fc結構域為人IgG1 Fc結構域(例如野生型人IgG1 Fc結構域)、人IgG2 Fc結構域(例如野生型人IgG2 Fc結構域)、人IgG3 Fc結構域(例如野生型人IgG3 Fc結構域)或人IgG4 Fc結構域(例如野生型人IgG4 Fc結構域)。於一些實施態樣中，該人Fc結構域包含與SEQ ID NO：3具有至少80%同一性(例如至少82%、至少84%、至少85%、至少86%、至少88%、至少90%、至少92%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性)之序列。

【0222】於一些實施態樣中，該對Fc結構域包含Fc結構域之鈕突變體(knob mutant)和孔突變體(hole mutant)。該鈕突變體和孔突變體可彼此交互作用以促進二聚化。於一些實施態樣中，該鈕突變體和孔突變體可在介於二個Fc結構域之間的界面內(例如在CH3結構域中)包含一或多個胺基酸修飾。於一實例中，該修飾包含在一條抗體重鏈中之胺基酸取代T366W和可選擇之胺基取代S354C，及在另一條抗體重鏈中之胺基酸取代T366S、L368A、Y407V和可選擇的Y349C(根據Kabat編號系統之EU索引編號)。該鈕突變體和孔突變體之實例包括SEQ ID NO：287和288之Fc突變體，以及美國專利案5,731,168；7,695,936；和10,683,368號(其全文以引用方式併入本文)中描述者。於一些實施態樣中，該二聚化結構域包含分別與SEQ ID NO：287和288具有至少80%同一性(例如至少82%、至少84%、至少85%、至少86%、至少88%、至少90%、至少

92%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性)之序列。

【0223】於一些實施態樣中，該DD1和/或該DD2可進一步包括血清半衰期延長部分(例如結合血清蛋白之多肽，諸如免疫球蛋白(例如IgG)或血清白蛋白(例如人血清白蛋白(HSA)))。半衰期延長部分之實例包括六-hat GST(麩胱甘肽S-轉移酶)麩胱甘肽親和力、鈣調蛋白結合肽(CBP)、Strep-標籤、纖維素結合結構域、麥芽糖結合蛋白、S-肽標籤、幾丁質結合標籤、免疫反應表位、表位標籤、E2標籤、HA表位標籤、Myc表位、FLAG表位、AU1和AU5表位、Glu-Glu表位、KT3表位、IRS表位、B標籤表位、蛋白激酶-C表位和VSV表位。

【0224】於一些實施態樣中，該DD1和/或該DD2各自包括總共約5個胺基酸至約250個胺基酸、約5個胺基酸至約200個胺基酸、約5個胺基酸至約180個胺基酸、約5個胺基酸至約160個胺基酸，約5個胺基酸至約140個胺基酸、約5個胺基酸至約120個胺基酸、約5個胺基酸至約100個胺基酸、約5個胺基酸至約80個胺基酸、約5個胺基酸至約60個胺基酸、約5個胺基酸至約40個胺基酸、約5個胺基酸至約20個胺基酸、約5個胺基酸至約10個胺基酸、約10個胺基酸至約250個胺基酸、約10個胺基酸至約200個胺基酸、約10個胺基酸至約180個胺基酸、約10個胺基酸至約160個胺基酸、約10個胺基酸至約140個胺基酸、約10個胺基酸至約120個胺基酸、約10個胺基酸至約100個胺基酸、約10

個胺基酸至約80個胺基酸、約10個胺基酸至約60個胺基酸、約10個胺基酸至約40個胺基酸、約10個胺基酸至約20個胺基酸、約20個胺基酸至約250個胺基酸、約20個胺基酸至約200個胺基酸、約20個胺基酸至約180個胺基酸、約20個胺基酸至約160個胺基酸、約20個胺基酸至約140個胺基酸、約20個胺基酸至約120個胺基酸、約20個胺基酸至約100個胺基酸、約20個胺基酸約80個胺基酸、約20個胺基酸至約60個胺基酸、約20個胺基酸至約40個胺基酸、約40個胺基酸至約250個胺基酸、約40個胺基酸至約200個胺基酸、約40個胺基酸至約180個胺基酸、約40個胺基酸至約160個胺基酸、約40個胺基酸至約140個胺基酸、約40個胺基酸至約120個胺基酸、約40個胺基酸至約100個胺基酸、約40個胺基酸至約80個胺基酸、約40個胺基酸至約60個胺基酸、約60個胺基酸至約250個胺基酸、約60個胺基酸至約200個胺基酸、約60個胺基酸至約180個胺基酸、約60個胺基酸至約160個胺基酸、約60個胺基酸至約140個胺基酸、約60個胺基酸至約120個胺基酸、約60個胺基酸至約100個胺基酸、約60個胺基酸至約80個胺基酸、約80個胺基酸至約250個胺基酸、約80個胺基酸至約200個胺基酸、約80個胺基酸至約180個胺基酸、約80個胺基酸至約160個胺基酸、約80個胺基酸至約140個胺基酸、約80個胺基酸至約120個胺基酸、約80個胺基酸至約100個胺基酸、約100個胺基酸至約250個胺基酸、約100個胺基酸至約200個胺基酸、約100個胺基酸至約180個胺基酸、約100個胺

基酸至約160個胺基酸、約100個胺基酸至約140個胺基酸酸、約100個胺基酸至約120個胺基酸、約120個胺基酸至約250個胺基酸、約120個胺基酸至約200個胺基酸、約120個胺基酸至約180個胺基酸、約120個胺基酸至約160個胺基酸、約120個胺基酸至約140個胺基酸、約140個胺基酸至約250個胺基酸、約140個胺基酸至約200個胺基酸、約140個胺基酸至約180個胺基酸、約140個胺基酸至約160個胺基酸、約160個胺基酸至約250個胺基酸、約160個胺基酸至約200個胺基酸、約160個胺基酸至約180個胺基酸、約180個胺基酸至約250個胺基酸、約180個胺基酸至約200個胺基酸、或約200個胺基酸至約250個胺基酸。於一些實施態樣中，該DD1和該DD2各自為包含該鉸鏈區之一部分的Fc結構域，該鉸鏈區包括二個半胱胺酸殘基、CH2結構域和CH3結構域。於一些實施態樣中，該DD1和該DD2各自為Fc結構域，該Fc結構域之N端為鉸鏈區中之第一半胱胺酸殘基(於N至C端之方閱讀)，其參與與第二Fc結構域之二硫鍵鍵聯(例如使用EU編號之人IgG1或IgG4的半胱胺酸226)。

【0225】於一些態樣中，直接或間接地(例如經由連接子)位於該CP與該DD組分之間，和/或位於該CP與該PM組分之間的為包含蛋白酶受質之可裂解部分(CM)。於一些實施態樣中，該CM可各自獨立地包含選自由下列所組成之群組的蛋白酶受質：ADAM8、ADAM9、ADAM10、ADAM12、ADAM15、ADAM17/TACE、ADEMDEC1、

ADAMTS1、ADAMTS4、ADAMTS5、BACE、腎素、組織蛋白酶D，組織蛋白酶E、凋亡蛋白酶1、凋亡蛋白酶2、凋亡蛋白酶3、凋亡蛋白酶4、凋亡蛋白酶5、凋亡蛋白酶6、凋亡蛋白酶7、凋亡蛋白酶8、凋亡蛋白酶9、凋亡蛋白酶10、凋亡蛋白酶14、組織蛋白酶A、組織蛋白酶B、組織蛋白酶C、組織蛋白酶G、組織蛋白酶K、組織蛋白酶L、組織蛋白酶S、組織蛋白酶V/L2、組織蛋白酶X/Z/P、凝乳酶(Chymase)、Cruzipain、DESC1、DPP-4、FAP、天冬醯胺內肽酶(Legumain)、Otubain-2、彈性蛋白酶、FVIIa、FiXA、FXa、FXIa、FXIIa、顆粒酶B、胍基苯甲酸酶、Hepsin、HtrA1、人嗜中性粒細胞彈性蛋白酶、KLK4、KLK5、KLK6、KLK7、KLK8、KLK10、KLK11、KLK13、KLK14、乳鐵蛋白、Marapsin、膜型絲胺酸蛋白酶(Matriptase)-2、Meprin、MT-SP1/膜型絲胺酸蛋白酶、腦啡肽酶、NS3/4A、PACE4、纖溶酶、PSMA、PSA、BMP-1、MMP1、MMP2、MMP3、MMP7、MMP8、MMP9、MMP10、MMP11、MMP12、MMP13、MMP14、MMP15、MMP16、MMP17、MMP19、MMP20、MMP23、MMP24、MMP26、MMP27、TMPRSS2、TMPRSS3、TMPRSS4、tPA、凝血酶、類胰蛋白酶(tryptase)和uPA，以及其二或更多種的任意組合。

【0226】於本文所描述之任何ACC的一些實施態樣中，該裂解本文所描述之任何CM的蛋白酶可為ADAM8、ADAM9、ADAM10、ADAM12、ADAM15、

ADAM17/TACE、ADAMDEC1、ADAMTS1、ADAMTS4、ADAMTS5、BACE、腎素(Renin)、組織蛋白酶(Cathepsin)D、組織蛋白酶E、凋亡蛋白酶(Caspase)1、凋亡蛋白酶2、凋亡蛋白酶3、凋亡蛋白酶4、凋亡蛋白酶5、凋亡蛋白酶6、凋亡蛋白酶7、凋亡蛋白酶8、凋亡蛋白酶9、凋亡蛋白酶10、凋亡蛋白酶14、組織蛋白酶B、組織蛋白酶C、組織蛋白酶K、組織蛋白酶L、組織蛋白酶S、組織蛋白酶V/L2、組織蛋白酶X/Z/P、Cruzipain、天冬醯胺內肽酶、Otubain-2、KLK4、KLK5、KLK6、KLK7、KLK8、KLK10、KLK11、KLK13、KLK14、Meprin、腦啡肽酶、PSMA、BMP-1、MMP-1、MMP-2、MMP-3、MMP-7、MMP-9、MMP-10、MMP-11、MMP-12、MMP-13、MMP-14、MMP-15、MMP-16、MMP-17、MMP-19、MMP-20、MMP-23、MMP-24、MMP-26、MMP-27、活化之蛋白C、組織蛋白酶A、組織蛋白酶G、凝乳酶、FVIIa、FIXa、FXa、FXIa、FXIIa、彈性蛋白酶、顆粒酶B、胍基苯甲酸酶、HtrA1、人嗜中性粒細胞裂解酶、乳鐵蛋白、marapsin、NS3/4A、PACE4、纖溶酶、PSA、tPA、凝血酶、類胰蛋白酶、uPA、DESC1、DPP-4、FAP、Hepsin、膜型絲胺酸蛋白酶-2、MT-SP1/Matripase、TMPRSS2、TMPRSS3和TMPRSS4，以及其二或更多種之任意組合。

【0227】於本文所描述之任何ACC之一些實施態樣中，該蛋白酶係選自下列群組：uPA、天冬醯胺內肽酶、MT-SP1、ADAM17、BMP-1、TMPRSS3、TMPRSS4、

MMP-2、MMP-9、MMP-12、MMP-13和MMP-14。

【0228】已有報告在許多癌症中具有已知受質之蛋白酶的水準增加。參見，例如La Roca et al., *British J. Cancer* 90(7):1414-1421, 2004。適合用於本文採用之CM組分的受質包括更普遍存在於癌細胞和組織中者。因此，於某些實施態樣中，該CM各自獨立地包含更普遍地存在於與癌症相關之患病組織中的蛋白酶受質。於一些實施態樣中，該癌症係選自下列群組：胃癌、乳癌、骨肉瘤和食道癌。於一些實施態樣中，該癌症為乳癌。於一些實施態樣中，該癌症為HER2陽性癌症。於一些實施態樣中，該癌症為卡波西氏肉瘤、髮樣細胞白血病、慢性骨髓性白血病(CML)、濾泡性淋巴瘤、腎細胞癌(RCC)、黑色素瘤、神經母細胞瘤、基底細胞癌、皮膚T細胞淋巴瘤、鼻咽腺癌、乳癌、卵巢癌、膀胱癌、BCG耐藥性非肌層浸潤性膀胱癌(NMIBC)、子宮內膜癌、胰臟癌、非小細胞肺癌(NSCLC)、結腸直腸癌、食道癌、膽囊癌、神經膠質瘤、頭頸部癌、子宮癌、子宮頸癌或睪丸癌，等。於一些上述之實施態樣中，該CM組分包含在腫瘤組織中更普遍存在之蛋白酶受質。

【0229】於一些實施態樣中，該CM各自獨立地包括選自由下列所組成之群組的序列：SEQ ID NO：5至SEQ ID NO：100，及其C端和N端截短變體。

【0230】於一些實施態樣中，該CM包括選自由下列所組成之群組的序列：ISSGLLSGRSDNH(SEQ ID NO：

28)、LSGRSDDH(SEQ ID NO：33)、ISSGLLSGRSDQH(SEQ ID NO：54)和ISSGLLSGRSDNI(SEQ ID NO：68)。

【0231】於某些實施態樣中，該CM1和/或該CM1包括選自下列群組之序列：AQNLLGMY (SEQ ID NO：237)、LSGRSDNHGGAVGLLAPP(SEQ ID NO：238)、VHMPLGFLGPGGLSGRSDNH(SEQ ID NO：239)、LSGRSDNHGGVHMPLGFLGP(SEQ ID NO：240)、LSGRSDNHGGSGGSISSGLLSS(SEQ ID NO：241)、ISSGLLSSGGSGGSLSGRSGNH(SEQ ID NO：242)、LSGRSDNHGGSGGSQNQALRMA(SEQ ID NO：243)、QNQALRMAGGSGGSLSGRSDNH(SEQ ID NO：244)、LSGRSGNHGGSGGSQNQALRMA(SEQ ID NO：245)、QNQALRMAGGSGGSLSGRSGNH(SEQ ID NO：246)、ISSGLLSGRSGNH(SEQ ID NO：247)及其C端和N端截短變體。該CM之實例亦包括描述於美國專利申請案發表物編號US20160289324、US20190284283及發表物編號WO 2010/081173、WO 2015/048329、WO 2015/116933、WO 2016/118629和WO 2020/118109(其全文以引用方式併入本文)中者。

【0232】適合用於該CM之上述胺基酸序列的截短變體為任何保留用於該對應蛋白酶之識別位點者。這些包括包含上述胺基酸序列之至少3個連續胺基酸、或至少4個、或至少5個、或至少6個、或至少7個胺基酸的C端和/或N端截短變體，其保留用於蛋白酶之識別位點。於某些實施態

樣中，上述胺基酸序列之截短變體為對應於上述任一者，但其C和/或N端截短1至約10個胺基酸、1至約9個胺基酸、1至約8個胺基酸、1至約7個胺基酸、1至約6個胺基酸、1至約5個胺基酸、1至約4個胺基酸或1至約3個胺基酸之胺基酸序列，且該胺基酸序列：(1)具有至少三個胺基酸殘基；及(2)保留用於蛋白酶之識別位點。於一些前述實施態樣中，該經截短之CM為N端截短之CM。於一些實施態樣中，該經截短之CM為C端截短之CM。於一些實施態樣中，該經截短之CM為C端和N端截短之CM。

【0233】於本文所描述之任何ACC或可經活化之抗體的一些實施態樣中，該CM可包含總共約3個胺基酸至約25個胺基酸。於一些實施態樣中，該CM可包含總共約3個胺基酸至約25個胺基酸、約3個胺基酸至約20個胺基酸、約3個胺基酸至約15個胺基酸、約3個胺基酸至約10個胺基酸、約3個胺基酸至約5個胺基酸、約5個胺基酸至約25個胺基酸、約5個胺基酸至約20個胺基酸、約5個胺基酸至約15個胺基酸、約5個胺基酸至約10個胺基酸、約10個胺基酸至約25個胺基酸、約10個胺基酸至約20個胺基酸、約10個胺基酸至約15個胺基酸、約15個胺基酸至約25個胺基酸、約15個胺基酸至約20個胺基酸或約20個胺基酸至約25個胺基酸。

【0234】於一些實施態樣中，該ACC、可經活化之抗PD1或可經活化之抗PD-L1可包含多個CM，該CM包含不同蛋白酶之受質。於一些實施態樣中，該ACC、可經活化

之抗PD1或可經活化之抗PD-L1可包含多個CM，該等CM為相同蛋白酶之受質。於一實例中，該介於各CP與PM之間的CM可為彼此相同蛋白酶之受質，且該介於各CP與DD之間的該CM可為彼此相同蛋白酶之受質，但可為與介於該CP與該PM之間的CM不同之蛋白酶的受質。於另一實例中，該介於該CP與該PM之間的CM和該介於該CP與該DD之間的CM可包含相同蛋白酶之受質。於另一實例中，該介於該CP與該PM之間的CM可包含不同蛋白酶之受質。於另一實例中，該介於該CP與該PM之間的CM可包含相同蛋白酶之受質。於另一實例中，該介於該CP與該DD之間的CM可包含不同蛋白酶之受質。於另一實例中，該介於該CP與該DD之間的CM可包含相同蛋白酶之受質。於一實例中，該介於各可經活化之抗PD1或可經活化之抗PD-L1與該MM之間的CM可為彼此相同之蛋白酶的受質。於另一實例中，該介於該可經活化之抗PD1或可經活化之抗PD-L1與該MM之間的CM可包含不同蛋白酶之受質。於另一實例中，該介於該可經活化之抗PD1或可經活化之抗PD-L1與該MM之間的CM可包含相同蛋白酶之受質。

【0235】該第一和第二單體構築體可包含一或多個額外組分，該額外組分包括一或多個連接子，等。於一些實施態樣中，該第一單體可包括一個位於該CP1與該CM1之間的連接子。於一些實施態樣中，該CP1與該CM1在該第一單體中彼此直接鄰接。於一些實施態樣中，該第一單體包含一個位於CM1與該DD1之間的連接子。於一些實施態

樣中，該CM1與該DD1在該第一單體中彼此直接鄰接。於一些實施態樣中，該第一單體可包括一個位於該CP1與該CM3之間的連接子。於一些實施態樣中，該CP1與該CM3在該第一單體中彼此直接鄰接。於一些實施態樣中，該第一單體可包括一個位於該CP1與該PM1之間的連接子。於一些實施態樣中，該CP1與該PM1在該第一單體中彼此直接鄰接。於一些實施態樣中，該連接子之總長度為1個胺基酸至約15個胺基酸。於一些實施態樣中，該CM和位於該CP1與該DD1之間的任何連接子的合併總長度為3至15個胺基酸、或3至10個胺基酸、或3至7個胺基酸。

【0236】於一些實施態樣中，該第二單體包含一個位於該CP2與該CM2之間的連接子。於一些實施態樣中，該CP2與該CM2在該第二單體中彼此直接鄰接。於一些實施態樣中，該第二單體包含一個位於該CM2與該DD2之間的連接子。於一些實施態樣中，該CM2(例如本文所描述之任何可裂解部分)與該DD2(例如本文所描述之任何DD)在該第二單體中彼此直接鄰接。於一些實施態樣中，該第二單體可包括一個位於該CP2與該CM4之間的連接子。於一些實施態樣中，該CP2與該CM4在該第二單體中彼此直接鄰接。於一些實施態樣中，該第二單體可包括一個位於該CP2與該PM2之間的連接子。於一些實施態樣中，該CP2與該PM2在該第二單體中彼此直接鄰接。於一些實施態樣中，該連接子之總長度為1個胺基酸至約15個胺基酸。於一些實施態樣中，該連接子包含GGGS(SEQ ID NO：2)之

序列。於一些實施態樣中，該CM和位於該CP2與該DD2之間的任何連接子的合併總長度為3至15個胺基酸、或3至10個胺基酸、或3至7個胺基酸。

【0237】於一些實施態樣中，該第一單體和/或該第二單體可包括總共約50個胺基酸至約800個胺基酸、約50個胺基酸至約750個胺基酸、約50個胺基酸至約700個胺基酸、約50個胺基酸至約650個胺基酸、約50個胺基酸至約600個胺基酸、約50個胺基酸至約550個胺基酸、約50個胺基酸至約500個胺基酸、約50個胺基酸至約450個胺基酸、約50個胺基酸至約400個胺基酸、約50個胺基酸至約350個胺基酸、約50個胺基酸至約300個胺基酸、約50個胺基酸至約250個胺基酸、約50個胺基酸至約200個胺基酸、約50個胺基酸至約150個胺基酸、約50個胺基酸至約100個胺基酸、約100個胺基酸至約800個胺基酸、約100個胺基酸至約750個胺基酸、約100個胺基酸至約700個胺基酸、約100個胺基酸至約650個胺基酸、約100個胺基酸約600個胺基酸、約100個胺基酸至約550個胺基酸、約100個胺基酸至約500個胺基酸、約100個胺基酸至約450個胺基酸、約100個胺基酸至約400個胺基酸、約100個胺基酸約350個胺基酸、約100個胺基酸至約300個胺基酸、約100個胺基酸至約250個胺基酸、約100個胺基酸至約200個胺基酸、約100個胺基酸至約150個胺基酸、約150個胺基酸約800個胺基酸、約150個胺基酸至約750個胺基酸、約150個胺基酸至約700個胺基酸、約150個胺基酸至約650個胺基酸、約150

個胺基酸至約600個胺基酸、約150個胺基酸約550個胺基酸、約150個胺基酸至約500個胺基酸、約150個胺基酸至約450個胺基酸、約150個胺基酸至約400個胺基酸、約150個胺基酸至約350個胺基酸、約150個胺基酸酸至大約300個胺基酸、約150個胺基酸至約250個胺基酸、約150個胺基酸至約200個胺基酸、約200個胺基酸至約800個胺基酸、約200個胺基酸至約750個胺基酸、約200個胺基酸至約700個胺基酸、約200個胺基酸至約650個胺基酸、約200個胺基酸至約600個胺基酸、約200個胺基酸至約550個胺基酸、約200個胺基酸至約500個胺基酸、約200個胺基酸至約450個胺基酸、約200個胺基酸至約400個胺基酸、約200個胺基酸至約350個胺基酸、約200個胺基酸至約300個胺基酸、約200個胺基酸至約250個胺基酸、約250個胺基酸至約800個胺基酸、約250個胺基酸至約750個胺基酸、約250個胺基酸至約700個胺基酸、約250個胺基酸至約650個胺基酸、約250個胺基酸至約600個胺基酸、約250個胺基酸至約550個胺基酸、約250個胺基酸至約500個胺基酸、約250個胺基酸至約450個胺基酸、約250個胺基酸至約400個胺基酸、約250個胺基酸至約350個胺基酸、約250個胺基酸至約300個胺基酸、約300個胺基酸至約800個胺基酸、約300個胺基酸至約750個胺基酸、約300個胺基酸至約700個胺基酸、約300個胺基酸至約650個胺基酸、約300個胺基酸至約600個胺基酸、約300個胺基酸至約550個胺基酸、約300個胺基酸至約500個胺基酸、約300個胺基

酸至約450個胺基酸、約300個胺基酸至約400個胺基酸、約300個胺基酸至約350個胺基酸、約350個胺基酸至約800個胺基酸、約350個胺基酸至約750個胺基酸、約350個胺基酸至約700個胺基酸、約350個胺基酸至約650個胺基酸、約350個胺基酸至約600個胺基酸、約350個胺基酸至約550個胺基酸、約350個胺基酸至約500個胺基酸、約350個胺基酸至約450個胺基酸、約350個胺基酸至約400個胺基酸、約400個胺基酸至約800個胺基酸、約400個胺基酸至約750個胺基酸、約400個胺基酸至約700個胺基酸、約400個胺基酸至約650個胺基酸、約400個胺基酸至約600個胺基酸、約400個胺基酸至約550個胺基酸、約400個胺基酸至約500個胺基酸、約400個胺基酸至約450個胺基酸、約450個胺基酸至約800個胺基酸、約450個胺基酸至約750個胺基酸、約450個胺基酸至約700個胺基酸、約450個胺基酸至約650個胺基酸、約450個胺基酸至約600個胺基酸、約450個胺基酸至約550個胺基酸、約450個胺基酸至約500個胺基酸、約500個胺基酸至約800個胺基酸、約500個胺基酸至約750個胺基酸、約500個胺基酸至約700個胺基酸、約500個胺基酸至約650個胺基酸、約500個胺基酸至約600個胺基酸、約500個胺基酸至約550個胺基酸、約550個胺基酸至約800個胺基酸、約550個胺基酸至約750個胺基酸、約550個胺基酸至約700個胺基酸、約550個胺基酸至約650個胺基酸、約550個胺基酸至約600個胺基酸、約600個胺基酸至約800個胺基酸、約600個胺基酸至約750

個胺基酸、約600個胺基酸至約700個胺基酸、約600個胺基酸至約650個胺基酸、約650個胺基酸至約800個胺基酸、約650個胺基酸至約750個胺基酸、約650個胺基酸至約700個胺基酸、約700個胺基酸至約800個胺基酸、約700個胺基酸至約750個胺基酸、或約750個胺基酸至約800個胺基酸。

【0238】於本文描述之任何ACC的一些實施態樣中，可將一或多個連接子(例如彈性連接子)引入該可經活化之細胞介素構築體中以在結構域之間、部分之間、部分與結構域之間的一或多個連接點，或在其中連接子有助益的任何其他連接點提供彈性。於一些實施態樣中，當提供之該ACC為構象上受限之構築體時，可插入彈性連接子以促進形成和維持該未經裂解之可經活化的細胞介素構築體中之結構。本文所描述之任何連接子均可提供合需之彈性以促進抑制標靶(例如細胞介素之受體)的結合，或促進蛋白酶裂解該CM。於一些實施態樣中，該ACC中包括全彈性或部分彈性之連接子，使得該連接子可包括彈性連接子以及一或多個賦予較不具彈性之結構的部分以提供合需之ACC。一些連接子可包括半胱胺酸殘基，該半胱胺酸殘基可形成二硫鍵並降低該構築體之彈性。現已發現，減少該連接子或連接區之長度會降低該ACC中之成熟細胞介素蛋白的活性(參見，例如圖16顯示不具有肽親和性掩蔽物的ACC之數據)。在大多數情況下，該於N至C方向之連接子長度係藉由計算從該連接子鄰接前一個組分之C端胺基酸

之N端至該連接子鄰接下一個組分之N端胺基酸的C端之胺基酸數目來確定(即，其中該連接子長度不包括前一組分之C端胺基酸或下一個組分之N端胺基酸)。於其中在該包含Fc結構域之DD的N端採用連接子之實施態樣中，該連接子長度係藉由計算從該連接子鄰接前一個組分之C端胺基酸之N端至該連接子鄰接Fc鉸鏈區(其參與與第二Fc結構域之二硫鍵鍵聯)之第一個半胱胺酸的C端之胺基酸數目來確定(即，其中該連接子長度不包括前一個組分之C端胺基酸或該Fc鉸鏈區之第一個半胱胺酸)。

【0239】從本揭示和圖17顯明，本發明之ACC在介於該CP與該在二聚化結構域交互作用之近端點之間包括胺基酸延伸段。該胺基酸延伸段可稱為連接區(LR)。如本文所使用之術語“連接區”或“LR”係指胺基酸殘基之延伸段，該胺基酸殘基之延伸段係介於該細胞介素之C端與該在鄰接該二聚化結構域交互作用之近端點之N端的胺基酸殘基之間(即，該連接區不包括該細胞介素之C端胺基酸或該DD之N端胺基酸，該DD之N端胺基酸形成該對應之第二單體的DD交互作用之近端點)。例如，當該DD為一對Fc結構域時，該連接區為介於該細胞介素C端與Fc之第一N端半胱胺酸殘基之間的胺基酸殘基延伸段，該Fc之第一N端半胱胺酸殘基參與與第二Fc結構域之二硫鍵聯(例如根據EU編號，IgG1或IgG4 Fc結構域之半胱胺酸226)。當該二聚化結構域不是肽時，則該連接區為接續在該細胞介素之C端後的一段胺基酸殘基延伸段，直到最後一個胺基酸。例如，

當該DD為生物素-鏈黴親和素對時，該含生物素單體之連接區為介於該細胞介素之C端與該生物素分子之間的胺基酸殘基延伸段，且該含鏈黴親和素單體之連接區為介於該細胞介素之C端與該鏈黴親和素分子之間的胺基酸殘基延伸段。

【0240】於一些實施態樣中，額外之胺基酸序列可位於任何該ACC之任何結構域的N端或C端。實例包括，但不限於靶向部分(例如存在於標靶組織中之細胞受體的配體)和血清半衰期延長部分(例如結合血清蛋白之多肽，諸如免疫球蛋白(例如IgG)或血清白蛋白(例如人血清白蛋白(HSA))。

【0241】該本文所描述之任何可經活化之細胞介素構築體的一些實施態樣中，該連接子可包括總共約1個胺基酸至約25個胺基酸(例如約1個胺基酸至約24個胺基酸、約1個胺基酸至約22個胺基酸、約1個胺基酸至約20個胺基酸、約1個胺基酸至約18個胺基酸、約1個胺基酸至約16個胺基酸、約1個胺基酸至約15個胺基酸、約1個胺基酸至約14個胺基酸、約1個胺基酸至約12個胺基酸、約1個胺基酸至約10個胺基酸、約1個胺基酸至約8個胺基酸、約1個胺基酸至約6個胺基酸、約1個胺基酸至約5個胺基酸、約1個胺基酸至約4個胺基酸、約1個胺基酸至約3個胺基酸、約1個胺基酸至約2個胺基酸、約2個胺基酸至約25個胺基酸、約2個胺基酸至約24個胺基酸、約2個胺基酸至約22個胺基酸、約2個胺基酸至約20個胺基酸、約2個胺基酸至約18個

胺基酸、約2個胺基酸至約16個胺基酸、約2個胺基酸至約15個胺基酸、約2個胺基酸至約14個胺基酸、約2個胺基酸至約12個胺基酸、約2個胺基酸至約10個胺基酸、約2個胺基酸至約8個胺基酸、約2個胺基酸至約6個胺基酸、約2個胺基酸至約5個胺基酸、約2個胺基酸至約4個胺基酸、約2個胺基酸至約3個胺基酸、約4個胺基酸至約25個胺基酸、約4個胺基酸至約24個胺基酸、約4個胺基酸至約22個胺基酸、約4個胺基酸至約20個胺基酸、約4個胺基酸至約18個胺基酸、約4個胺基酸至約16個胺基酸、約4個胺基酸至約15個胺基酸、約4個胺基酸至約14個胺基酸、約4個胺基酸至約12個胺基酸、約4個胺基酸至約10個胺基酸、約4個胺基酸至約8個胺基酸、約4個胺基酸約6個胺基酸、約4個胺基酸至約5個胺基酸、約5個胺基酸至約25個胺基酸、約5個胺基酸至約24個胺基酸、約5個胺基酸至約22個胺基酸、約5個胺基酸至約20個胺基酸、約5個胺基酸至約18個胺基酸、約5個胺基酸至約16個胺基酸、約5個胺基酸至約15個胺基酸、約5個胺基酸至約14個胺基酸、約5個胺基酸約12個胺基酸、約5個胺基酸至約10個胺基酸、約5個胺基酸至約8個胺基酸、約5個胺基酸至約6個胺基酸、約6個胺基酸至約25個胺基酸、約6個胺基酸至約24個胺基酸、約6個胺基酸至約22個胺基酸、約6個胺基酸至約20個胺基酸、約6個胺基酸至約18個胺基酸、約6個胺基酸至約16個胺基酸、約6個胺基酸至約15個胺基酸、約6個胺基酸至約14個胺基酸、約6個胺基酸至約12個胺基酸、約6個胺基酸

至約10個胺基酸、約6個胺基酸至約8個胺基酸、約8個胺基酸至約25個胺基酸、約8個胺基酸至約24個胺基酸、約8個胺基酸至約22個胺基酸、約8個胺基酸至約20個胺基酸、約8個胺基酸至約18個胺基酸、約8個胺基酸至約16個胺基酸、約8個胺基酸至約15個胺基酸、約8個胺基酸至約14個胺基酸、約8個胺基酸至約12個胺基酸、約8個胺基酸至約10個胺基酸、約10個胺基酸至約25個胺基酸、約10個胺基酸至約24個胺基酸、約10個胺基酸至約22個胺基酸、約10個胺基酸至約20個胺基酸、約10個胺基酸至約18個胺基酸、約10個胺基酸至約16個胺基酸、約10個胺基酸至約15個胺基酸、約10個胺基酸至約14個胺基酸、約10個胺基酸至約12個胺基酸、約12個胺基酸至約25個胺基酸、約12個胺基酸至約24個胺基酸、約12個胺基酸至約22個胺基酸、約12個胺基酸至約20個胺基酸、約12個胺基酸至約18個胺基酸、約12個胺基酸至約16個胺基酸、約12個胺基酸至約15個胺基酸、約12個胺基酸至約14個胺基酸、約14個胺基酸至約25個胺基酸、約14個胺基酸至約24個胺基酸、約14個胺基酸至約22個胺基酸、約14個胺基酸至約20個胺基酸、約14個胺基酸至約18個胺基酸、約14個胺基酸至約16個胺基酸、約14個胺基酸至約15個胺基酸、約15個胺基酸至約25個胺基酸、約15個胺基酸至約24個胺基酸、約15個胺基酸至約22個胺基酸、約15個胺基酸至約20個胺基酸、約15個胺基酸至約18個胺基酸、約15個胺基酸至約16個胺基酸、約16個胺基酸至約25個胺基酸、約16個胺基酸

至約24個胺基酸、約16個胺基酸至約22個胺基酸、約16個胺基酸至約20個胺基酸、約16個胺基酸至約18個胺基酸、約18個胺基酸至約25個胺基酸、約18個胺基酸至約24個胺基酸、約18個胺基酸至約22個胺基酸、約18個胺基酸至約20個胺基酸、約20個胺基酸至約25個胺基酸、約20個胺基酸至約24個胺基酸、約20個胺基酸至約22個胺基酸、約22個胺基酸至約25個胺基酸、約22個胺基酸至約24個胺基酸或約24個胺基酸至約25個胺基酸。

【0242】於本文所描述之任何ACC的一些實施態樣中，該連接子包括總共約1個胺基酸、約2個胺基酸、約3個胺基酸、約4個胺基酸、約5個胺基酸、約6個胺基酸、約7個胺基酸、約8個胺基酸、約9個胺基酸、約10個胺基酸、約11個胺基酸、約12個胺基酸、約13個胺基酸、約14個胺基酸、約15個胺基酸、約16個胺基酸、約17個胺基酸、約18個胺基酸、約19個胺基酸、約20個胺基酸、約21個胺基酸、約22個胺基酸、約23個胺基酸、約24個胺基酸或約25個胺基酸。

【0243】令人驚訝地，本申請者已發現與在連接區中包括連接子或額外序列之ACC相比較，在該CP與該DD之間不包含任何連接子之ACC顯示出相對於該野生型成熟細胞介素而言細胞介素活性降低最顯著。參見，例如圖16(顯示不具有肽親和性掩蔽物之ACC的數據)。此外，其中在該CP與該DD之間沒有連接子之構形仍然允許位於該CP與該DD之間的CM有效裂解。參見，例如圖7A、7B、

10A和10B。因此，於一些實施態樣中，該ACC在該CP與該DD之間不包含任何連接子，且介於該CP與該DD之間的該CM包含不超過10、9、8、7、6、5、4或3個胺基酸。於一些實施態樣中，該LR中之胺基酸總數包含不超過25個胺基酸，例如不超過25、24、23、22、21、20、19、18、17、16、15、14、13 、12、11、10、9、8、7、6、5、4或3個胺基酸、或3至10個胺基酸、或5至15個胺基酸、或7至12個胺基酸、或選自包含3至25個胺基酸之任何範圍或特定胺基酸數量。

【0244】於本文所描述之任何ACC的一些實施態樣中，該連接子可富含甘胺酸(Gly或G)殘基。於一些實施態樣中，該連接子可富含絲胺酸(Ser或S)殘基。於一些實施態樣中，該連接子可富含甘胺酸和絲胺酸殘基。於一些實施態樣中，該連接子具有一或多個甘胺酸-絲胺酸殘基對(GS)(例如1、2、3、4、5、6、7、8、9或10個或更多個GS對)。於一些實施態樣中，該連接子具有一或多個Gly-Gly-Gly-Ser(GGGS)序列(例如1、2、3、4、5、6、7、8、9或10個或更多個GGGS序列)。於一些實施態樣中，該連接子具有一或多個Gly-Gly-Gly-Gly-Ser(GGGGS)序列(例如1、2、3、4、5、6、7、8、9或10個或更多個GGGGS序列)。於一些實施態樣中，該連接子具有一或多個Gly-Gly-Ser-Gly(GGSG)序列(例如1、2、3、4、5、6、7、8、9或10個或更多個GGSG序列)。

【0245】於本文所描述之任何ACC的一些實施態樣

中，該連接子包括下列任一者或下列一或多者之組合：GSSGGSGGSGG(SEQ ID NO：210)、GGGS(SEQ ID NO：2)、GGGSGGGS(SEQ ID NO：211)、GGGSGGGSGGGS(SEQ ID NO：212)、GGGGSGGGGSGGGGS(SEQ ID NO：213)、GGGGSGGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)、GGGGSGGGGS(SEQ ID NO：215)、GGGGS(SEQ ID NO：216)、GS、GGGGSGS(SEQ ID NO：217)、GGGGSGGGGSGGGGSGS(SEQ ID NO：218)、GGSLDPKGGGGS(SEQ ID NO：219)、PKSCDKTHTCPPCPAPELLG(SEQ ID NO：220)、SKYGPPCPPCPAPEFLG(SEQ ID NO：221)、GKSSGSGSESKS(SEQ ID NO：222)、GSTSGSGKSSEGKG(SEQ ID NO：223)、GSTSGSGKSSEGSGSTKG(SEQ ID NO：224)和GSTSGSGKPGSGEGSTKG(SEQ ID NO：225)。

【0246】連接子之非限制性實例可包括與下列者具有至少70%同一性(例如至少72%、至少74%、至少75%、至少76%、至少78%、至少80%、至少82%、至少84%、至少85%、至少86%、至少88%、至少90%、至少92%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性)之序列：GGGS(SEQ ID NO：2)、GSSGGSGGSGG(SEQ ID NO：210)、GGGGSGGGGSGGGGS(SEQ ID NO：213)、GGGGSGS(SEQ ID NO：217)、GGGGSGGGGSGGGGSGS(SEQ ID

NO：218)、GGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)、GGSLDPKGGGGS(SEQ ID NO：215)和GSTSGSGKPGSSEGST(SEQ ID NO：226)。

【0247】於一些實施態樣中，該連接子包括選自下列群組之序列：GGSLDPKGGGGS(SEQ ID NO：219)、GGGGSGGGGSGGGGSGS(SEQ ID NO：218)、GGGGSGS(SEQ ID NO：217)、GS、(GS)n、(GGS)n、(GSGGS)n(SEQ ID NO：227)和(GGGS)n(SEQ ID NO：228)、GGSG(SEQ ID NO：229)、GGSGG(SEQ ID NO：230)、GSGSG(SEQ ID NO：231)、GSGGG(SEQ ID NO：232)、GGGSG(SEQ ID NO：233)、GSSSG(SEQ ID NO：234)、GGGGSGGGGSGGGGS(SEQ ID NO：213)、GGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)、GSTSGSGKPGSSEGST(SEQ ID NO：226)、(GGGGS)n(SEQ ID NO：216)，其中n為至少1之整數。於一些實施態樣中，該連接子包括選自由下列所組成之群組的序列：GGSLDPKGGGGS(SEQ ID NO：219)、GGGGSGGGGSGGGGSGS(SEQ ID NO：218)、GGGGSGS(SEQ ID NO：217)和GS。於本文所描述之任何ACC的一些實施態樣中，該連接子包括選自下列群組之序列：GGGGSGGGGSGGGGS(SEQ ID NO：213)、GGGGSGGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)和GSTSGSGKPGSSEGST(SEQ ID NO：226)。於本文所描述之任何可經活化之細胞介素構築體的一些實施態樣中，該

連接子包括選自下列群組之序列：GGGGSGGGGSGGGGS(SEQ ID NO：213)或GGGGS(SEQ ID NO：216)。於一些實施態樣中，該連接子包含GGGS(SEQ ID NO：2)之序列。該連接子之其他實例包括表23中所列者。

【0248】於一些實施態樣中，該ACC可包括一、二、三、四、五、六、七、八、九或十個連接子序列(例如與本文所描述或本技藝已知之任何示例性連接子序列相同或不同之連接子序列)。於一些實施態樣中，該連接子包含磺基-SIAB、SMPB和磺基-SMPB，其中該連接子與初級胺甾基反應。

【0249】於本文所描述之任何ACC的一些實施態樣中，該ACC之特徵在於與該CP1和/或該CP2之至少一種活性的對照水準相比較，該CP1和/或該CP2之該至少一種活性降低。於一些實施態樣中，該對照水準可為重組CP1和/或CP2(例如市售之重組CP1和/或CP2、重組野生型CP1和/或CP2，等)的活性水準。於一些實施態樣中，該對照水準可為該ACC之裂解(經活化的)形式的活性水準。於某些實施態樣中，該對照水準可為該聚乙二醇化CP1和/或CP2之活性水準。

【0250】於一些實施態樣中，該至少一種活性為如使用表面等離子共振所測定(例如在攝氏25度下在磷酸鹽緩衝之鹽水中進行)之該CP1和/或該CP2對其同源受體之結合親和力。於某些實施態樣中，該至少一種活性為淋巴瘤細胞之增殖水準。在其他實施態樣中，該至少一種活性為淋

巴瘤細胞中JAK/STAT/ISGF3路徑活化之水準。於一些實施態樣中，該至少一種活性為淋巴瘤細胞中SEAP產生的水準。於進一步之實施態樣中，至少一種該CP1和/或該CP2之活性為使用例如RNAseq方法之細胞介素刺激的基因誘導水準(參見，例如Zimmerer et al., *Clin. Cancer Res.* 14(18):5900-5906, 2008；Hilkens et al., *J. Immunol.* 171: 5255-5263, 2003)。

【0251】於一些實施態樣中，該ACC之特徵在於與該CP1和/或該CP2活性中至少一者的對照水準相比較，該CP1和/或該CP2活性中至少一者降低至少2倍。於一些實施態樣中，該ACC之特徵在於與該CP1和/或該CP2活性中至少一者的對照水準相比較，該CP1和該CP2活性中至少一者降低至少5倍。於一些實施態樣中，該ACC之特徵在於與該CP1和/或該CP2活性中至少一者的對照水準相比較，該CP1和該CP2活性中至少一者降低至少10倍。於一些實施態樣中，該ACC之特徵在於與該CP1和/或該CP2活性中至少一者的對照水準相比較，該CP1和該CP2活性中至少一者降低至少20倍。於一些實施態樣中，該ACC之特徵在於與該CP1和/或該CP2活性中至少一者的對照水準相比較，該CP1和該CP2活性中至少一者降低至少30倍、40倍、50倍、60倍、70倍、80倍、90倍、100倍、500倍、1000倍、2000倍、3000倍、5000倍或5,000倍。於一些實施態樣中，該ACC之特徵在於與該CP1和/或該CP2活性中至少一者的對照水準相比較，該CP1和該CP2活性中至少

一者至少降低1至20倍、降低200至2000倍、降低300至2000倍、降低400至2000倍、降低500至2000倍、降低1000至2000倍、降低1500至2000倍、降低100至1500倍、降低200至1500倍、降低300至1500倍、降低400至1500倍、降低500至1500倍、降低1000至1500倍、降低100至1000倍、降低200至1000倍、降低300至1000倍、降低400至1000倍、降低500至1000倍、降低1000至5000倍、降低2000至5000倍、降低3000至5000倍、降低4000至5000倍、降低1000至4000倍、降低2000至4000倍、降低3000至4000倍、降低1000至3000倍、降低2000至3000倍或降低1000至2000倍。

【0252】於一些實施態樣中，該CP1和/或該CP2活性中至少一者的對照水準為該CM被蛋白酶裂解後從該ACC釋放之該CP1和/或該CP2(“裂解產物”)的活性。於一些實施態樣中，該CP1和/或該CP2活性中至少一者的對照水準為對應之野生型成熟細胞介素(例如重組野生型成熟細胞介素)的活性。

【0253】於一些實施態樣中，該ACC與蛋白酶一起溫育產生經活化之細胞介素產物，其中該經活化之細胞介素產物之該CP1和/或該CP2的一或多種活性較該完整ACC之該CP1和/或該CP2的一或多種活性高。於一些實施態樣中，該經活化之細胞介素產物之該CP1和/或該CP2的一或多種活性較該ACC之該CP1和/或該CP2的一或多種活性高至少1倍。於一些實施態樣中，該經活化之細胞介素產物

之該CP1和/或該CP2的一或多種活性較該ACC之該CP1和/或該CP2的一或多種活性高至少2倍。於一些實施態樣中，該經活化之細胞介素產物之該CP1和/或該CP2的一或多種活性較該ACC之該CP1和/或該CP2的一或多種活性高至少5倍。於一些實施態樣中，該經活化之細胞介素產物之該CP1和/或該CP2的一或多種活性較該ACC之該CP1和/或該CP2的一或多種活性高至少10倍。於一些實施態樣中，該經活化之細胞介素產物之該CP1和/或該CP2的一或多種活性較該ACC之該CP1和/或該CP2的一或多種活性高至少20倍。於一些實施態樣中，該經活化之細胞介素產物之該CP1和/或該CP2的一或多種活性較該ACC之該CP1和/或該CP2的一或多種活性至少高1至20倍、高200至2000倍、高300至2000倍、高400至2000倍、高500至2000倍、高1000至2000倍、高1500至2000倍、高100至1500倍、高200至1500倍、高300至1500倍、高400至1500倍、高500至1500倍、高1000至1500倍、高100至1000倍、高200至1000倍、高300至1000倍、高400至1000倍、高500至1000倍、高1000至5000倍、高2000至5000倍、高3000至5000倍、高4000至5000倍、高1000至4000倍、高2000至4000倍、高3000至4000倍、高1000至3000倍、高2000至3000倍，或高1000至2000倍。

【0254】於一些實施態樣中，該ACC可包括與SEQ ID NO：290或291具有至少80%(例如至少82%、至少84%、至少86%、至少88%、至少90%、至少92%、至少與至少

94%、至少96%、至少98%、至少99%或100%)同一性之序列。於一些實施態樣中，該ACC可由包括與編碼SEQ ID NO：290或291之核酸序列具有至少80%(例如至少82%、至少84%、至少86%、至少88%、至少90%、至少92%、至少94%、至少96%、至少98%、至少99%或100%)同一性之序列的核酸編碼。於一些態樣中，該ACC可包括該等序列，或不具有信號序列之該等序列。該信號序列並無特別限制。該信號序列之一些非限制性實例包括，例如SEQ ID NO：470及其他序列中之對應殘基和核苷酸，或被來自另一物種或細胞株之信號序列取代者。該信號序列之其他實例包括MRAWIFFLLCLAGRALA(SEQ ID NO：468)和MALTFALLVALLVLSCKSSCSVG(SEQ ID NO：469)。

【0255】下文中描述該等ACC及可經活化之抗體的各種不同示例性態樣且可用於本文提供之方法的任何組合中，但不限於此。該ACC和可經活化之抗體，以及製造ACC和可經活化之抗體的方法之示例性態樣描述於下文中。

【0256】於一些實施態樣中，選擇與特定蛋白酶一起使用之CM。該蛋白酶可為一種由腫瘤細胞產生者(例如該腫瘤細胞可表現較健康組織更大量之蛋白酶)。於一些實施態樣中，該CM為至少一種選自下列群組之蛋白酶的受質：ADAM 17、BMP-1、半胱胺酸蛋白酶(諸如組織蛋白酶)、HtrA1、天冬醯胺內肽酶、馬曲肽酶(MT-SP1)、基質金屬蛋白酶(MMP)、嗜中性粒細胞彈性蛋白酶、TMPRSS

(諸如TMPRSS3或TMPRSS4、凝血酶和u型纖溶酶原活化劑(uPA，亦稱為尿激酶)。

【0257】於一些實施態樣中，該CM為至少一種基質金屬蛋白酶(MMP)之受質。該MMP之實例包括MMP1、MMP2、MMP3、MMP7、MMP8、MMP9、MMP10、MMP11、MMP12、MMP13、MMP14、MMP15、MMP16、MMP17、MMP19、MMP20、MMP23、MMP24、MMP26和MMP27。於一些實施態樣中，該CM為MMP9、MMP14、MMP1、MMP3、MMP13、MMP17、MMP11和MMP19之受質。於一些實施態樣中，該CM為MMP7之受質。於一些實施態樣中，該CM為MMP9之受質。於一些實施態樣中，該CM為MMP14之受質。於一些實施態樣中，該CM為二或更多種MMP之受質。於一些實施態樣中，該CM為MMP9和MMP14中至少一者之受質。於一些實施態樣中，該CM包括用於相同MMP之二或更多種受質。於一些實施態樣中，該CM包括至少二或更多種MMP9受質。於一些實施態樣中，該CM包括至少二或更多種MMP14受質。

【0258】於一些實施態樣中，該CM為MMP之受質且包括序列ISSGLLSS(SEQ ID NO：19)；QNQALRMA(SEQ ID NO：16)；AQNLLGMV(SEQ ID NO：15)；STFPFGMF(SEQ ID NO：18)；PVGYTSSL(SEQ ID NO：74)；DWLYWPGI(SEQ ID NO：75)；MIAPVAYR(SEQ ID NO：42)；RPSPMWAY(SEQ ID NO：43)；WATPRPMR(SEQ ID NO：44)；FRLLDWQW(SEQ ID NO：45)；LKAAPRWA

(SEQ ID NO：76)；GPSHLVLT(SEQ ID NO：77)；LPGGLSPW(SEQ ID NO：78)；MGLFSEAG(SEQ ID NO：79)；SPLPLRVP(SEQ ID NO：80)；RMHLRSLG(SEQ ID NO：81)；LAAPLGLL(SEQ ID NO：17)；AVGLLAPP(SEQ ID NO：14)；LLAPSHRA(SEQ ID NO：82)；PAGLWLDP(SEQ ID NO：20)；和/或ISSGLSS(SEQ ID NO：73)。

【0259】於一些實施態樣中，該CM為凝血酶之受質。於一些實施態樣中，該CM為凝血酶之受質且包括序列GPRSFGL(SEQ ID NO：83)或GPRSFG(SEQ ID NO：84)。

【0260】於一些實施態樣中，該CM 包括選自下列群組之胺基酸序列：NTLSGRSENHSG(SEQ ID NO：9)；NTLSGRSGNHGS(SEQ ID NO：10)；TSTSGRSANPRG(SEQ ID NO：11)；TSGRSANP(SEQ ID NO：12)；VAGRSMRP(SEQ ID NO：21)；VVPEGRRS(SEQ ID NO：22)；ILPRSPAF(SEQ ID NO：23)；MVLGRSLL(SEQ ID NO：24)；QGRAITFI(SEQ ID NO：25)；SPRSIMLA(SEQ ID NO：26)；和SMLRSMPL(SEQ ID NO：27)。

【0261】於一些實施態樣中，該CM為嗜中性粒細胞彈性蛋白酶之受質。於一些實施態樣中，該CM為絲胺酸蛋白酶之受質。於一些實施態樣中，該CM為uPA之受質。於一些實施態樣中，該CM為天冬醯胺內肽酶之受質。於一些實施態樣中，該CM為馬曲肽酶之受質。於一些實施

態樣中，該CM為半胱胺酸蛋白酶之受質。於一些實施態樣中，該CM為半胱胺酸蛋白酶，諸如組織蛋白酶之受質。

【0262】於一些實施態樣中，該CM包括下列群組之序列：ISSGLLSGRSDNH(SEQ ID NO：28)；ISSGLLSSGGSGGSLSGRSDNH(SEQ ID NO：30)；AVGLLAPPGGTSTSGRSANPRG(SEQ ID NO：275)；TSTSGRSANPRGGGAVGLLAPP(SEQ ID NO：276)；VHMPLGFLGPGGTSTSGRSANPRG(SEQ ID NO：277)；TSTSGRSANPRGGGVHMPLGFLGP(SEQ ID NO：278)；AVGLLAPPGGLSGRSDNH(SEQ ID NO：29)；LSGRSDNHGGAVGLLAPP(SEQ ID NO：70)；VHMPLGFLGPGGLSGRSDNH(SEQ ID NO：266)；LSGRSDNHGGVHMPLGFLGP(SEQ ID NO：267)；LSGRSDNHGGSGGSISSGLLSS(SEQ ID NO：268)；LSGRSGNHGGSGGSISSGLLSS(SEQ ID NO：279)；ISSGLLSSGGSGGSLSGRSGNH(SEQ ID NO：269)；LSGRSDNHGGSGGSQNQALRMA(SEQ ID NO：270)；QNQALRMAGGSGGSLSGRSDNH(SEQ ID NO：271)；LSGRSGNHGGSGGSQNQALRMA(SEQ ID NO：272)；QNQALRMAGGSGGSLSGRSGNH(SEQ ID NO：273)和/或ISSGLLSGRSGNH(SEQ ID NO：274)。

【0263】於一些實施態樣中，該CM包含選自由下列所組成之群組的序列：SEQ ID NO：5至SEQ ID NO：

100。於一些實施態樣中，該CM包含選自由下列所組成之群組的序列：ISSGLLSGRSDNH(SEQ ID NO：28)、LSGRSDDH(SEQ ID NO：33)、ISSGLLSGRSDQH(SEQ ID NO：54)、SGRSDNI(SEQ ID NO：100)和ISSGLLSGRSDNI(SEQ ID NO：68)。本文揭示之任一CM或弦CM之組合可用於本揭示之任何ACC及可經活化之抗體的背景下。

【0264】於一些態樣中，該ACC包括第一單體，該第一單體包含選自SEQ ID NO：1和101至209之CP1、選自SEQ ID NO：5至100和237至281之CM1、選自SEQ ID NO：297、298、292和299至446之PM1、選自SEQ ID NO：5至100和237至281之CM3，及與第二單體二聚化之DD1，該第二單體包含選自SEQ ID NO：1和101至209之CP2、選自SEQ ID NO：5至100和237至281之CM2、選自SEQ ID NO：297、298、292和299至446之PM2、選自SEQ ID NO：5至100和237至281之CM3及DD2。於一些態樣中，該ACC可在該CP1與該CM1之間、該CP1與該PM1之間、該CP1與該CM3之間、該PM1與該CM3之間和/或該CM1與該DD1之間包括選自SEQ ID NO：2和210至263之連接子，及在該CP2與該CM2之間、該CP2與該PM2之間、該CP2與該CM4之間、該PM2與該CM4之間和/或該CM2與該DD2之間包括選自SEQ ID NO：2和210至2236之連接子。於一些態樣中，根據表24選擇與該CP1一起使用之PM1，並根據表24選擇與該CP2一起使用之PM2。

【0265】於一些實施態樣中，該ACC包括DD1和/或

DD2，該DD1和/或該DD2具有與SEQ ID NO：3或SEQ ID NO：4具有至少80%同一性(例如至少82%、至少84%、至少85%、至少86%、至少88%、至少90%、至少92%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性)之胺基酸序列。於一些實施態樣中，該ACC包括DD1，該DD1具有與SEQ ID NO：287或SEQ ID NO：288具有至少80%同一性(例如至少82%、至少84%、至少85%、至少86%、至少88%、至少90%、至少92%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性)之胺基酸序列。於一些實施態樣中，該ACC包括DD2，該DD2具有與SEQ ID NO：287或SEQ ID NO：288具有至少80%同一性(例如至少82%、至少84%、至少85%、至少86%、至少88%、至少90%、至少92%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性)之胺基酸序列。

【0266】本文之ACC的一或二種單體可包含一或多種肽掩蔽物(PM)，該肽掩蔽物(PM)可干擾該CP與其結合配偶體(例如受體)結合。於一些實施態樣中，當該ACC未被活化時，該ACC中之該PM阻止該CP與標靶結合；但是當該ACC被活化時，該PM不會實質性或顯著地干擾該CP與其結合配偶體結合。於一些實施態樣中，該PM藉由CM及可選擇地本文所描述之一或多個連接子與該CP偶聯。

【0267】於一些實施態樣中，該PM可與該CP交互作用，從而減少或抑制該CP與其結合配偶體之間的交互作

用。於一些實施態樣中，該PM可能不與該CP特異結合，而是透過非特異性交互作用(諸如空間位阻)干擾該CP與其結合配偶體結合。例如，該PM可位於該未經裂解之ACC中，使得該ACC之三級或四級結構允許該PM透過基於電荷之交互作用來掩蔽該CP，從而將該PM固定在干擾該結合配偶體接近該CP之位置。

【0268】該PM之結構特性可根據諸如干擾該蛋白質與標靶結合所需之最小胺基酸序列、關注之標靶蛋白質-蛋白質結合對、該細胞介素之大小、連接子存在與否，等因素選擇。

【0269】該PM可透過篩選程序從具有可變之PM的候選ACC庫鑑定和/或進一步優化。例如可選擇CP和CM以提供合需之酶/標靶組合，且該PM之胺基酸序列可藉由下述篩選程序鑑別以鑑別可提供可轉換之表型的PM。例如隨機肽集合庫(例如具有包含約2至約40個胺基酸或更多個胺基酸之肽的集合)可用於本文揭示之篩選方法以鑑定合適之PM。於具體之實施態樣中，可透過篩選程序鑑別對CP具有特異結合親和力之PM，該篩選程序包括提供由候選PM所組成之肽支架集合庫，其中各支架係由跨膜蛋白和候選PM組成。然後可將該集合庫與全部或部分蛋白質，諸如全長蛋白質、天然存在之蛋白質片段或含有蛋白質之非天然存在的片段(亦能夠與所關注之結合配偶體結合)接觸，並鑑別一或多種具有可檢測之結合蛋白的候選PM。該篩選可藉由一或多輪之磁活化的分選(MACS)或螢光活

化之分選(FACS)並測定該PM對該CP之結合親和力，且隨後測定該掩蔽效率來執行，例如依US20200308243A1(其全文以引用方式併入本文)之描述。

【0270】於一些實施態樣中，該PM對該經偶聯之CP具獨特性。該PM之實例包括經特異篩選以結合該細胞介素或蛋白質片段之結合結構域的PM(例如親和性肽掩蔽物)。本發明提供用於篩選PM的方法以獲得對該細胞介素具獨特性及特異地和/或選擇性地結合該結合配偶體/標靶之結合結構域之PM，並可包括蛋白質表現方法。表7揭示適用於各種示例性CP之示例性PM。

【0271】於一些實施態樣中，當在掩蔽效率分析中測量時(例如依實施例1中之描述)，當該CP與該PM偶聯且存在該CP之天然結合配偶體時，該CP與該結合配偶體未結合或基本上未結合，或與未與PM偶聯之該CP的結合相比較，該CP與其結合配偶體之結合不超過0.001%、0.01%、0.1%、1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、15%、20%、25%、30%、35%、40%或50%，持續至少2、4、6、8、12、28、24、30、36、48、60、72、84、96小時、或5、10、15、30、45、60、90、120、150、180天、或1、2、3、4、5、6、7、8、9 10、11、12個月或更久。

【0272】本揭示考量之該PM可在1至50個胺基酸之範圍內(例如至少3、4、5、6、7、8、9、10、12、15、20、30或40個胺基酸，或不多於40、30、20、15、12、10、

9、8、7、6、5、4或3個胺基酸)。於一些實例中，該PM之長度可為8至15個胺基酸。

【0273】該PM可含有遺傳編碼或非遺傳編碼之胺基酸。該非遺傳編碼之胺基酸的實例為，但不限於D-胺基酸、β-胺基酸和γ-胺基酸。於具體之實施態樣中，該PM含有不超過50%、40%、30%、20%、15%、10%、5%或1%之非遺傳編碼之胺基酸。

【0274】當該細胞介素與PM偶聯時，該細胞介素對標靶或結合配偶體之結合親和力可能較該細胞介素未與該PM偶聯時，該細胞介素對其結合配偶體之結合親和力低至少5、10、25、50、100、250、500、1,000、2,500、5,000、10,000、50,000、100,000、500,000、1,000,000、5,000,000、10,000,000、50,000,000或更多倍，或低5至10、10至100、10至1,000、10至10,000、10至100,000、10至1,000,000、10至10,000,000、100至1,000、100至10,000、100至100,000、100至1,000,000、100至10,000,000、1,000至10,000、1,000至100,000、1,000至1,000,000、1000至10,000,000、10,000至100,000、10,000至1,000,000、10,000至10,000,000、100,000至1,000,000或100,000至10,000,000倍。

【0275】與該細胞介素未與PM偶聯時，該細胞介素與其結合配偶體之特異結合相比較，當該細胞介素與該PM偶聯且存在結合配偶體時，該細胞介素與其結合配偶體之特異性結合可能會降低或受抑制。當在活體內或掩蔽

效率分析(例如，如實施例1所示)、活體外免疫吸附分析(例如，如US20200308243A1中之描述)中測量時，當與未與PM偶聯之該細胞介素與其結合配偶體之結合相比較，該與PM偶聯之細胞介素與其結合配偶體結合的能力可能降低至少50%、60%、70%、80%、90%、92%、93%、94%、95%、96%、97%、98%、99%，且甚至100%，並持續至少2、4、6、8、12、28、24、30、36、48、60、72、84、96小時、或5、10、15、30、45、60、90、120、150、180天、或1、2、3、4、5、6、7、8、9 10、11、12個月或更久。

【0276】該PM對該細胞介素之K_D通常可大於該細胞介素對該細胞介素之結合配偶體的K_D。該PM對該細胞介素之K_D可較該細胞介素對其結合配偶體之K_D高至少5、10、25、50、100、250、500、1,000、2,500、5,000、10,000、100,000、1,000,000或甚至10,000,000倍。或者，該PM對該細胞介素之結合親和力可能通常較該細胞介素對該細胞介素之結合配偶體的結合親和力低。該PM對該細胞介素之結合親和力可能較該細胞介素對其結合配偶體之結合親和力低至少5、10、25、50、100、250、500、1,000、2,500、5,000、10,000、100,000、1,000,000或10,000,000倍。

【0277】於一些實施態樣中，該PM包含至少部分或完整之該CP之天然存在的結合配偶體(例如該CP之受體)的胺基酸序列。該PM可為天然存在之結合配偶體的片段。

該片段可保留不超過95%、90%、80%、75%、70%、60%、50%、40%、30%、25%或20%之與該天然存在之結合配偶體同源的核酸或胺基酸序列。

【0278】於一些實施態樣中，該PM包含非天然存在之胺基酸序列或不含有天然存在之結合配偶體或靶蛋白之胺基酸序列。於某些實施態樣中，該PM不是該CP之天然結合配偶體。該PM可為該CP之經修飾的結合配偶體，其含有至少略微降低對該CP之結合親和力(affinity)和/或親和性(avidity)的胺基酸變化。於一些實施態樣中，該PM不含或基本上不含有與該CP之天然結合配偶體同源的核酸或胺基酸。於其他實施態樣中，該PM與該CP之天然結合配偶體的相似度不超過5%、10%、15%、20%、25%、30%、35%、40%、45%、50%、55%、60%、65%、70%、75%或80%。

【0279】於一些實施態樣中，該PM包含與選自SEQ ID NO：297、298、292和299至446之序列具有至少80%同一性(例如至少82%、至少84%、至少86%、至少88%、至少90%、至少92%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性)之胺基酸序列。與為干擾素(較佳為IFN-α)之CP一起使用的示例性PM可含有共有序列：TDVDYYREWXXXXXXXX(SEQ ID NO：329)，其中X為任何胺基酸。

【0280】於一些實施態樣中，該ACC可包含表7中所列之一對PM1和CP1或一對PM2和CP2，表7中含有與特定

之示例性細胞介素一起使用之示例性PM。於一些實例中，該PM1包含選自SEQ ID NO：297、298、292和299至336之序列，且該CP1為干擾素；該PM1包含選自SEQ ID NO：297、298、292和299至332之序列，且該CP1為干擾素α；該PM1包含選自SEQ ID NO：299至328和330至332之序列，且該CP1為干擾素β；該PM1包含選自SEQ ID NO：299至328和333至336之序列，且該CP1為干擾素γ；該PM1包含選自SEQ ID NO：337至341之序列，且該CP1為IL-12；該PM1包含選自SEQ ID NO：342至349、436至444、478之序列，且該CP1為IL-15；該PM1包含選自SEQ ID NO：350至435、436至445之序列，且該CP1為IL-2；或者該PM1包含選自SEQ ID NO：445和446之序列，且該CP1為IL-21。於一些實例中，該PM2包含選自SEQ ID NO：297、298、292和299至336之序列，且該CP2為干擾素；該PM2包含選自SEQ ID NO：297、298、292和299至332之序列，且該CP2為干擾素α；該PM2包含選自SEQ ID NO：299至328和330至332之序列，且該CP2為干擾素β；該PM2包含選自SEQ ID NO：299至328和333至336之序列，且該CP2為干擾素γ；該PM2包含選自SEQ ID NO：337至341之序列，且該CP2為IL-12；該PM2包含選自SEQ ID NO：342至349、436至444、478之序列，且該CP2為IL-15；該PM2包含選自SEQ ID NO：350至435、436至445之序列，且該CP2為IL-2；或者該PM2包含選自SEQ ID NO：445和446之序列，且該CP2為IL-21。

【0281】於一些實施態樣中，該PM可包含非活性細胞介素。例如該非活性細胞介素可能與該ACC中之該CP組分交互作用並干擾該CP與其結合配偶體之間的交互作用。於一實例中，該非活性細胞介素可包含突變，例如具有L130P突變之IFNα-2b((SEQ ID NO：297和298)。於另一實例中，該非活性細胞介素可為截短之野生型細胞介素，例如具有胺基酸1至150之IFNα-2b。

【0282】於一些實施態樣中，一旦與該細胞介素解偶聯並處於游離狀態，則該PM可具有生物活性或治療效果，諸如結合能力。例如，該游離肽可與相同或不同結合配偶體結合。於某些實施態樣中，該游離PM(未經偶聯之PM)可發揮治療效果對本文揭示之組成物提供第二功能。於一些實施態樣中，一旦與該細胞介素解偶聯並處於游離狀態，則該PM可能有利地不表現出生物活性。例如，於一些實施態樣中，該處於游離狀態之PM不會在該個體中引起免疫反應。

與作用劑結合

【0283】本發明亦提供用於在本文所描述之任何該ACC和抗體中包含額外元素之方法和材料，包括，例如用於促進遞送至所欲細胞或組織之靶向部分、作用劑(例如治療劑、抗贅瘤劑)、毒素或其片段。以下任何關於將作用劑與ACC結合之揭示內容亦同樣適用且應被解釋為支持將作用劑與本發明之抗體結合。

【0284】於本文描述之任何ACC之一些實施態樣中，該ACC可與細胞毒性劑結合，該細胞毒性劑包括，但不限於毒素(例如細菌、真菌、植物或動物來源之酶活性毒素或其片段)或放射性同位素。於本文所描述之任何ACC的一些實施態樣中，該可經活化之細胞介素構築體可與細胞毒性劑結合，該細胞毒性劑包括，但不限於毒素(例如細菌、真菌、植物或動物來源之酶活性毒素或其片段)或放射性同位素。

【0285】可與本文所描述之任何ACC結合之非限制性示例性細胞毒性劑包括：多拉司他汀(dolastatin)及其衍生物(例如澳瑞他汀(auristatin)E、AFP、單甲基澳瑞他汀D(MMAD)、單甲基澳瑞他汀F(MMAF)、單甲基澳瑞他汀E(MMAE))、去甲基澳瑞他汀E(DMAE)、澳瑞他汀F、去甲基澳瑞他汀F(DMAF)、多拉司他汀16(DmJ)、多拉司他汀16(Dpv)、澳瑞他汀衍生物(例如澳瑞他汀酪胺、澳瑞他汀喹諾酮)、類美登素(maytansinoid)(例如DM-1、DM-4)、類美登素衍生物、倍癌黴素(duocarmycin)、α-鵝膏蕈鹼(α-amanitin)、渦輪他汀(turbostatin)、芬他汀(phenstatin)、羥基芬他汀(hydroxyphenstatin)、海綿抑素5(spongistatin 5)、海綿抑素7、哈里司汀1(halistatin 1)、哈里司汀2、哈里司汀3、哈洛康汀(halocomstatin)、吡咯並苯並咪唑(pyrrolobenzimidazole)(PBI))、西伯他汀6(cibrostatin 6)、多索里風(doxaliform)、西馬多丁(cemadotin)類似物(CemCH2-SH)、假單胞菌毒素A(PES8)變體、假單胞菌毒

素A(ZZ-PE38)變體、ZJ-101、蒽環類、多柔比星、柔紅黴素、苔蘚抑素(bryostatin)、喜樹鹼、7-取代之喜樹鹼、10,11-二氟伸甲基二氧基喜樹鹼、康普瑞汀(combretastatin)、脫溴海兔毒素(debromoaplysiatoxin)、KahaMide-F、盤皮海綿內酯(discodermolide)和依特那斯汀(Ecteinascidin)。

【0286】可與本文所描述之任何ACC結合之非限制性示例性酶活性毒素包括：白喉毒素、來自綠膿桿菌之外毒素A鏈、蓖麻毒蛋白A鏈、雞母珠毒素(abrin)A鏈、現代毒菌素(modeccin)A鏈、α-帚麴菌素(alpha-sarcin)、油桐(Aleurites fordii)蛋白、康乃馨(dianthin)蛋白、洋商陸(Phytolaca americana)蛋白(例如PAPI、PAPII及PAP-8)、苦瓜(momordica charantia)抑制劑、麻瘋樹毒蛋白(curcin)、巴豆毒素(crotin)、肥皂草(sapaonaria officinalis)抑制劑、白樹素(gelonin)、有絲分裂素(mitogellin)、侷限麴菌素(restrictocin)、酚黴素(phenomycin)、新黴素(neomycin)及單端孢黴烯族毒素(tricothecene)。

【0287】可與本文所描述之任何ACC結合之非限制性示例性抗腫瘤劑包括：阿黴素(adriamycin)、道諾黴素(cerubidine)、博來黴素(bleomycin)、威克瘤(alkeran)、長春鹼(velban)、安可平(oncovin)、氟尿嘧啶(fluorouracil)、甲胺喋呤(methotrexate)、噻替派(thiotepa)、比生群(bisantrene)、諾凡群(novantrone)、硫鳥嘌呤(thioguanine)

、丙卡巴嗪(procarabizine)和阿糖胞苷(cytarabine)。

【0288】可與本文所描述之任何ACC結合之非限制性示例性抗病毒藥包括：阿昔洛韋、病毒A和西美翠(symmetrel)。

【0289】可與本文所描述之任何ACC結合之非限制性示例性抗真菌劑包括：耐絲菌素(nystatin)。

【0290】可與本文所描述之任何ACC結合之非限制性示例性可結合之檢測試劑包括：螢光素及其衍生物、異硫氰酸螢光素(FITC)。

【0291】可與本文所描述之任何可經活化之細胞介素構築體結合之非限制性示例性抗菌劑包括：胺基糖苷類、鏈黴素、新黴素、卡那黴素、阿米卡黴素、慶大黴素和妥布黴素。

【0292】可與本文所描述之任何可經活化之細胞介素構築體結合之非限制性示例性3β,16β,17α-三羥基膽固-5-烯-22-酮16-O-(2-O-4-甲氧基苯甲醯基-β-D-吡喃木糖基)-(1-->3)-(2-O-乙醯基-α-L-阿拉伯吡喃糖苷(OSW-1)包括：O6-苄基鳥嘌呤之s-硝基苄氧羰基衍生物、拓撲異構酶抑制劑、哈米特林(hemiasterlin)、頭孢紫杉醇、高三尖杉酯鹼、吡咯苯並二氮雜䓬二聚體(PBD)、官能化之吡咯苯並二氮雜䓬類、卡奇黴素、鬼孔毒素、紫杉烷和長春花生物鹼。

【0293】可與本文所描述之任何可經活化之細胞介素構築體結合之非限制性示例性放射性藥物包括：^{123}I、^{89}Zr

、^{125}I、^{131}I、^{99}mTc、^{201}Tl、^{62}Cu、^{18}F、^{68}Ga、^{13}N、^{15}O、^{38}K、^{82}Rb、^{111}In、^{133}Xe、^{11C}和^{99}mTc(鍀)。

【0294】可與本文所描述之任何ACC結合之非限制性示例性重金屬包括：鋇、金和鉑。

【0295】可與本文所描述之任何ACC結合之非限制性示例性抗支原體藥物包括：泰黴素(tylosine)、壯觀黴素(spectinomycin)、鏈黴素B、胺苄青黴素、磺胺、多黏菌素和氯黴素。

【0296】本技藝之一般技術人士將察知很多種可能可與本文所描述之任何可經活化之細胞介素構築體結合的部分。結合可包括任何將該二個分子結合之化學反應，只要該ACC和該其他部分保持其各自的活性。結合可包括許多化學機制，例如共價結合、親和力結合、嵌入、配位結合和複合。於一些實施態樣中，該較佳之結合為共價結合。共價結合可藉由現有側鏈之直接縮合或藉由併入外部橋接分子來實現。許多二價或多價連接劑可用於結合本文所描述之任何可經活化之細胞介素構築體。例如，結合可包括有機化合物，諸如硫酯、碳二亞胺、琥珀醯亞胺酯、戊二醛、重氮苯和六亞甲基二胺。於一些實施態樣中，該可經活化之細胞介素構築體可包括或以其他方式引入一或多個非天然胺基酸殘基以提供合適之結合位點。

【0297】於本文所描述之任何ACC的一些實施態樣中，作用劑和/或結合物係藉由二硫鍵(例如半胱胺酸分子上之二硫鍵)連接至抗原結合結構域。由於許多癌症自然

釋放高水準之麩胱甘肽(一種還原劑)，存在於該癌組織微環境中之麩胱甘肽可還原該二硫鍵，並隨後在遞送部位釋放該作用劑和/或結合物。

【0298】於本文所描述之任何ACC的一些實施態樣中，當該結合物在補體的存在下在靶位點(例如患病組織(例如癌性組織))內與其標靶結合時，將該結合物和/或作用劑連接至該連接子的醯胺鍵或酯鍵被裂解，導致該結合物和/或作用劑以其活性形式釋放。該等結合物和/或作用劑當被投予至個體時將在靶位點(例如患病組織(例如癌組織))完成遞送和釋放該結合物和/或作用劑。該等結合物和/或作用劑對本文所描述之任何結合物和/或作用劑之活體內遞送特別有效。

【0299】於一些實施態樣中，該連接子不可被該補體系統之酶裂解。例如該結合物和/或作用劑在無補體活化下釋放，因為補體活化最終裂解該靶細胞。於該等實施態樣中，該結合物和/或作用劑將被遞送至靶細胞(例如激素、酶、皮質類固醇、神經遞質或基因)。進一步地，該連接子對血清蛋白酶之裂解作用輕微敏感，且該結合物和/或作用劑在該靶位點被緩慢釋放。

【0300】於本文所描述之任何ACC的一些實施態樣中，該結合物和/或作用劑經過設計使得該結合物和/或作用劑被遞送至該靶位點(例如疾病組織(例如癌性組織))，但該結合物和/或作用劑未被釋放。

【0301】於本文所描述之任何ACC的一些實施態樣

中，該結合物和/或作用劑直接連接或經由不可裂解之連接子連接該抗原結合結構域。示例性不可裂解之連接子包括可經修飾以包括官能基之胺基酸(例如D-胺基酸)、肽或其他有機化合物，該官能基隨後可藉由本文描述之方法用於連接抗原結合結構域。

【0302】於本文所描述之任何ACC的一些實施態樣中，該ACC包括至少一個作用劑之結合點。於一些實施態樣中，所有可能之結合點均可用於與作用劑結合。於一些實施態樣中，該一或多個結合點包括，但不限於參與二硫鍵之硫原子、參與鏈間二硫鍵之硫原子、參與鏈間硫鍵的硫原子，但不包括參與鏈內二硫鍵的硫原子，和/或半胱胺酸或其他含有硫原子之胺基酸殘基的硫原子。於該等情況下，殘基可天然存在於該蛋白質構築體結構中或可使用包括，但不限於下列方法被併入蛋白質構築體中：定點誘變、化學轉化或錯誤併入非天然胺基酸。

【0303】本發明亦提供用於製備用於結合之ACC的方法和材料。於本文所描述之任何ACC的一些實施態樣中，該ACC係經修飾以包括一或多個鏈間二硫鍵。例如，該ACC中之二硫鍵可在暴露於還原劑(諸如，但不限於TCEP、DTT或β-巰基乙醇)後發生還原。於一些情況下，該二硫鍵之還原僅為部分的。如本文所使用者，術語部分還原係指其中ACC與還原劑接觸而所有可能之結合位點的一部分經歷還原(例如並非所有二硫鍵均被還原)的情況。於一些實施態樣中，該可經活化之細胞介素構築體在與還

原劑接觸後，若少於99%(例如少於98%、97%、96%、95%、90%、85%、80%、75%、70%、65%、60%、55%、50%、45%、40%、35%、30%、25%、20%、15%、10%或少於5%)之所有可能之結合位點被還原則該可經活化之細胞介素構築體被部分還原。於一些實施態樣中，該具有一或多個鏈間二硫鍵還原之ACC與藥物結合，該藥物具有與游離硫醇反應之反應性。

【0304】本發明亦提供用於將治療劑結合至ACC上之特定位置的方法和材料。於本文所描述之任何ACC的一些實施態樣中，該ACC係經修飾使得該治療劑可在該ACC上之特定位置處結合至ACC。例如，可以能促進與該ACC結合之方式將該ACC部分還原。於該等情況下，該ACC之部分還原係以該ACC中之結合位點未被還原的方式發生。於一些實施態樣中，選擇在該ACC上之結合位點以促進作用劑在該蛋白質構築體上之特定位置處結合。在使用還原劑處理後，多種不同因素會影響該ACC之“還原水準”。例如，但不限於還原劑與ACC之比例、培育時間長度、培育溫度和/或該還原反應溶液之pH可能需要優化以能夠藉由本文所描述之方法和材料達成將該ACC部分還原。可使用任何適當之因素組合(例如還原劑與該ACC之比例、與還原劑一起培育之時間長度和溫度，和/或還原劑之pH)來達成將該ACC部分還原(例如整體還原可能的結合位點或還原特定結合位點)。

【0305】該還原劑與該ACC之有效比例可為以允許與

作用劑結合之方式至少部分還原該ACC的任何比例(例如整體還原可能的結合位點或還原特定結合位點)。於一些實施態樣中，該還原劑與該ACC之比例將在下列範圍：約20:1至1:1、約10:1至1:1、約9:1至1:1、約8:1至1:1、約7:1至1:1、約6:1至1:1、約5:1至1:1、約4:1至1:1、約3:1至1:1、約2:1至1:1、約20:1至1:1.5、約10:1至1:1.5、約9:1至1:1.5、約8:1至1:1.5、約7:1至1:1.5、約6:1至1:1.5、約5:1至1:1.5、約4:1至1:1.5、約3:1至1:1.5、約2:1至1:1.5、約1.5:1至1:1.5、或約1:1至1:1.5。於一些實施態樣中，該比例係在約5:1至1:1之範圍內。於一些實施態樣中，該比例係在約5:1至1.5:1之範圍內。於一些實施態樣中，該比例係在約4:1至1:1之範圍內。於一些實施態樣中，該比例係在約4:1至1.5:1之範圍內。於一些實施態樣中，該比例係在約8:1至約1:1之範圍內。於一些實施態樣中，該比例係在約2.5:1至1:1之範圍內。

【0306】用於以還原劑處理該ACC之有效培育時間和溫度可為以允許該作用劑與該ACC結合之方式至少部分還原該ACC(例如整體還原可能的結合位點或還原特定結合位點)的任何時間和溫度。於一些實施態樣中，用於處理該ACC之培育時間和溫度的範圍將為在37℃下約1小時至在37℃下約12小時(或其中之任何子範圍)。

【0307】用於以還原劑處理該ACC之還原反應的有效pH值可為以允許該ACC與該作用劑結合之方式至少部分地還原該ACC(例如整體還原可能的結合位點或還原特定結

合位點)的任何pH值。

【0308】當將經部分還原之ACC與含有硫醇之作用劑接觸時，該作用劑可與該ACC中之鏈間硫醇結合。可使用含硫醇試劑(例如半胱胺酸或N-乙醯半胱胺酸)以能將硫醇包括在內之方式修飾該作用劑。例如，在約37℃下，以合需之還原劑對ACC之比例將該ACC與還原劑(例如TEPC)培育約1小時後，該ACC可被部分還原。還原劑對ACC之有效比例可為以允許結合含硫醇作用劑之方式部分還原至少二個位於該ACC中之鏈間二硫鍵(例如整體還原可能的結合位點或還原特定結合位點)的任何比例。

【0309】於本文所描述之任何ACC的一些實施態樣中，該ACC係以避免還原任何鏈內二硫鍵之方式被還原劑還原。於本文所描述之任何ACC的一些實施態樣中，該ACC係以避免還原任何鏈內二硫鍵並還原至少一個鏈間二硫鍵之方式被還原劑還原。

【0310】於本文所描述之任何ACC的一些實施態樣中，該ACC亦可包括與該ACC結合的作用劑。於一些實施態樣中，該結合劑為治療劑。

【0311】於一些實施態樣中，該作用劑(例如結合至可經活化之細胞介素構築體的作用劑)為可檢測部分，諸如，例如標記或其他標記物。例如，該作用劑為或包括經放射性標記之胺基酸、一或多種可藉由經標記之抗生物素蛋白(例如含有可藉由光學或量熱法檢測之螢光標記或酶活性的鏈黴抗生物素蛋白)檢測的生物素基部分、一或多

種放射性同位素或放射性核素、一或多種螢光標記、一或多種酶性標記和/或一或多種化學發光劑。於一些實施態樣中，該可檢測部分係藉由間隔子分子連接。

【0312】於一些實施態樣中，該作用劑(例如結合至可經活化之細胞介素構築體的細胞毒性劑)係使用碳水化合物部分、巯基、胺基或羧酸酯基團連接至該ACC。

【0313】於本文所描述之與作用劑結合之任何ACC的一些實施態樣中，該作用劑(例如結合至可經活化之細胞介素構築體的細胞毒性劑)係經由連接子和/或CM(亦稱為可裂解之序列)結合至該ACC。於一些實施態樣中，該作用劑(例如結合至可經活化之細胞介素構築體的細胞毒性劑)係與該ACC中之半胱胺酸或離胺酸結合。於一些實施態樣中，該作用劑(例如結合至可經活化之細胞介素構築體的細胞毒性劑)係與該ACC之另一殘基(諸如本文揭示之那些殘基)結合。於一些實施態樣中，該連接子為含硫醇之連接子。表1中提供該連接子和/或CM的一些非限制性實例。

表1.

可裂解之序列/CM的類型	胺基酸序列
纖溶酶CM	
尿激酶原	PRFKIIGG (SEQ ID NO: 253)
	PRFRIIGG (SEQ ID NO: 254)
TGFβ	SSRHRRALD (SEQ ID NO: 255)
纖溶酶原	RKSSIIIRMRDVVL (SEQ ID NO: 256)
葡激酶	SSSFDKGKYKKGDDA (SEQ ID NO: 257)
	SSSFDKGKYKRGDDA (SEQ ID NO: 258)
第Xa因子CM	IEGR (SEQ ID NO: 259)
	IDGR (SEQ ID NO: 260)
	GGSIDGR (SEQ ID NO: 261)
MMP CM	
明膠酶A	PLGLWA (SEQ ID NO: 262)
膠原蛋白酶CM	
小牛皮膠原蛋白(α1(I)鏈)	GPQGIAGQ (SEQ ID NO: 263)
小牛皮膠原蛋白(α2(I)鏈)	GPQGLLGA (SEQ ID NO: 264)
牛軟骨膠原蛋白(α1(II)鏈)	GIAGQ (SEQ ID NO: 265)
人肝膠原蛋白(α1(III)鏈)	GPLGIAGI (SEQ ID NO: 266)
人 α_2M	GPEGLRVG (SEQ ID NO: 267)
人PZP	YGAGLGVV (SEQ ID NO: 268)
	AGLGVVER (SEQ ID NO: 269)
	AGLGISST (SEQ ID NO: 270)
大鼠α_1M	EPQALAMS (SEQ ID NO: 271)
	QALAMSAI (SEQ ID NO: 272)
大鼠α_2M	AAYHLVSQ (SEQ ID NO: 273)
	MDAFLESS (SEQ ID NO: 274)
大鼠α_1I_3(2J)	ESLPVVAV (SEQ ID NO: 275)
大鼠α_1I_3(27J)	SAPAVESE (SEQ ID NO: 276)
人纖維母細胞膠原蛋白酶	DVAQFVLT (SEQ ID NO: 277)
(自溶裂解)	VAQFVLT (SEQ ID NO: 278)
	VAQFVLTE (SEQ ID NO: 279)
	AQFVLTEG (SEQ ID NO: 280)
	PVQPIGPQ (SEQ ID NO: 281)

【0314】本技藝之一般技術人士將察知許多不同的可能部分可與本揭示之ACC偶聯。(參見，例如“Conjugate Vaccines”, Contributions to Microbiology and Immunology, J. M. Cruse and R. E. Lewis, Jr (eds), Carger Press, New York, (1989)，其全文以引用方式併入本文)。一般而言，可藉由任何能將該作用劑與該ACC結合且同時亦允許該作用劑和該ACC保留功能的化學反應來達成將作用劑(例如細胞毒性劑)與ACC有效結合。

【0315】於與作用劑結合之任何ACC的一些實施態樣中，可使用多種不同之雙功能蛋白偶聯劑來將該作用劑與該ACC結合，包括，但不限於N-琥珀醯亞胺基-3-(2-吡啶基二硫醇)丙酸酯(SPDP)、亞胺基硫雜環戊烷(iminothiolane)(IT)、亞胺基酯之雙官能衍生物(例如己二亞胺鹽酸二甲酯)、活性酯(例如辛二酸二琥珀醯亞胺酯)、醛類(例如戊二醛)、雙疊氮基化合物(例如雙(對-疊氮基苯甲醯基)己二胺)、雙重氮衍生物(例如雙(對-重氮基苯甲醯基)-乙二胺)、二異氰酸酯(例如甲苯2,6-二異氰酸酯)和雙活性氟化合物(例如1,5-二氟-2,4-二硝基苯)。例如，可依Vitetta et al., Science 238: 1098(1987)中之描述製備蓖麻毒素免疫毒素。於一些實施態樣中，可使用經碳14標記之1-異硫氰基苄基-3-甲基二伸乙基三胺五醋酸(MX-DTPA)螯合劑將放射性核苷酸與該ACC結合。(參見，例如WO94/11026)。

【0316】合適之連接子和CM描述於文獻中(參見，例

如Ramakrishnan, S. et al., Cancer Res. 44:201-208 (1984)描述MBS(M-馬來醯亞胺基苯甲醯基-N-羥基琥珀醯亞胺酯)之用途)。亦參見美國專利案5,030,719號，其描述藉由寡肽連接子偶聯至ACC之鹵化的乙醯肼衍生物之用途。於一些實施態樣中，合適之連接子包括：(i)EDC(1-乙基-3-(3-二甲胺基-丙基)碳二亞胺鹽酸鹽；(ii)SMPT(4-琥珀醯亞胺氧羰基-α-甲基-α-(2-吡啶基-二硫代)-甲苯(Pierce化學公司，目錄編號(21558G))；(iii)SPDP(琥珀醯亞胺基-6[3-(2-吡啶基二硫代)丙醯胺基]己酸酯(Pierce化學公司，目錄編號21651G)；(iv)磺基-LC-SPDP(磺基琥珀醯亞胺基6[3-(2-吡啶基二硫代)-丙醯胺]己酸酯(Pierce化學公司，目錄編號2165-G)；和(v)磺基-NHS(N-羥磺基-琥珀醯亞胺：Pierce化學公司，目錄編號24510，其與EDC結合。其他連接子包括，但不限於SMCC、磺基-SMCC、SPDB或磺基-SPDB。

【0317】上述連接子和CM含有具有不同屬性之組分，因此導致具有不同物理化學性質之結合物。例如，烷基羧酸酯類之磺基-NHS酯較芳香族羧酸酯類之磺基-NHS酯更穩定。含有NHS酯之連接子較磺基-NHS酯類之溶解度低。此外，該連接子SMPT含有空間上被阻擋之二硫鍵並可形成穩定性更高之結合物。二硫鍵鍵聯通常不如其他鍵聯穩定，因為該二硫鍵聯在活體外被裂解，導致可用之結合物較少。特別是磺基-NHS可提高碳二亞胺偶聯之穩定性。當與磺基-NHS結合使用時，碳二亞胺偶聯(諸如EDC)

會形成較使用單獨之碳二亞胺偶聯反應對水解更具抗力的酯。

【0318】於任何該ACC的一些實施態樣中，可使用包括在該ACC之胺基酸序列中之經修飾的胺基酸序列將作用劑與該ACC結合。藉由在該ACC之胺基酸序列內的特定位置處插入能夠結合之胺基酸，可設計蛋白質構築體以控制該結合劑(例如細胞毒性劑)之放置和/或劑量。例如，該ACC可經修飾以在該第一單體、該第二單體、該第三單體和/或第四單體上之位置包括半胱胺酸胺基酸殘基，其提供反應性硫醇基團且不會負面影響蛋白質折疊和/或組裝，且不會改變抗原結合特性。於一些實施態樣中，該ACC可經修飾以在該ACC之胺基酸序列內包括一或多個非天然胺基酸殘基以提供合適之結合位點。於一些實施態樣中，該ACC可經修飾以在該ACC之胺基酸序列內包括酶催化性可經活化之肽序列。

核酸

【0319】本發明提供核酸，該核酸包括編碼本文所描述之任何ACC的第一單體構築體(或該第一單體構築體之蛋白質部分)(例如本文所描述之任何第一單體構築體)和第二單體構築體(或該第二單體構築體之蛋白質部分)(例如本文所描述之任何第二單體構築體)的序列。於一些實施態樣中，一對核酸一起編碼該第一單體構築體(或該第一單體構築體的蛋白質部分)和該第二單體構築體(或該第二單

體構築體的蛋白質部分)。於一些實施態樣中，編碼該第一單體構築體(或該第一單體構築體之蛋白質部分)之核酸序列與編碼該第二單體構築體(或該第二單體構築體的蛋白質部分)之核酸序列具有至少70%同一性(例如至少72%同一性、至少74%同一性、至少76%同一性、至少78%同一性、至少80%同一性、至少82%同一性、至少84%同一性、至少86%同一性、至少88%同一性、至少90%同一性、至少92%同一性、至少94%同一性、至少96%同一性、至少98%同一性、至少99%同一性或100%同一性)。

【0320】於一些實施態樣中，編碼該第一單體構築體之蛋白質部分的核酸編碼包含該PM1、該CP1、該CM1和該CM3部分之多肽。於一些實施態樣中，編碼該第二單體之蛋白質部分的核酸編碼包含該該CP2和該CM2部分之多肽。於一些實施態樣中，編碼該第二單體之蛋白質部分的核酸編碼包含該CP2、該CM2、該PM2和該CM4部分之多肽。於一些實施態樣中，一對核酸一起編碼該第一單體構築體之蛋白質部分和該第二單體構築體之蛋白質部分，其中該蛋白質部分再分別與該DD1和該DD2部分結合(在隨後之結合步驟中)。

【0321】於一些實施態樣中，編碼該第一單體構築體之核酸編碼包含該DD1部分的多肽。於一些實施態樣中，編碼該第二單體構築體之核酸編碼包含該DD2部分的多肽。

載體

【0322】本發明提供包括本文所描述之任何核酸的載體和載體組。本技藝之技術熟習人士將能夠選擇合適之載體或載體組(例如表現載體)來製造本文所描述之任何ACC，並使用該載體或載體組來表現本文所描述之任何ACC。例如，在選擇載體或載體組時，必須考慮該細胞，因為該載體可能需要能夠整合入該細胞之染色體中和/或在其中複製。下文中亦描述可用於產生ACC之示例性載體。

【0323】如本文所使用之術語“載體”係指能夠在細胞(例如本文所描述之任何細胞)中誘導重組蛋白(例如該第一或第二單體)表現的多核苷酸。“載體”能夠將核酸及其片段遞送入宿主細胞中，並包括調節序列(例如啟動子、增進子、多聚(A)信號)。可將外源多核苷酸插入表現載體中以被表現出來。術語“載體”亦包括人工染色體、質粒、逆轉錄病毒和桿狀病毒載體。

【0324】用於構建包括本文所描述之任何核酸且適合用於轉化細胞(例如哺乳動物細胞)之合適載體的方法為本技藝眾所周知。參見，例如Sambrook et al., Eds. “Molecular Cloning: A Laboratory Manual,” 2nd Ed., Cold Spring Harbor Press, 1989和Ausubel et al., Eds. “Current Protocols in Molecular Biology,” Current Protocols, 1993。

【0325】載體之非限制性實例包括質粒、轉座子(transposon)、黏粒和病毒載體(例如任何腺病毒載體(例如

pSV或pCMV載體)、腺相關病毒(AAV)載體、慢病毒載體和逆轉錄病毒載體)及任何Gateway®載體。載體可，例如包括足夠之用於表現的順式作用元件；其他用於表現之元件可由該宿主哺乳動物細胞提供或在活體外表現系統中。熟練之從業者將能夠選擇合適之載體和哺乳動物細胞來製造本文所描述之任何ACC。

【0326】於本文所描述之任何ACC的一些實施態樣中，該ACC可使用重組DNA技術以生物合成方式製造並在真核或原核物種中表現。

【0327】於一些實施態樣中，該載體包括編碼本文所描述之任何ACC的第一單體和第二單體之核酸。於一些實施態樣中，該載體為表現載體。

【0328】於一些實施態樣中，一對載體一起包括一對核酸，該核酸對一起編碼本文描述之任何ACC的第一單體和第二單體。於一些實施態樣中，該載體對為一對表達載體。

細胞

【0329】本文亦提供包括本文所描述之任何載體或載體組的宿主細胞，該宿主細胞包括本文所描述之任何核酸。

【0330】本文所描述之任何ACC和抗體可由任何細胞(例如哺乳動物細胞)產生。於一些實施態樣中，該宿主細胞為哺乳動物細胞(例如人細胞)、嚙齒動物細胞(例如小鼠

細胞、大鼠細胞、倉鼠細胞或天竺鼠細胞)或非人靈長類動物細胞。

【0331】將核酸和載體(例如本文所描述之任何載體或任何載體組)引入細胞之方法為本技藝已知。可用於將核酸引入細胞之方法的非限制性實例包括：脂質體轉染、轉染、磷酸鈣轉染、陽離子聚合物轉染、病毒轉導(例如腺病毒轉導、慢病毒轉導)、奈米顆粒轉染和電穿孔。

【0332】於一些實施態樣中，該引入步驟包括在細胞中引入載體(例如本文所描述之任何載體或載體組)，該載體包括編碼構成本文所描述之任何ACC和抗體之單體的核酸。

【0333】於本文所描述之任何方法的一些實施態樣中，該細胞可為真核細胞。如本文所使用之術語“真核細胞”係指具有獨特之膜結合核的細胞。該等細胞可包括，例如哺乳動物(例如嚙齒動物、非人靈長類動物或人)、昆蟲、真菌或植物細胞。於一些實施態樣中，該真核細胞為酵母細胞，諸如釀酒酵母。於一些實施態樣中，該真核細胞為高等真核生物，諸如哺乳動物、鳥類、植物或昆蟲細胞。哺乳動物細胞之非限制性實例包括中國倉鼠卵巢(CHO)細胞和人胚腎細胞(例如HEK293細胞)。

【0334】於一些實施態樣中，該細胞含有編碼本文所描述之任一ACC和抗體之第一單體和第二單體的核酸。於一些實施態樣中，該細胞含有一起編碼本文所描述之任何ACC和抗體的第一單體和第二單體的一對核酸。

產生可經活化之細胞介素構築體的方法

【0335】本發明提供產生本文所描述之任何ACC之方法，其包括：(a)在足以產生該ACC之條件下在液體培養基中培養本文所描述之任何重組宿主細胞；和(b)從該宿主細胞和/或該液體培養基中回收該ACC。

【0336】培養細胞之方法為本技藝所周知。可將細胞維持在活體外有利於細胞增殖、細胞分化和細胞生長之條件下。例如，可藉由將細胞(例如本文所描述之任何細胞)與細胞培養基接觸來培養細胞，該細胞培養基包括足以支持細胞存活力和生長之必需生長因子和補充劑。

【0337】於本文所描述之任何方法的一些實施例中，該方法進一步包括分離該經回收的ACC。分離方法之非限制性實例包括：硫酸銨沉澱、聚乙二醇沉澱、尺寸排阻色層分析法、配體親和力色層分析法、離子交換色層分析法(例如陰離子或陽離子)和疏水交互作用色層分析法。

【0338】於一些實施態樣中，該細胞可產生包括該CP1、該CM1、該PM2和該CM3之第一單體構築體的蛋白質部分及包括該CP2和該CM2，和可選擇地該PM2和該CM4之第二單體構築體的蛋白質部分，然後該蛋白質部分隨後分別與該DD1和該DD2部分結合。

【0339】本文所描述之組成物和方法可能涉及使用非還原或部分還原條件以允許在該二聚化結構域之間形成二硫鍵以形成和維持該ACC之二聚化。

【0340】於本文所描述之任何方法的一些實施態樣中，該方法進一步包括將該經分離之ACC配製成醫藥組成物。本技藝中已知多種不同配製劑且描述於本文中。本文所描述之任何經分離的ACC和/或抗體可配製成用於任何投予路徑(例如靜脈內、瘤內、皮下、皮內、口服(例如吸入)、經皮(例如局部)、經黏膜或肌肉內)。

【0341】本發明亦提供藉由本文所描述之任何方法產生的ACC。本發明亦提供包括藉由本文所描述之任何方法產生之任何ACC的組成物(例如醫藥組成物)。本發明亦提供套組，其包括至少一個本文所描述之任何組成物(例如醫藥組成物)的劑量。

治療方法

【0342】本發明提供用於治療個體之疾病(例如癌症(例如本文所描述之任何癌症)或傳染病)的方法，其包括對該個體投予治療有效量之本文所描述之任何ACC和抗體。

【0343】如本文所使用之術語“個體”係指任何哺乳動物。於一些實施態樣中，該個體為貓科動物(例如貓)、犬科動物(例如狗)、馬科動物(例如馬)、兔、豬、嚙齒動物(例如小鼠、大鼠、倉鼠或天竺鼠)、非人靈長類動物(例如猿猴(例如猴子(例如狒狒、狨猴)、或猿(例如黑猩猩、大猩猩、猩猩或長臂猿))或人。於一些實施態樣中，該個體為人。

【0344】於一些實施態樣中，該個體先前已被鑑定或

診斷為患有疾病(例如癌症(例如本文所描述之任何癌症))。

【0345】如本文所使用之術語“治療”包括減少該個體(例如本文所描述之任何個體)之疾病(例如癌症(例如本文所描述之任何癌症))的一或多種(例如1、2、3、4或5)症狀或病徵的嚴重性、頻率或數目。於其中該疾病為癌症的一些實施態樣中，治療導致患有癌症之個體中減少癌症生長、抑制癌症進展、抑制癌症轉移或降低癌症復發的風險。

【0346】於一些實施態樣中，本發明之方法和用途包括同時或依次投予(例如以任何順序連續投予)該ACC和PD-1/PD-L1路徑抑制劑。於一些實施態樣中，本發明之方法和用途包括分別投予該ACC和PD-1/PD-L1路徑抑制劑。於一些態樣中，投予治療劑量或亞治療劑量之各作用劑。於一些態樣中，本發明之方法和用途包括依次或同時投予該ACC和PD-1/PD-L1路徑抑制劑從而在該個體中實現加成或協同治療效果。如本文所使用之術語“組合”廣義地包括同時或依次投予且亦包括分別投予該活性物質或在相同之組成物或容器中投予該活性物質。特別地，組合使用之ACC可含有IL-2、IL-7、IL-8、IL-10、IL-12、IL-15、IL-21、IFNα、IFNβ、IFNγ、GM-CSF、TGF-β、LIGHT、GITR-L、CD40L、CD27L、4-1BB-L、OX40、OX40L。

【0347】於一些實施態樣中，本發明之方法和用途包括任何投予路徑，包括靜脈內、輸注、瘤內、皮下、腹膜

內、皮內、口服(例如吸入)、鼻內、透皮(例如局部)、透黏膜和/或肌肉內。

【0348】於本文所描述之任何方法的一些實施態樣中，該疾病為癌症。本文亦提供治療有此需要之個體(例如本文描述的或本技藝已知之任何示例性個體)的方法，該方法包括對該個體投予治療有效量之本文描述的任何ACC或本文描述的任何組成物(例如醫藥組成物)。

【0349】於該等方法之一些實施態樣中，該個體已被鑑定或診斷為患有癌症。該癌症之非限制性實例包括：實體瘤、血液腫瘤、肉瘤、骨肉瘤、膠質母細胞瘤、神經母細胞瘤、黑色素瘤、橫紋肌肉瘤、尤文肉瘤、骨肉瘤、B細胞腫瘤、多發性骨髓瘤、淋巴瘤(例如B細胞淋巴瘤、B-細胞非何杰金氏淋巴瘤、何杰金氏淋巴瘤、皮膚T細胞淋巴瘤)、白血病(例如髮樣細胞白血病、慢性淋巴細胞白血病(CLL)、急性髓細胞白血病(AML)、慢性髓細胞白血病(CML)、急性淋巴細胞白血病(ALL))、骨髓增生異常症候群(MDS)、卡波西氏肉瘤、視網膜母細胞瘤、胃癌、尿路上皮癌、肺癌、腎細胞癌、胃癌和食道癌、胰臟癌、前列腺癌、腦癌、結腸癌、骨癌、肺癌、乳癌、結腸直腸癌、卵巢癌、鼻咽腺癌、非小細胞肺癌(NSCLC)、鱗狀細胞頭頸癌、子宮內膜癌、膀胱癌、子宮頸癌、肝癌和肝細胞癌。於一些實施態樣中，該癌症為淋巴瘤。於一些實施態樣中，該淋巴瘤為伯基特氏淋巴瘤。於一些態樣中，該個體已被鑑定或診斷為患有家族性癌症症候群，諸如Li

Fraumeni症候群、家族性乳癌-卵巢癌(BRCA1或BRAC2突變)症候群，等。本發明之方法亦可用於治療非實體癌。示例性實體瘤包括各種不同器官系統之惡性腫瘤(例如肉瘤、腺癌和癌瘤)，諸如肺、乳房、淋巴、胃腸道(例如結腸)和泌尿生殖系統(例如腎、尿路上皮或睪丸腫瘤)管道、咽、前列腺和卵巢之惡性腫瘤。示例性腺癌包括結腸直腸癌、腎細胞癌、肝癌、肺之非小細胞癌和小腸癌。

【0350】國家癌症研究所描述之示例性癌症包括：成人急性淋巴母細胞白血病；兒童急性淋巴母細胞白血病；成人急性髓性白血病；腎上腺皮質癌；兒童腎上腺皮質癌；與AIDS相關之淋巴瘤；與AIDS相關之惡性腫瘤；肛門癌；兒童小腦星形細胞瘤；兒童腦部星形細胞瘤；肝外膽管癌；膀胱癌；兒童膀胱癌；骨癌、骨肉瘤/惡性纖維組織細胞瘤；兒童腦幹膠質瘤；成人腦瘤；兒童腦瘤，腦幹膠質瘤；兒童腦瘤，小腦星形細胞瘤；兒童腦瘤，腦星形細胞瘤/惡性膠質瘤；兒童腦瘤，室管膜瘤(ependymoma)；兒童腦瘤，髓母細胞瘤；兒童腦瘤，幕上原始神經外胚層腫瘤(supratentorial primitive neuroectodermal tumor)；兒童腦瘤，視覺路徑和下丘腦神經膠質瘤；兒童腦瘤(其他)；乳癌；乳癌和懷孕；兒童乳癌；男性乳癌；兒童支氣管腺瘤/類癌；兒童類癌腫瘤；胃腸道類癌腫瘤；腎上腺皮質癌；胰島細胞癌；不明原發性癌；原發性中樞神經系統淋巴瘤；兒童小腦星形細胞瘤；兒童腦星形細胞瘤/惡性膠質瘤；子宮頸癌；兒童癌

症；慢性淋巴細胞白血病；慢性髓細胞白血病；慢性骨髓增生性疾病；腱鞘透明細胞肉瘤；結腸癌；兒童結腸直腸癌；皮膚T細胞淋巴瘤；子宮內膜癌；兒童室管膜瘤；卵巢上皮癌；食道癌；兒童食管癌；尤因氏家族腫瘤；兒童顱外生殖細胞腫瘤；性腺外生殖細胞腫瘤；肝外膽管癌；眼癌，眼內黑色素瘤；眼癌，視網膜母細胞瘤；膽囊癌；胃癌；兒童胃癌；胃腸道類癌腫瘤；兒童顱外生殖細胞腫瘤；性腺外生殖細胞腫瘤；卵巢生殖細胞腫瘤；妊娠滋養細胞腫瘤；兒童腦幹膠質瘤；兒童視覺路徑和下丘腦膠質瘤；髮樣細胞白血病；頭頸癌；成人(原發性)肝細胞(肝)癌；兒童(原發性)肝細胞(肝)癌；成人何杰金氏淋巴瘤；兒童何杰金氏淋巴瘤；懷孕期間之何杰金氏淋巴瘤；下嘴癌；兒童下丘腦和視覺路徑膠質瘤；眼內黑色素瘤；胰島細胞癌(內分泌胰腺)；卡波西氏肉瘤；腎癌；喉癌；兒童喉癌；成人急性淋巴細胞白血病；兒童急性淋巴細胞白血病；成人急性髓系白血病；兒童急性髓系白血病；慢性淋巴細胞性白血病；慢性骨髓性白血病；髮樣細胞白血病；唇和口腔癌；成人(原發性)肝癌；兒童(原發性)肝癌；非小細胞肺癌；小細胞肺癌；成人急性淋巴母細胞白血病；兒童急性淋巴母細胞白血病；慢性淋巴細胞白血病；與AIDS相關之淋巴瘤；中樞神經系統(原發性)淋巴瘤；皮膚T細胞淋巴瘤；成人何杰金氏淋巴瘤；兒童何杰金氏淋巴瘤；懷孕期間之何杰金氏淋巴瘤；成人非何杰金氏淋巴瘤；兒童非何杰金氏淋巴瘤；妊娠期間之非何杰金氏淋巴

瘤；原發性中樞神經系統淋巴瘤；華氏巨球蛋白血症(Waldenstrom macroglobulinemia)；男性乳癌；成人惡性間皮瘤；兒童惡性間皮瘤；惡性胸腺瘤；兒童髓母細胞瘤；黑色素瘤；眼內黑色素瘤；默克爾(Merkel)細胞癌；惡性間皮瘤；隱匿性原發性轉移性鱗狀頸癌；兒童多發性內分泌腫瘤症候群；多發性骨髓瘤/漿細胞腫瘤；蕈樣肉芽腫；骨髓增生異常症候群；慢性骨髓性白血病；兒童急性骨髓性白血病；多發性骨髓瘤；慢性骨髓增生性疾病；鼻腔和鼻竇癌；鼻咽癌；兒童鼻咽癌；神經母細胞瘤；成人非何杰金氏淋巴瘤；兒童非何杰金氏淋巴瘤；妊娠期間之非何杰金氏淋巴瘤；非小細胞肺癌；兒童口腔癌；口腔和唇癌；口咽癌；骨肉瘤/惡性骨纖維組織細胞瘤；兒童卵巢癌；卵巢上皮癌；卵巢生殖細胞腫瘤；卵巢低度惡性潛在腫瘤；胰臟癌；兒童胰臟癌；胰島細胞胰臟癌；鼻旁竇和鼻腔癌；甲狀旁腺癌；陰莖癌；嗜鉻細胞瘤(pheochromocytoma)；兒童松果體和幕上原始神經外胚層腫瘤；腦下垂體瘤；漿細胞腫瘤/多發性骨髓瘤；胸膜肺母細胞瘤；懷孕和乳癌；妊娠和何杰金氏淋巴瘤；妊娠和非何杰金氏淋巴瘤；原發性中樞神經系統淋巴瘤；成人原發性肝癌；兒童原發性肝癌；前列腺癌；直腸癌；腎細胞(腎)癌；兒童腎細胞癌；腎盂和輸尿管移行細胞癌；視網膜母細胞瘤；兒童橫紋肌肉瘤；唾液腺癌；兒童唾液腺癌；尤因氏肉瘤家族腫瘤；卡波西氏肉瘤；骨頭肉瘤(骨肉瘤)/惡性骨纖維組織細胞瘤；兒童橫紋肌肉瘤；成人軟

組織肉瘤；兒童軟組織肉瘤；塞扎里症候群(Sezary syndrome)；皮膚癌；兒童皮膚癌；皮膚癌(黑色素瘤)；默克爾細胞皮膚癌；小細胞肺癌；小腸癌；成人軟組織肉瘤；兒童軟組織肉瘤；隱匿性原發性轉移性鱗狀細胞頸癌；胃(胃部)癌；兒童胃(胃部)癌；兒童幕上原始神經外胚層腫瘤；皮膚T細胞淋巴瘤；睪丸癌；兒童胸腺瘤；惡性胸腺瘤；甲狀腺癌；兒童甲狀腺癌；腎盂和輸尿管移行細胞癌；妊娠滋養細胞腫瘤；兒童之未知原發位點癌症；兒童之不尋常癌症；輸尿管和腎盂移行細胞癌；尿道癌；子宮肉瘤；陰道癌；兒童視覺路徑和下丘腦神經膠質瘤；外陰癌；華氏巨球蛋白血症；和威姆斯氏瘤(Wilm's Tumor)。

【0351】其他示例性癌症包括瀰漫性大B細胞淋巴瘤(DLBCL)和套細胞淋巴瘤(MCL)。

【0352】上述癌症之轉移亦可根據本文描述之方法治療或預防。

【0353】於一些實施態樣中，該等方法可導致個體之癌症的一或多種症狀之數量、嚴重性或頻率減少(例如與個體癌症治療前之一或多種症狀的數量、嚴重性或頻率相比較)。

【0354】於本文所描述之任何方法的一些實施態樣中，該疾病為傳染病。本發明之ACC和抗體亦可用於預防或治療感染和傳染性疾病。該ACC和抗體可用於刺激針對病原體、毒素和自身抗原的免疫反應。該ACC和抗體可用

於刺激針對致病病毒之免疫反應，包括，但不限於HIV、肝炎(A、B或C)病毒、皰疹病毒(例如VZV、HSV-1、HAV-6、HSV-II、CMV和愛潑斯坦-巴爾(Epstein-Barr)病毒)、腺病毒、流感病毒、黃病毒、埃可病毒、鼻病毒、克沙奇病毒、冠狀病毒、呼吸道融合病毒、腮腺炎病毒、輪狀病毒、麻疹病毒、風疹病毒、細小病毒、痘苗病毒、HTLV病毒、登革熱病毒、乳頭瘤病毒、軟疣病毒(molluscum virus)、脊髓灰質炎病毒、狂犬病病毒、JC病毒和蟲媒病毒性腦炎(arboviral encephalitis)病毒。該ACC和抗體亦可用於刺激針對由細菌、真菌、寄生蟲或其他病原體引起之感染的免疫反應。

【0355】於本文描述之任何方法的一些實施態樣中，該方法進一步包括對個體投予另外之治療劑(例如表2中所列之一或多種治療劑)。

表 2. 其他治療劑

抗體商品名(抗體名稱)	標靶
Raptiva™(依法珠單抗)	CD11a
Arzerra™(奧法木單抗)	CD20
Bexxar™(托西莫單抗)	CD20
Gazyva™(歐必努突單抗(obinutuzumab))	CD20
Ocrevus™ (歐克利珠單抗(ocrelizumab))	CD20
Rituxan™(利妥昔單抗(rituximab)	CD20
Zevalin™(替伊莫單抗(ibritumomab tiuxetan))	CD20
Adcetris™(布倫昔單抗(brentuximab vedotin))	CD30
Myelotarg™(吉妥珠單抗(Gemtuzumab))	CD33
Mylotarg™吉妥珠單抗奧佐米星(Gemtuzumab ozogamicin)	CD33
(瓦達妥昔單抗(vadastuximab))	CD33
(瓦達妥昔單抗他立林(vadastuximab talirine)	CD33
Campath™(阿崙單抗(Alemtuzumab))	CD52
Lemtrada™(阿崙單抗)	CD52
Tactress™(譚土維單抗(tamtuvetmab))	CD52
Soliris™(依庫珠單抗(eculizumab))	補體C5
Ultomiris™(拉武珠單抗(ravulizumab))	補體C5
(奧崙珠單抗(olendalizumab))	補體C5
Yervoy ™(易普利姆單抗(ipilimumab))	CTLA-4
(曲美木單抗(tremelimumab))	CTLA-4
Orencia™(阿巴西普(abatacept))	CTLA-4
Hu5c8	CD40L
(來托珠單抗(letolizumab))	CD40L
Rexomun™(伊托馬舒單抗(ertumaxomab))	CD3/Her2
Erbitux™(西妥昔單抗(cetuximab))	EGFR
Portrazza™(奈西妥木單抗(necitumumab))	EGFR
Vectibix™(帕尼單抗(panitumumab))	EGFR
CH806	EGFR
(迪帕西珠單抗(depatuxizumab))	EGFR
(迪帕西珠單抗馬杜汀(depatuxizumab mafodotin))	EGFR
(夫突西單抗：莫突西單抗(futuximab:modotuximab))	EGFR

ICR62(伊加珠單抗(imgatuzumab))	EGFR
(拉普妥昔單抗(laprituximab))	EGFR
(洛沙妥珠單抗(losatuxizumab))	EGFR
(洛沙妥珠單抗維多汀(losatuxizumab vedotin))	EGFR
mAb528	EGFR
(馬珠單抗(matuzumab))	EGFR
(尼妥珠單抗(nimotuzumab))	EGFR
(托莫妥昔單抗(tomuzotuximab))	EGFR
(沙路妥木單抗(zalutumumab))	EGFR
MDX-447	EGFR/CD64
(戴卡妥木單抗(adecatumumab))	EpCAM
Panorex™(依瑞科洛單抗(edrecolomab))	EpCAM
Vicinium™	EpCAM
Synagis™(帕利珠單抗(palivizumab))	RSV之F蛋白
ReoPro™(阿比昔單抗(abiciximab))	糖蛋白受體 IIb/IIIa
赫賽汀™(曲妥珠單抗(trastuzumab))	Her2
Herceptin™ Hylecta(曲妥珠單抗；透明質酸酶)	Her2
(曲妥珠單抗德路堤肯(trastuzumab deruxtecan))	Her2
(赫妥珠單抗維多汀(hertuzumab verdotin))	Her2
Kadcyla™(曲妥珠單抗伊坦辛(trastuzumab emtansine))	Her2
(馬妥西單抗(margetuximab))	Her2
(替米古珠單抗(timigutuzumab))	Her2
Xolair™(奧馬珠單抗(omalizumab))	IgE
(利吉利珠單抗(ligelizumab))	IgE
(非吉妥單抗(figitumumab))	IGF1R
(替普木單抗(teprotumumab))	IGF1R
Simulect™(巴利昔單抗(basiliximab))	IL2R
Zenapax™(達珠單抗(daclizumab))	IL2R
Zinbryta™(達珠單抗(daclizumab))	IL2R
Actemra™(托珠單抗(tocilizumab))	IL-6受體
Kevzara™(沙里路單抗(sarilumab))	IL-6受體
(渥巴利珠單抗(vobarilizumab))	IL-6受體
Stelara™(優特克單抗(ustekinumab))	IL-12/IL-23
Tysabri™(那他珠單抗(natalizumab))	整合素α4

(阿里路單抗(abrilumab))	整合素α4
	Jagged 1或Jagged 2
(法西單抗(fasinumab))	NGF
(富蘭單抗(fulranumab))	NGF
(坦尼珠單抗(tanezumab))	NGF
	缺口，例如缺口 1
匹地珠單抗(Pidilizumab)	Delta樣-1(PD-1路徑抑制劑)
Opdivo®(尼維魯單抗)	PD1
Keytruda®(派姆單抗)	PD1
Libtayo®(西米利單抗(cemiplimab))	PD1
BGB-A317(提利珠單抗)	PD1
PDR001(巴泰利珠單抗)	PD1
JNJ-63723283(賽特利單抗)	PD1
TSR042(多塔利單抗)	PD1
AGEN2034(巴西利單抗)	PD1
JS001(托巴利單抗)	PD1
IOBI308(西提利單抗)	PD1
BCD100(普戈利單抗)	PD1
CBT-501(吉諾單抗(genolimzumab))	PD1
ABBV181(布嘉利單抗)	PD1
AK105	PD1
BI-754091	PD1
INCSHR-1210	PD1
MEDI0680	PD1
MGA012	PD1
SHR-1210	PD1
Imfinzi™(德維魯單抗)	PD-L1
Tecentriq®(阿舒利珠單抗)	PD-L1
Bavencio®(阿維魯單抗)	PD-L1
KN035(英佛利單抗)	PD-L1
BMS936559(MDX1105)	PD-L1
BGBA 333	PD-L1
FAZ053	PD-L1
LY-3300054	PD-L1

SH-1316	PD-L1
AMP-224	PD-L2
(巴維妥昔單抗(bavituximab))	磷脂醯絲胺酸
huJ591	PSMA
RAV12	RAAG12
Prolia™(狄諾舒單抗(denosumab))	RANKL
GC1008(非索利單抗(fresolimumab))	TGFβ
Cimzia™(西托利珠單抗沛高(Certolizumab Pegol)	TNFα
Remicade™(英夫利昔單抗(infliximab))	TNFα
Humira™(阿達木單抗(adalimumab))	TNFα
Simponi™(戈利木單抗(golimumab))	TNFα
Enbrel™(依那西普(etanercept))	TNF-R
(馬帕木單抗(mapatumumab))	TRAIL-R1
Avastin™(貝伐珠單抗(bevacizumab))	VEGF
Lucentis™(雷珠單抗(ranibizumab))	VEGF
(溴魯西單抗(brolucizumab))	VEGF
(凡努西珠單抗(vanucizumab))	VEGF

組成物/套組

【0356】本文亦提供組成物(例如醫藥組成物)，該組成物包含本文所描述之任何ACC和/或抗體及一或多種(例如1、2、3、4或5種)醫藥上可接受之載體(例如本文所描述之任何醫藥上可接受之載體)、稀釋劑或賦形劑。

【0357】於一些實施態樣中，可將包含本文所描述之任何ACC和/或抗體之組成物(例如醫藥組成物)置於無菌小瓶或預先裝填之注射器中。

【0358】於一些實施態樣中，可將包含本文所描述之任何ACC和/或抗體之組成物(例如醫藥組成物)配製成用於不同投予路徑(例如靜脈內、皮下、肌肉內、腹膜內或瘤

內)。

【0359】於一些實施態樣中，本文所描述之任何醫藥組成物可包含一或多種緩衝液(例如中性緩衝之鹽水、磷酸鹽緩衝之鹽水(PBS)、胺基酸(例如甘胺酸)、一或多種碳水化合物(例如葡萄糖、甘露糖、蔗糖、葡聚醣或甘露醇)、一或多種抗氧化劑、一或多種螯合劑(例如EDTA或麩胱甘肽)、一或多種防腐劑和/或醫藥上可接受之載體(例如抑菌水、PBS或生理鹽水)。

【0360】如本文所使用之短語“醫藥上可接受之載體”係指與藥物投予相容之任何和所有溶劑、分散介質、塗層、抗菌劑、抗微生物劑、等張劑和吸收延遲劑，等。合適之載體包括，但不限於：水、鹽水、林格氏溶液、右旋糖溶液和約5%之人血清白蛋白。

【0361】於本文描述之任何醫藥組成物的一些實施態樣中，本文描述之任何ACC和/或抗體係與防止從身體快速排除之載體(例如緩釋和控釋配製劑，包括植入物和微囊化之遞送系統)一起製備。可使用可生物降解、生物相容之聚合物，例如乙烯醋酸乙烯酯、聚酐、聚乙醇酸、膠原蛋白、聚原酸酯和聚乳酸。用於製備該等醫藥組成物和配製劑之方法對本技藝之技術熟習人士而言是顯明易知的。

【0362】本發明亦提供套組，該套組包括本文所描述之任何ACC和/或抗體、包括本文所描述之任何ACC和/或抗體的任何組成物、或包括本文所描述之任何ACC和/或

抗體的任何醫藥組成物。本發明亦提供除了本文所描述之ACC和/或抗體之外還包括一或多種選自表2之第二治療劑的套組。該第二治療劑可在與該ACC和/或抗體分開之劑量投予形式中提供。或者，可將該第二治療劑與該ACC和/或抗體一起配製。

【0363】本文所描述之任何套組可包括使用本文所描述之任何組成物(例如醫藥組成物)和/或任何ACC和/或抗體的用法說明。於一些實施態樣中，該套組可包括用於執行本文所描述之任何方法的指示。於一些實施態樣中，該套組可包括至少一個本文所描述之任何組成物(例如醫藥組成物)的劑量。於一些實施態樣中，該套組可提供用於投予本文所描述之任何醫藥組成物的注射器。

抗PD1序列

【0364】於一些實施態樣中，該抗PD-1(於某些態樣中其可配置為可經活化之抗體，而於其他態樣中不配置為可經活化之抗體)包含如下列所示之序列：

【0365】m136-M13-MHC723 mIgG1/K MHC723HC.1重鏈可變區胺基酸序列：

EVKLVESGGGLVKPGGSLKLSCAASGFTFSGYAMSWVRQTPAKRLEWV AYISNSGGNAHYPDSVKGRFTISRDNAKNTLYLQMSSLRSEDTAMYYCTREDYG TSPFVYWGQGTLVTVSA (SEQ ID NO: 610).

【0366】MHC723LC.3 輕鏈可變區胺基酸序列：

DIVLTQSPASLAVSLGQRTTISCRASESVDNYGISFMNWFQQKPGQPPKLL IYAASNQGSGVPARFSGSGSGTDFSLNIHPMEEDDTAVYFCQQSKDVPWTFGGG TKLEIR (SEQ ID NO: 615).

【0367】MHC725HC.2重鏈可變區胺基酸序列：

EVQLQQSGPELVKPGDSVKMSCKASGYTFTDYYMDWVKQSHGKSLEWI GYIYPKNGGSSYNQKFKGKATLTVDKSSSTAYMELHSLTSEDSAVYYCARKVV ATDYWGQGTTLTVSS (SEQ ID NO: 611).

【0368】MHC725LC.2輕鏈可變區胺基酸序列：

DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSSNQKNYLAWYQQKPGQSPKLLIF WASIRESGVPDRFTGSGSGTDFTLTISSVKAEDRAVYYCQQCDSYPWTFGGGTK LEIK (SEQ ID NO: 616).

【0369】MHC728HC.4重鏈可變區胺基酸序列：

EVKLVESGGGLVKPGGSLKLSCAASGFTFSNYAMSWVRQTPAKRLEWV AYISNGGGDTHYPDSLKGRFTVSRDNAKNTLYLQMSSLKSEDTAMYYCARENY GTSPFVYWGQGTLVTVSA (SEQ ID NO: 612).

【0370】MHC728LC.2輕鏈可變區胺基酸序列：

DIVLTQSPASLAVSLGQRATISCRASESVDNYGISFMNWFQQKPGQPPKLL IYAASNQGSGVPARFSGSGSGTDFSLNIHPMEEDDTAMYFCQQSKDVPWTFGGG TKLEIK (SEQ ID NO: 617).

【0371】MHC729HC.1重鏈可變區胺基酸序列：

EVQLVESGGGLVKSGGSLKLSCAHSGFSFSSYDMSWVRQTPAKRLEWVA TISGGGRYTYYPDSVKGRFTISRDNAKNTLYLQMSGLRSEDTAMYYCASNYYGF DYWGQGTTLTVSS (SEQ ID NO: 613).

【0372】MHC729LC.3輕鏈可變區胺基酸序列：

DIVMTQSHKFMSTSVGDRVSITCKASQDVGTAVAWYQQKPGQSPKLLIY WASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPWTFGGGTK LEIK (SEQ ID NO: 618).

【0373】MHC724HC.3重鏈可變區胺基酸序列：

KVMLVESGGDLVKPGGSLKLSCAASGFTFSSYGMSWVRQTPEKRLEWV ATISGGGRDIYYADTVKGRFTISRDNAKNTLYLQMSSLRSEDTALYFCARLYLGF DYWGQGTTLTVSS (SEQ ID NO: 614).

【0374】MHC724LC.1輕鏈可變區胺基酸序列：

DIQMTQSPASQSASLGESVTITCLASQTIGTWLAWYQQKPGKSPQLLIYAA TSLADGVPSRFSG SGSGTKFSFKISSLQAEDFVSYYCQQLYSIPWTFGGGTKLEIK (SEQ ID NO: 619).

【0375】PD-1 A Hv重鏈可變區胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWV AYISNSGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYG TSPFVYWGQGTLVTVSS (SEQ ID NO: 620).

【0376】PD-1 Ab Hv重鏈可變區胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWV SYISNSGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKEDYG TSPFVYWGQGTLVTVSS (SEQ ID NO: 621).

【0377】PD-1 Ae Hv重鏈可變區胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWV AYISNSGGNTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREDYG TSPFVYWGQGTLVTVSS (SEQ ID NO: 622).

【0378】PD-1 Af Hv重鏈可變區胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWV AYISNSGGNTHYADSLKGRFTVSRDNSKNTLYLQMNSLRAEDTAVYYCAREDY GTSPFVYWGQGTLVTVSS (SEQ ID NO: 623).

【0379】PD-1 Ba Hv重鏈可變區胺基酸序列：

QVQLVQSGAEVKKPGASVKMSCKASGYTFTDYYMDWVRQAPGQGLEW IGYIYPKNGGSSYAQKFQGRATLTVDTSTSTAYMELSSLRSEDTAVYYCARKVV ATDYWGQGTLLTVSS (SEQ ID NO: 624).

【0380】PD-1 Bb Hv重鏈可變區胺基酸序列：

QVQLVQSGAEVKKPGASVKMSCKASGYTFTDYYMDWVRQAPGQGLEW IGYIYPKNGGSSYAQKFQGRATLTVDKSTSTAYMELSSLRSEDTAVYYCARKVV ATDYWGQGTLLTVSS (SEQ ID NO: 625).

【0381】PD-1 C Hv重鏈可變區胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWV AYISNGGGDTHYADSLKGRFTVSRDNSKNTLYLQMNSLRAEDTAVYYCARENY GTSPFVYWGQGTLVTVSS (SEQ ID NO: 626).

【0382】PD-1 Ca Hv重鏈可變區胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWV AYISNQGGDTHYADSLKGRFTVSRDNSKNTLYLQMNSLRAEDTAVYYCARENY GTSPFVYWGQGTLVTVSS (SEQ ID NO: 627).

【0383】PD-1 D Hv重鏈可變區胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAHSGFSFSSYDMSWVRQAPGKGLEWVA TISGGGRYTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASNYYGF DYWGQGTLLTVSS (SEQ ID NO: 628).

【0384】PD-11.0 Lv輕鏈可變區胺基酸序列：

DIQLTQSPSSLSASVGDRVTITCRASESVDNYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 629).

【0385】PD-11.1 Lv輕鏈可變區胺基酸序列：

DIQLTQSPSSLSVSVGDRATITCRASESVDNYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 630).

【0386】Lv輕鏈可變區胺基酸序列：

DIQLTQSPSSLSASVGDRVTITCRASESVDQYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 631).

【0387】PD-11.4 Lv輕鏈可變區胺基酸序列：

DIQLTQSPSSLSASVGDRVTITCRASESVDSYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 632).

【0388】PD-11.5 Lv輕鏈可變區胺基酸序列：

DIQLTQSPSSLSASVGDRVTITCRASESVDAYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 633).

【0389】PD-11.6 Lv輕鏈可變區胺基酸序列：

DIQLTQSPSSLSASVGDRVTITCRASESVDNYGISFMNWFQQKPGKAPKLL IYAASDQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 634).

【0390】PD-11.7 Lv輕鏈可變區胺基酸序列：

DIQLTQSPSSLSVSVGDRATITCRASESVDAYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 635).

【0391】PD-11.9 Lv輕鏈可變區胺基酸序列：

DIQLTQSPSSLSASVGDRVTITCRASESVDAYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KVEIK (SEQ ID NO: 636).

【0392】PD-11.10 Lv輕鏈可變區胺基酸序列：

DIQLTQSPSSLSASVGDRVTITCRASESVDAYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPYTFGQGT KLEIK (SEQ ID NO: 637).

【0393】PD-12 Lv輕鏈可變區胺基酸序列：

DIQMTQSPSSLSASVGDRVTMTCKSSQSLLYSSNQKNYLAWYQQKPGKA PKLLIFWASIRESGVPSRFSGSGSGTDFTLTISSVQPEDFATYYCQQSDSYPWTFG QGTKLEIK (SEQ ID NO: 638).

【0394】PD-14 Lv輕鏈可變區胺基酸序列：

DIQMTQSPSSLSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIY WASTRHTGVPSRFSGSGSGTDFTLTISSVQPEDFATYYCQQYSSYPWTFGQGTKL EIK (SEQ ID NO: 639).

【0395】κ恆定區胺基酸序列：

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC (SEQ ID NO: 640).

【0396】hIgG4 S228P胺基酸序列：

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPP CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL SLGK (SEQ ID NO: 641).

【0397】於一些實施態樣中，該抗PD1 CDR序列包含下表中列出之序列。

表3

VH		
CDRl (SEQ ID NO)	CDR2 (SEQ ID NO)	CDR3 (SEQ ID NO)
GFTFSGYAMS (487)	YISNSGGNAH (488)	EDYGTSPFVY (489)
GYTFTDYYMD (642)	YIYPKNGGSS (646)	KVVATDY (652)
GFTFSNYAMS (643)	YISNGGGDTH (647)	ENYGTSPFVY (653)
GFSFSSYDMS (644)	TISGGGRYTY (648)	NYYGFDY (654)
GFTFSSYGMS (645)	TISGGGRDIY (649)	LYLGFDY (655)
GFTFSGYAMS (487)	YISNSGGNAH (488)	EDYGTSPFVY (489)
GFTFSGYAMS (487)	YISNSGGNAH (488)	EDYGTSPFVY (489)
GFTFSGYAMS (487)	YISNSGGNTH (650)	EDYGTSPFVY (489)
GFTFSGYAMS (487)	YISNSGGNTH (650)	EDYGTSPFVY (489)
GYTFTDYYMD (487)	YIYPKNGGSS (646)	KVVATDY (652)
GYTFTDYYMD (487)	YIYPKNGGSS (646)	KVVATDY (652)
GFTFSNYAMS (643)	YISNGGGDTH (647)	ENYGTSPFVY (653)
GFTFSNYAMS (643)	AYISNQGGDTH (651)	ENYGTSPFVY (653)
GFSFSSYDMS (644)	TISGGGRYTY (648)	NYYGFDY (654)

表4

VL		
CDRl (SEQ IDNO)	CDR2 (SEQ IDNO)	CDR3 (SEQ IDNO)
RASESVDNYGISFMN (656)	AASNQGS (691)	QQSKDVPWT (492)
KSSQSLLYSSNQKNY L(657)	WASIRES (664)	QQCDSYPWT (667)
RASESVDNYGISFMN (656)	AASNQGS (691)	QQSKDVPWT (492)
KASQDVGTAVA (658)	WASTRHT (665)	QQYSSYPWT (668)
LASQTIGTWLA (659)	AATSLAD (666)	QQLYSIPWT (669)
RASESVDNYGISFMN (660)	AASNQGS (691)	QQSKDVPWT (492)
RASESVDQYGISFM N (661)	WASIRES (664)	QQCDSYPWT (667)
RASESVDSYGISFM N (662)	WASTRHT (665)	QQYSSYPWT (668)
RASESVDAYGISFM N (490)		QQLYSIPWT (669)
KSSQSLLYSSNQKN YLA (663)		QQSDSYPWT (670)

【0398】於一些實施態樣中，該PD-1路徑抑制劑為包含WO2017011580A2之表7至9中之一或多個序列的抗體。於一些實施態樣中，該PD-1路徑抑制劑包含可經活化之PD-1抗體，該可經活化之PD-1抗體包含：(i)包含WO2017011580A2之表7至9中之一或多個序列的抗體或其抗原結合片段(AB)；(ii)掩蔽部分(MM)，其當該可經活化之抗體處於未裂解狀態時抑制該AB與PD-1結合；及(iii)與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶的

受質之多肽；及可選擇地第一連接肽和/或第二連接肽。

【0399】上述任何多肽均可與人免疫球蛋白恆定區組合以產生完整人IgG(包括IgG1、IgG2、IgG4)或與突變之恆定區組合以產生功能改變之人IgG(諸如IgG1 N297A、IgG1 N297Q或IgG4 S228P)。上述多肽不受特定組合之限制且包括與任何受質序列匹配之任何掩蔽物序列，該受質序列與任何VL序列匹配、該VL序列與任何VH序列匹配。除了該受質序列之外，可使用本發明揭示之任何CM。

抗PD-L1序列

【0400】於一些實施態樣中，該抗PD-L1(其於某些態樣中可配置為可經活化之抗體，而於其他態樣中不配置為可經活化之抗體)包含如下列所示之序列：

【0401】輕鏈可變區胺基酸序列：

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYYA STLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTFGQGTKVEIK R (SEQ ID NO: 671).

【0402】輕鏈可變區胺基酸序列：

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTFGGGTKVEIK R (SEQ ID NO: 672).

【0403】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGQ SRPGFDYWGQGTLVTVSS (SEQ ID NO: 673).

【0404】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGQ SWPGFDYWGQGTLVTVSS (SEQ ID NO: 674).

【0405】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGQ SFPGFDYWGQGTLVTVSS (SEQ ID NO: 675).

【0406】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF DYWGQGTLVTVSS (SEQ ID NO: 676).

【0407】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAG YDYWGQGTLVTVSS (SEQ ID NO: 677).

【0408】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSKGF DYWGQGTLVTVSS (SEQ ID NO: 678).

【0409】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWKQGIVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTV (SEQ ID NO: 679).

【0410】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRNGIVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 680).

【0411】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS DIWKQGMVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGF DYWGQGTLVTVSS (SEQ ID NO: 681).

【0412】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRQGLATAYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 682).

【0413】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS EIVATGILTSYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFDY WGQGTLVTVSS (SEQ ID NO: 683).

【0414】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIGRQGLITVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFDY WGQGTLVTVSS (SEQ ID NO: 684).

【0415】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWYQGLVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 685).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS DIWKQGFATADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 686).

【0416】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWKQGIVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 687).

【0417】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRQGLATAYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 688).

【0418】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF DYWGQGTLVTVSS (SEQ ID NO: 689).

【0419】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAG YDYWGQGTLVTVSS (SEQ ID NO: 690).

【0420】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSKGF DYWGQGTLVTVSS (SEQ ID NO: 691).

【0421】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWYQGLVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAA FDYWGQGTLVTVSS (SEQ ID NO: 692).

【0422】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWYQGLVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAG YDYWGQGTLVTVSS (SEQ ID NO: 693).

【0423】重鏈可變區胺基酸序列：

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWYQGLVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSKG FDYWGQGTLVTVSS (SEQ ID NO: 694).

【0424】於一些實施態樣中，該抗PD-L1 CDR序列包含下表中列出之序列。

表5

VH		
CDR1 (SEQ ID NO)	CDR2 (SEQ ID NO)	CDR3 (SEQ ID NO)
SYAMS (SEQ ID NO: 538)	DITASGQRTTYADS (SEQ IDNO: 695)	SKAIFDY (SEQ ID NO: 696)
	SINKDGHYTSYADS (SEQ IDNO: 697)	NLDEFDY (SEQ ID NO: 698)
	SIMATGAGTLYADS (SEQ IDNO: 699)	DGAGEDY (SEQ ID NO: 700)
	TITSSGAATYYADS (SEQ IDNO: 701)	NYTGFDY (SEQ ID NO: 702)
	SIYSTGGATAYADS (SEQ ID NO: 703)	SSAGFDY (SEQ ID NO: 704)
	SSIYSTGGATAYADS (SEQ IDNO: 705)	SSAGOSRPGFDY (SEQ ID NO: 706)
	SSIWKQGIVTVYDS (SEQ ID NO: 707)	SSAGQSWPGFDY (SEQ ID NO: 708)
	SSIWRNGIVTVYDS (SEQ ID NO: 709)	SSAGQSFPGFDY (SEQ IDNO: 710)
	SDIWKQGMVTVYDS (SEQ ID NO: 711)	WSAAFDY (SEQ ID NO: 540)
	SSIWROGLATAYDS (SEQ IDNO: 712)	WSAGYDY (SEQ ID NO: 713)

	SEIVATGILTSYDS (SEQ IDNO: 714)	WSKGFDY (SEQ ID NO: 715)
	SSIGRQGLITVYDS (SEQ ID NO: 716)	
	SSIWYQGLVTVYD (SEQ ID NO: 717)	
	SDIWKQGFATADS (SEQ ID NO: 718)	
	SSIWRNGIVTVYADS (SEQ ID NO: 539)	
	SSIWYQGLVTVYADS (SEQ ID NO: 719)	

表6

VL		
CDRl (SEQ ID NO)	CDR2 (SEQ ID NO)	CDR3 (SEQID NO)
RASQSISSYLN (SEQ ID NO: 535)	KASRLOS (SEQ ID NO: 720)	RALKPVT (SEQ ID NO: 721)
	AASSLQS (SEQ ID NO: 536)	SYSTPNT (SEQ IDNO: 722)
	SASQLQS (SEQ ID NO: 723)	ANSRPST (SEQ ID NO: 724)
	NASSLOS (SEQ ID NO: 725)	YPYGPG (SEQ IDNO: 726)
	YASTLQS (SEQ ID NO: 727)	DNGYPST (SEQ ID NO: 537)

【0425】上述任何多肽均可與人免疫球蛋白恆定區組合以產生完整人IgG(包括IgG1、IgG2、IgG4)或與突變之恆定區組合以產生功能改變之人IgG(諸如IgG1 N297A、IgG1 N297Q或IgG4 S228P)。上述多肽不受特定組合之限制且包括與任何受質序列匹配之任何掩蔽物序列，該受質序列與任何VL序列匹配、該VL序列與任何VH序列匹配。除了該受質序列之外，可使用本發明揭示之任何CM。

【0426】作為非限制性實例，間隔子序列和掩蔽物可與受質組合並與人κ恆定結構域組合以產生SEQ ID NO：496；或者該掩蔽物可與受質組合並與人κ恆定結構域組合以產生SEQ ID NO：728。此外，VH結構域可與人免疫球蛋白重鏈恆定結構域組合以產生人IgG1(SEQ ID NO：729)、突變之人IgG4 S228P(SEQ ID NO：485)、突變之人IgG1 N297A(SEQ ID NO：730)或突變之人IgG1 N297Q(SEQ ID NO：731)。共同表現將產生可經活化之抗體。

【0427】具有間隔子之輕鏈序列：

[QGQSGS][GIALCPSHFCQLPQTGGGSSGGSGGSGGISSGLLSGRSDNHGG SDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC] (SEQ ID NO: 496).

【0428】不具有間隔子之輕鏈序列：

GIALCPSHFCQLPQTGGGSSGGSGGSGGISSGLLSGRSDNHGGSDIQMTQS
PSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTFGGGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 728).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS
SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO: 729).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS
SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF
DYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH
NHYTQKSLSLSLG (SEQ ID NO: 485).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS
SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO: 730).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS
SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO: 731).

【0429】於一些實施態樣中，該PD-L1路徑抑制劑為包含WO2016149201A2之表15至17中的一或多個序列之抗體。於一些實施態樣中，該PD-L1路徑抑制劑包含可經活化之PD-L1抗體，該可經活化之PD-L1抗體包含：(i)包含WO2016149201A2之表15至17中的一或多個序列之抗體或其抗原結合片段(AB)；(ii)掩蔽部分(MM)，其當該可經活化之抗體處於未裂解狀態時抑制該AB與PD-L1結合；及(iii)與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶的受質之多肽；及可選擇地第一連接肽和/或第二連接肽。

【0430】於一些實施態樣中，該PD1/PD-L1路徑抑制劑為包含下列表7中之一或多個序列的抗體。於一些實施態樣中，該PD1/PD-L1路徑抑制劑包含可經活化之PD-1抗體或可經活化之PD-L1抗體，該可經活化之PD-1抗體或可經活化之PD-L1抗體包含：(i)包含下列表7中之一或多個序列的抗體或其抗原結合片段(AB)；(ii)掩蔽部分(MM)，其當該可經活化之抗體處於未裂解狀態時抑制該AB與PD-

1或PD-L1結合；及(iii)與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶的受質之多肽；及可選擇地第一連接肽和/或第二連接肽。

表7. PD-1/PD-L1 路徑抑制劑

肽類	序列	**SEQ ID NOs**
尼維魯單抗 VH_CDR1	NSGMH	732
尼維魯單抗 VH_CDR2	VIWYDGSKRYYADSVKG	733
尼維魯單抗 VH_CDR3	NDDY	734
尼維魯單抗 VL_CDR1	RASQSVS SYLA	735
尼維魯單抗 VL_CDR2	DASNRAT	736
尼維魯單抗 VL_CDR3	QQSSNWPRT	529
尼維魯單抗重鏈 VH 區下方劃線	QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK	737
尼維魯單抗輕鏈 VL 區下方劃線	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ SSNWPRTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT	738

	LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	
派姆單抗 VH_CDR1	NYYMY	739
派姆單抗 VH_CDR2	GINPSNGGTNFNEKFKN	740
派姆單抗 VH_CDR3	RDYRFDMGFDY	741
派姆單抗 VL_CDR1	RASKGVSTSGYSYLH	742
派姆單抗 VL_CDR2	LASYLES	743
派姆單抗 VL_CDR3	QHSRDLPLT	534
派姆單抗重鏈 VH 區下方劃線	QVQLVQSGVE VKKPGASVKV SCKASGYTFT NYYMYWVRQA PGQGLEWMGG INPSNGGTNF NEKFKNRVTL TTDSSTTTAY MELKSLQFDD TAVYYCARRD YRFDMGFDYW GQGTTVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK	744

派姆單抗輕鏈 VL 區下方劃線	EIVLTQSPAT LSLSPGERAT LSCRASKGVS TSGYSYLHWY QQKPGQAPRL LIYLASYLES GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRDLPL TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC	745
提利珠單抗 VH_CDR1	SYGVH	746
提利珠單抗 VH_CDR2	VIYADGSTNYNPSLKS	747
提利珠單抗 VH_CDR3	AYGNYWYIDV	748
提利珠單抗 VL_CDR1	KSSESVSNDVA	749
提利珠單抗 VL_CDR2	YAFHRFT	750
提利珠單抗 VL_CDR3	HQAYSSPYT	751
提利珠單抗重鏈 VH 區下方劃線	QVQLQESGPG LVKPSETLSL TCTVSGFSLT SYGVHWIRQP PGKGLEWIGV IYADGSTNYN PSLKSRVTIS KDTSKNQVSL KLSSVTAADT AVYYCARAYG NYWYIDVWGQ GTTVTVSSAS TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTKTYT CNVDHKPSNT KVDKRVESKY GPPCPPCPAP PVAGGPSVFL FPPKPKDTLM ISRTPEVTCV VVAVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVVHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP	752

	PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK	
提利珠單抗輕鏈 VL 區下方劃線	DIVMTQSPDS LAVSLGERAT INCKSSESVS NDVAWYQQKP GQPPKLLINY AFHRFTGVPD RFSGSGYGTD FTLTISSLQA EDVAVYYCHQ AYSSPYTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	753
巴泰利單抗 VH_CDR1	TYWMH	754
巴泰利單抗 VH_CDR2	NIYPGTGGSNFDEKFKN	755
巴泰利單抗 VH_CDR3	WTTGTGAY	756
巴泰利單抗 VL_CDR1	KSSQSLLDSGNQKNFLT	757
巴泰利單抗 VL_CDR2	WASTRES	758
巴泰利單抗 VL_CDR3	QNDYSYPYT	759
巴泰利單抗重鏈 VH 區下方劃線	EVQLVQSGAE VKKPGESLRI SCKGSGYTFT TYWMHWVRQA TGQGLEWMGN IYPGTGGSNF DEKFKNRVTI TADKSTSTAY MELSSLRSED TAVYYCTRWT TGTGAYWGQG TTVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE	760

	FLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLG	
巴泰利單抗輕鏈 VL 區下方劃線	EIVLTQSPAT LSLSPGERAT LSCKSSQSLL DSGNQKNFLT WYQQKPGQAP RLLIYWASTR ESGVPSRFSG SGSGTDFTFT ISSLEAEDAA TYYCQNDYSY PYTFGQGTKV EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC EVTHQGLSSP VTKSFNRGEC	761
卡利珠單抗 VH_CDR1	SYMMS	762
卡利珠單抗 VH_CDR2	TISGGGNTYYPDSVKG	763
卡利珠單抗 VH_CDR3	QLYYFDY	764
卡利珠單抗 VL_CDR1	LASQTIGTWLT	765
卡利珠單抗 VL_CDR2	TATSLAD	766
卡利珠單抗 VL_CDR3	QQVYSIPWT	767
卡利珠單抗重鏈	EVQLVESGGGLVQPGGSLRLSCAASGFTF SSYMMSWVRQAPGKGLEWVATISGGGANTYYP DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARQLYYFDYWGQGTTVTVSSASTKGPSVFPL	768

VH 區下方劃線	APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKT YTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK	
卡利珠單抗輕鏈 VL 區下方劃線	DIQMTQSPSSLSASVGDRVTITCLASQTIGT WLTWYQQKPGKAPKLLIYT ATSLADGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQVYSIPWTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQG LSSPVTKSFNRGEC	769
賽特利單抗 VH_CDR1	SYAIS	770
賽特利單抗 VH_CDR2	GIIPIFDTANYAQKFQG	771
賽特利單抗 VH_CDR3	PGLAAAYDTGSLDY	772
賽特利單抗 VL_CDR1	RASQSVRSYLA	773
賽特利單抗 VL_CDR2	DASNRAT	774
賽特利單抗 VL_CDR3	QQRNYWPLT	775
賽特利單抗重鏈 VH 區下方劃線	QVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAISWVRQAPGQGLEWMGGIIPIFDTANYAQ KFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARPGLAAAYDTGSLDYWGQGTLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP	776

	PCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLGK	
賽特利單抗輕鏈 VL 區下方劃線	EIVLTQSPATLSLSPGERATLSCRASQSVRS YLAWYQQKPGQAPRLLIYDASNRATGIPARFSGS GSGTDFTLTISSLEPEDFAVYYCQQRNYWPLTFG QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	777
巴西利單抗 VH_CDR1	SYGMH	778
巴西利單抗 VH_CDR2	VIWYDGSNKYYADSVKG	779
巴西利單抗 VH_CDR3	NGDH	780
巴西利單抗 VL_CDR1	RASQSVSSNLA	781
巴西利單抗 VL_CDR2	GASTRAT	782
巴西利單抗 VL_CDR3	QQYNNWPRT	783
巴西利單抗重鏈 VH 區下方劃線	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYGMHWVRQAPGKGLEWVAVIWYDGSNKYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCASNGDHWGQGTLVTVSSASTKGPSVFPLAP CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYT CNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF	784

	FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLGK	
巴西利單抗輕鏈 VL 區下方劃線	EIVMTQSPATLSVSPGERATLSCRASQSVS SNLAWYQQKPGQAPRLLIYGASTRATGIPARFSG SGSGTEFTLTISSLQSEDFAVYYCQQYNNWPRTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	785
多塔利單抗 VH_CDR1	GFTFSSYDMS	786
多塔利單抗 VH_CDR2	TISGGGSYTY	787
多塔利單抗 VH_CDR3	PYYAMDY	788
多塔利單抗 VL_CDR1	KASQDVGTAVA	789
多塔利單抗 VL_CDR2	WASTLHT	790
多塔利單抗 VL_CDR3	QHYSSYPWT	791
多塔利單抗重鏈 VH 區下方劃線	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYDMSWVRQAPGKGLEWVSTISGGGSYTYYQD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CASPYYAMDYWGQGTTVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTY TCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQE DPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL	792

	VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLGK	
多塔利單抗輕鏈 VL 區下方劃線	DIQLTQSPSFLSAYVGDRVTITCKASQDVG TAVAWYQQKPGKAPKLLIYWASTLHTGVPSRFS GSGSGTEFTLTISSLQPEDFATYYCQHYSSYPWTF GQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	793
普戈利單抗 VH_CDR1	SSYWMY	794
普戈利單抗 VH_CDR2	AIDTGGGRTYYADSVKG	795
普戈利單抗 VH_CDR3	DEGGGTGWGVLKDWPYGLDA	796
普戈利單抗 VL_CDR1	GGNNIGSKNVH	797
普戈利單抗 VL_CDR2	RDSNRPS	798
普戈利單抗 VL_CDR3	QVWDSSTAV	799
普戈利單抗重鏈 VH 區下方劃線	QVQLVQSGGGLVQPGGSLRLSCAASGFTF SSYWMYWVRQVPGKGLEWVSAIDTGGGRTYYA DSVKGRFAISRVNAKNTMYLQMNSLRAEDTAV YYCARDEGGGTGWGVLKDWPYGLDAWGQGTL VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR VEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW	800

	LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
普戈利單抗輕鏈 VL 區下方劃線	QPVLTQPLSVSVALGQTARITCGGNNIGSK NVHWYQQKPGQAPVLVIYRDSNRPSGIPERFSGS NSGNTATLTISRAQAGDEADYYCQVWDSSTAVF GTGTKLTVLQRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC	801
沙山利單抗 VH_CDR1	SYWIN	802
沙山利單抗 VH_CDR2	NIYPGSSLTNYNEKFKN	803
沙山利單抗 VH_CDR3	LSTGTFAY	804
沙山利單抗 VL_CDR1	KSSQSLWDSGNQKNFLT	805
沙山利單抗 VL_CDR2	WTSYRES	806
沙山利單抗 VL_CDR3	QNDYFYPHT	807
沙山利單抗重鏈 VH 區下方劃線	QVQLVQSGAEVKKPGASVKVSCKASGYT FTSYWINWVRQAPGQGLEWMGNIYPGSSLTNYN EKFKNRVTMTRDTSTSTVYMELSSLRSEDTAVY YCARLSTGTFAYWGQGTLVTVSSASTKGPSVFPL APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKT YTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEF LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD	808

	GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLGK	
沙山利單抗輕鏈 VL 區下方劃線	DIVMTQSPDSLAVSLGERATINCKSSQSLW DSGNQKNFLTWYQQKPGQPPKLLIYWTSYRESG VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQND YFYPHTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	809
辛布利單抗 VH_CDR1	STTYYWV	810
辛布利單抗 VH_CDR2	SISYSGSTYYNPSLKS	811
辛布利單抗 VH_CDR3	HLGYNGRYLPFDY	812
辛布利單抗 VL_CDR1	TGTSSDVGFYNYVS	813
辛布利單抗 VL_CDR2	DVSNRPS	814
辛布利單抗 VL_CDR3	SSYTSISTWV	815
辛布利單抗重鏈 VH 區下方劃線	QLQLQESGPG LVKPSETLTL TCTVSADSIS STTYYWVWIR QPPGKGLEWI GSISYSGSTY YNPSLKSRVT VSVDTSKNQF SLKLNSVAAT DTALYYCARH LGYNGRYLPF DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT VLHQDWLNGK EYKCKVSNKG	816

	LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK	
辛布利單抗輕鏈 VL 區下方劃線	QSALTQPASV SGSPGQSITI SCTGTSSDVG FYNYVSWYQQ HPGKAPELMI YDVSNRPSGV SDRFSGSKSG NTASLTISGL QAEDEADYYC SSYTSISTWV FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS	817
阿舒利珠單抗 VH_CDR1	DSWIH	818
阿舒利珠單抗 VH_CDR2	WISPYGGSTYYADSVKG	819
阿舒利珠單抗 VH_CDR3	RHWPGGFDY	820
阿舒利珠單抗 VL_CDR1	RASQDVSTAVA	821
阿舒利珠單抗 VL_CDR2	SASFLYS	822
阿舒利珠單抗 VL_CDR3	QQYLYHPAT	823
阿舒利珠單抗重鏈 VH 區下方劃線	EVQLVESGGGLVQPGGSLRLSCAASGFTF SDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVY YCARRHWPGGFDYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV	824

	VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YASTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK	
阿舒利珠單抗輕鏈 VL 區下方劃線	DIQMTQSPSSLSASVGDRVTITCRASQDVS TAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFG QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	825
阿維魯單抗VH_CDR1	SYIMM	826
阿維魯單抗VH_CDR2	SIYPSGGITFYADTVKG	827
阿維魯單抗VH_CDR3	IKLGTVTTVDY	828
阿維魯單抗VL_CDR1	TGTSSDVGGYNYVS	829
阿維魯單抗VL_CDR2	DVSNRPS	830
阿維魯單抗VL_CDR3	SSYTSSSTRV	831
阿維魯單抗重鏈 VH 區下方劃線	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYIMMWVRQAPGKGLEWVSSIYPSGGITFYADT VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARIKLGTVTTVDYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL	832

	DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPG	
阿維魯單抗輕鏈 VL 區下方劃線	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSNRPSGVSNRF SGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTR VFGTGTKVTVLGQPKANPTVTLFPPSSEELQANK ATLVCLISDFYPGAVTVAWKADGSPVKAGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV THEGSTVEKTVAPTECS	833
德維魯單抗 VH_CDR1	RYWMS	834
德維魯單抗 VH_CDR2	NIKQDGSEKYYVDSVKG	835
德維魯單抗 VH_CDR3	EGGWFGELAFDY	836
德維魯單抗 VL_CDR1	RASQRVSSSYLA	837
德維魯單抗 VL_CDR2	DASSRAT	838
德維魯單抗 VL_CDR3	QQYGSLPWT	839
德維魯單抗重鏈 VH 區下方劃線	EVQLVESGGGLVQPGGSLRLSCAASGFTF SRYWMSWVRQAPGKGLEWVANIKQDGSEKYY VDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCAREGGWFGELAFDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT HTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPASIEKTISKAKGQPREPQVYTLPPSREE	840

	MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK	
德維魯單抗輕鏈 VL 區下方劃線	EIVLTQSPGTLSLSPGERATLSCRASQRVSS SYLAWYQQKPGQAPRLLIYDASSRATGIPDRFSG SGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	841
德布利單抗 VH_CDR1	SYWMH	842
德布利單抗 VH_CDR2	RIGPNSGFTSYNEKFKN	843
德布利單抗 VH_CDR3	GGSSYDYFDY	844
德布利單抗 VL_CDR1	RASESVSIHGTHLMH	845
德布利單抗 VL_CDR2	AASNLES	846
德布利單抗 VL_CDR3	QQSFEDPLT	847
德布利單抗重鏈 VH 區下方劃線	QVQLVQSGAEVKKPGASVKVSCKASGYT FTSYWMHWVRQAPGQGLEWMGRIGPNSGFTSY NEKFKNRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARGGSSYDYFDYWGQGTTVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL	848

	PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLGK	
德布利單抗輕鏈 VL 區下方劃線	DIVLTQSPASLAVSPGQRATITCRASESVSI HGTHLMHWYQQKPGQPPKLLIYAASNLESGVPA RFSGSGSGTDFTLTINPVEAEDTANYYCQQSFED PLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	849
洛普利單抗 VH_CDR1	SYAIS	850
洛普利單抗 VH_CDR2	GIIPIFGTANYAQKFQG	851
洛普利單抗 VH_CDR3	SPDYSPYYYYGMDV	852
洛普利單抗 VL_CDR1	SGSSSNIGSNTVN	853
洛普利單抗 VL_CDR2	GNSNRPS	854
洛普利單抗 VL_CDR3	QSYDSSLSGSV	855
洛普利單抗重鏈 VH 區下方劃線	QVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQ KFQGRVTITADKSTSTAYMELSSLRSEDTAVYYC ARSPDYSPYYYYGMDVWGQGTTVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH TCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP	856

	REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPSSIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK	
洛普利單抗輕鏈 VL 區下方劃線	QSVLTQPPSASGTPGQRVTISCSGSSSNIGS NTVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFS GSKSGTSASLAISGLQSEDEADYYCQSYDSSLSGS VFGGGIKLTVLGQPKAAPSVTLFPPSSEELQANK ATLVCLISDFYPGAVTVAWKADSSPVKAGVETT TPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT HEGSTVEKTVAPAECS	857
英佛利單抗 VH_CDR1	RRCMA	858
英佛利單抗 VH_CDR2	KLLTTSGSTYLADSVKG	859
英佛利單抗 VH_CDR3	DSFEDPTCTLVTSSGAFQY	860
英佛利單抗單鏈抗體 VH 區下方劃線	QVQLVESGGGLVQPGGSLRLSCAASGKM SSRRCMAWFRQAPGKERERVAKLLTTSGSTYLA DSVKGRFTISRDNSKNTVYLQMNSLRAEDTAVY YCAADSFEDPTCTLVTSSGAFQYWGQGTLVTVS SEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAGIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	861
科貝利單抗 VH_CDR1	RSAIS	862

科貝利單抗 VH_CDR2	VIIPAFGEANYAQKFQG	863
科貝利單抗 VH_CDR3	GRQMFGAGIDF	864
科貝利單抗 VL_CDR1	TRSSGSIDSNYVQ	865
科貝利單抗 VL_CDR2	EDNQRPS	866
科貝利單抗 VL_CDR3	QSYDSNNRHVI	867
科貝利單抗重鏈 VH 區下方劃線	EVQLVQSGAEVKKPGSSVKVSCKASGGTF SRSAISWVRQAPGQGLEWMGVIIPAFGEANYAQ KFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARGRQMFGAGIDFWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK	868
科貝利單抗輕鏈 VL 區下方劃線	NFMLTQPHSVSESPGKTVTISCTRSSGSIDS NYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFS GSIDSSSNSASLTISGLKTEDEADYYCQSYDSNNR HVIFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGVE TTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ VTHEGSTVEKTVAPTECS	869

布嘉利單抗重鏈	EIQLVQSGAEVKKPGSSVKVSCKASGYTF THYGMNWVRQAPGQGLEWVGWVNTYTGEPTY ADDFKGRLTFTLDTSTSTAYMELSSLRSEDTAVY YCTREGEGLGFGDWGQGTTVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK	870
布嘉利單抗輕鏈	DVVMTQSPLSLPVTPGEPASISCRSSQSIVH SHGDTYLEWYLQKPGQSPQLLIYKVSNRFSGVPD RFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIP VTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	871
薩本利單抗重鏈	EVMLVESGGGLVQPGGSLRLSCTASGFTF SKSAMSWVRQAPGKGLEWVAYISGGGGDTYY SSSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARHSNVNYYAMDYWGQGTLVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ	872

	FNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLG	
薩本利單抗輕鏈	EIVLTQSPATLSLSPGERATMSCRASENID VSGISFMNWYQQKPGQAPKLLIYVASNQGS GIPARFSGSGSGTDFTLTISRLEPEDFAVYYCQQS KEVPWTFGQGTKLEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	873
芬托利單抗重鏈	EVQLVESGGGLVKPGGSLRLSCAASGFTF SSYGMSWVRQAPGKRLEWVATISGGGRDTYY SDSVKGRFTISRDNAKNNLYLQMNSLRAEDTAV YYCSRQYGTVWFFNWGQGTLVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMHEALHNHYTQKSLSLSLGK	874
芬托利單抗輕鏈	EIVLTQSPATLSLSPGERATLSCRASESVDS YGNSFMHWYQQKPGQPPRLLIYAASNQGS	875

	GVPARFSGSGSGTDFTLTISSLEPEDFAMYFCQQS KEVPWTFGQGTKVEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	
杰諾利單抗重鏈	QIQLVQSGSELKKPGASVKVSCKASGYTF TNFGMNWVRQAPGQGLKWMGWISGYTREPTY AADFKGRFVISLDTSVSTAYLQISSLKAEDTAVY YCARDVFDYWGQGTLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVES KYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK GQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLSLG	876
杰諾利單抗輕鏈	DIVLTQSPASLAVSPGQRATITCRASESVD NYGYSFMNWFQQKPGQPPKLLIYRASNLES GVPARFSGSGSRTDFTLTINPVEADDTANYYCQQ SNADPTFGQGTKLEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	877

洛普利單抗重鏈	QVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAISWVRQAPGQGLEWMGGIIPIFGTANY AQKFQGRVTITADKSTSTAYMELSSLRSEDTAVY YCARSPDYSPYYYYGMDVWGQGTTVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPEA EGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPSSIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	878
洛普利單抗輕鏈	QSVLTQPPSASGTPGQRVTISCSGSSSNIGS NTVNWYQQLPGTAPKLLIYGNSNRPSGVP DRFSGSKSGTSASLAISGLQSEDEADYYCQSYDS SLSGSVFGGGIKLTVLGQPKAAPSVT LFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPA ECS	879
潘普利單抗重鏈	EVQLVESGGGLVQPGGSLRLSCAASGFAF SSYDMSWVRQAPGKGLDWVATISGGGRYTYY PDSVKGRFTISRDNSKNNLYLQMNSLRAEDTAL YYCANRYGEAWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGAPS	880

	VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	
潘普利單抗輕鏈	DIQMTQSPSSMSASVGDRVTFTCRASQDI NTYLSWFQQKPGKSPKTLIYRANRLVSGVPS RFSGSGSGQDYTLTISSLQPEDMATYYCLQYDEF PLTFGAGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	881
皮瓦利單抗重鏈	QVQLVQSGAEVKKPGASVKVSCKASGYT FPSYYMHWVRQAPGQGLEWMGIINPEGGSTAY AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARGGTYYDYTYWGQGTLVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMHEALHNHYTQKSLSLSLGK	882

皮瓦利單抗輕鏈	DIQMTQSPSTLSASVGDRVTITCRASQSISS WLAWYQQKPGKAPKLLIYEASSLESGVPS RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSFP PTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	883
樸可利單抗重鏈	EVQLVQSGGGLVQPGGSLKLSCAASGFTF SSYGMSWVRQAPGKGLDWVATISGGGRDTYY PDSVKGRFTISRDNSKNNLYLQMNSLRAEDTAL YYCARQKGEAWFAYWGQGTLVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFL FPPKPKDTLMITRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRV VSVLTPLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMHEALHAHYTQKSLSLSLGK	884
樸可利單抗輕鏈	DIVLTQSPASLAVSPGQRATITCRASESVD NYGISFMNWFQQKPGQPPKLLIYAASNKGT GVPARFSGSGSGTDFTLNINPMEENDTAMYFCQ QSKEVPWTFGGGTKLEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	885

思普利單抗重鏈	QVQLVESGGGLVKPGGSLRLSCAASGFTF SNYGMSWIRQAPGKGLEWSTISGGGSNIYYA DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCVSYYYGIDFWGQGTSVTVSSASKYG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSV VLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	886
思普利單抗輕鏈	DIQMTQSPSSLSASVGDRVTITCKASQDVT TAVAWYQQKPGKAPKLLIYWASTRHTGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQHYTIP WTFGGGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	887
西提利單抗重鏈	QVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAISWVRQAPGQGLEWMGLIIPMFDTAGY AQKFQGRVAITVDESTSTAYMELSSLRSEDTAVY YCARAEHSSTGTFDYWGQGTLVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV	888

	DKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK	
西提利單抗輕鏈	DIQMTQSPSSVSASVGDRVTITCRASQGIS SWLAWYQQKPGKAPKLLISAASSLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQANHLP FTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	889
托巴利單抗重鏈	QGQLVQSGAEVKKPGASVKVSCKASGYT FTDYEMHWVRQAPIHGLEWIGVIESETGGTAY NQKFKGRVTITADKSTSTAYMELSSLRSEDTAVY YCAREGITTVATTYYWYFDVWGQGTT VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKP SNTKVDKRVESKYGPPCPPCPAPEFL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQE DPEVQFNWYVDGVEVHNAKTKPREEQ FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	890

托巴利單抗輕鏈	DVVMTQSPLSLPVTLGQPASISCRSSQSIV HSNGNTYLEWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCF QGSHVPLTFGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC	891
哲瓦利單抗重鏈	EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYDMSWVRQA PGKGLEWVSL ISGGGSQTYY AESVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYFCASPS GHYFYAMDVW GQGTTVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPCEEQYG STYRCVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	892
哲瓦利單抗輕鏈	DIQMTQSPSS VSASVGDRVT ITCRASQGIS NWLAWYQQKP GKAPKLLIFA ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ AESFPHTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	893

巴洛利單抗重鏈	QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWIHWVRQA PGQGLEWMGE IDPYDSYTNY NQKFKGRVTM TVDKSTSTVY MELSSLRSED TAVYYCARPG FTYGGMDFWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEFLGGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLGK	894
巴洛利單抗輕鏈	DIQMTQSPSS LSASVGDRVT ITCKSSQSLF NSGNQKNYLA WYQQKPGKVP KLLIYGASTR DSGVPYRFSG SGSGTDFTLT ISSLQPEDVA TYYCQNDHYY PYTFGGGTKV EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC EVTHQGLSSP VTKSFNRGEC	895
諾辛利單抗重鏈	QVQLVQSGAE VKKPGSSVKV SCKASGFTFT TYYISWVRQA PGQGLEYLGY INMGSGGTNY NEKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCAIIG YFDYWGQGTM VTVSSASTKG PSVFPLAPCS RSTSESTAAL GCLVKDYFPE	896

	PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTKTYTCNV DHKPSNTKVD KRVESKYGPP CPPCPAPEFL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSQEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KGLPSSIEKT ISKAKGQPRE PQVYTLPPSQ EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSRLTVDKS RWQEGNVFSC SVMHEALHNH YTQKSLSLSL GK	
諾辛利單抗輕鏈	DVVMTQSPLS LPVTLGQPAS ISCRSSQSLL DSDGGTYLYW FQQRPGQSPR RLIYLVSTLG SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCMQLTHWP YTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLLSPV TKSFNRGEC	897
魯洛利單抗重鏈	EVQLVESGGG LVKPGGSLRL SCAASGFTFS SYGMSWVRQT PEKRLEWVAT ISGGGRDTYY PDSVKGRFTI SRDNAKNNLY LQMSSLRSED TALYYCARQK DTSWFVHWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD QLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYAST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN	898

	NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVLH EALHNHYTQK SLSLSPGK	
魯洛利單抗輕鏈	EIVLTQSPAT LAVSPGERAT ISCRASESVD DYGISFMNWF QQKPGQPPKL LIYVASNQGS GVPARFSGSG SGTDFTLNIH PMEEDDTAMY FCQQSKEVPW TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC	899
嘉維利單抗重鏈	EVQLVESGGGLVQPGGSLRLSCAVSGFSL TSYGVHWVRQAPGKGLEWVAVIWAGGSTNYA DSVKGRFTISKDTSKNTVYLQMNSLRAEDTAVY YCAKPYGTSAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPPAAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALAAPIEK TISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK	900
嘉維利單抗輕鏈	DIQMTQSPSSLSASVGDRVTITCKASQDVG IVVAWYQQKPGKAPKLLIYWASIRHTGVPS RFSGSGSGTEFTLTISSLQPDDFATYYCQQYSNYP LYTFGQGTKVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTL	901

	TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC	
曼利單抗重鏈	EVQLVESGGGVVRPGGSLRLSCAASGFTF DDYAMSWVRQAPGKGLEWVSDISWSGSNTNY ADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YHCARAPLLLAMTFGVGSWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	902
曼利單抗輕鏈	QTVVTQEPSLSVSPGGTVTLTCGLSSGTVT AINYPGWYQQTPGQAPRTLIYNTNTRHSGV PDRFSGSISGNKAALTITGAQAEDEADYYCALYM GNGGHMFGGGTKLTVLGQPKAAPSVT LFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTE CS	903
歐普利單抗重鏈	EVQLVQSGGGLVKPGGSLRLSCAASGFTF SSYTMNWVRQAPGKGLEWVSSISSGSDYLYY ADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARNELRWYPQAGAFDRWGQGTMVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD	904

	YFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREE QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
歐普利單抗輕鏈	QSVVTQPPSMSAAPGQRVTISCSGSSSYIES SYVGWYQQLPGTAPRLLIYDDDMRPSGIP DRFSGSKSGTSATLAITGLQTGDEADYYCEIWRS GLGGVFGGGTKLTVLSQPKAAPSVTL FPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSY LSLTPEQWKSHKSYSCQVTHEGSTVERTVALTEC	905
帕米單抗重鏈	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSSIWRNGIVTVY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKWSAAFDYWGQGTLVTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCPAPEFLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV	906

	LDSDGSFFLYSRLTVDKSRWQEGNVF SCSVMHEALHNHYTQKSLSLSLG	
帕米單抗輕鏈	QGQSGSGIALCPSHFCQLPQTGGGSSGGSG GSGGISSGLLSGRSDNHGGSDIQMTQSPSS LSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQDNGYPSTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC	907
舒多利單抗重鏈	EVQLVESGGGLVQPGGSLRLSCAASGFTF SETWLHWVRQAPGKGLEWVAWVSPFGGSTYY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAV YYCARRHWPGGFDYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG	908
舒多利單抗輕鏈	DIQMTQSPSSLSASVGDRVTITCRASQDVS TAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQFLYHP ATFGQGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN	909

	ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	
舒馬利單抗重鏈	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSGISGSGGFTYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKPPRGYNYGPFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPCPAPEFLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK	910
舒馬利單抗輕鏈	YVLTQPPSVSVAPGQTARITCGGNNIGSKS VHWYQQKPGQAPVLVVYDDSDRPSGIPERF SGSNSGNTATLTISRVEAGDEADYYCQVWDSSS DHVVFGGGTKLTVLGQPKAAPSVTLFP PSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLS LTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	911
索卡利單抗重鏈	EVQLVESGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPIFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARAP YYYYYMDVWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG	912

	TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKP DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIETISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLPGK	
索卡利單抗輕鏈	QSALTQPASV SGSLGQSVTI SCTGSSSDVG SYNLVSWYQQ HPGKAPNLMI YDVSKRSGVS NRFSGSKSGN TASLTISGLQ AEDEADYYCS SYTGISTVVF GGGTKLTVLG QPKAAPSVTL FPPSSEELQA NKATLVCLIS DFYPGAVTVA WKADSSPVKA GVETTTPSKQ SNNKYAASSY LSLTPEQWKS HRSYSCQVTH EGSTVEKTVA PTECS	913
吉坦利單抗重鏈	QVQLQESGPG LVKPSETLSI TCTVSGFSLS NYDISWIRQP PGKGLEWLGV IWTGGATNYN PALKSRLTIS RDNSKNQVSL KMSSVTAADT AVYYCVRDSN YRYDEPFTYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPEAAGA PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP	914

	ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	
吉坦利單抗輕鏈	EIVLTQSPDT LSVTPKEKVT LTCRASQSIG TNIHWFQQKP GQSPKLLIKY ASESISGVPS RFSGSGSGTD FTLTINSVEA EDAATYYCQQ SNSWPYTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	915
ProC1239 臂 1	QSGQTDVDYYREWSWTQVSGSSGGSLSGRSDNI GSGGSCDLPQTHSLGSRRTLMLLAQMRRISLFSC LKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIF NLFSTKDSSAAWDETLLDKFYTELYQQLNDLEA CVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK EKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE LSGRSDNICPPCPAPEFEGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP CQEEMTKNQVSLWCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK	916
ProC1239 臂 2	SDNICPPCPAPEFEGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVCTLPPSQEE MTKNQVSLSCAVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLVSRLTVDKSRWQEGNVFS CSVMHEALHNRFTQKSLSLSLG	917

具有臼突變之 ProC1468 臂2重鏈	QVTLRESGPALVKPTQTLTLTCTFSGFSLSTSGMS VGWIRQPPGKALEWLADIWWDDKKDYNPSLKS RLTISKDTSKNQVVLKVTNMDPADTATYYCARS MITNWYFDVWGAGTTVTVSSASTKGPSVFPLAP CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYT CNVDHKPSNTKVDKRVECPPCPAPEFEGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVCTLPPSQEEMTKNQVSLSCAVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSR LTVDKSRWQEGNVFSCSVMHEALHNRFTQKSLS LSLGK	918
具有杵突變之帕利珠 單抗重鏈	QVTLRESGPALVKPTQTLTLTCTFSGFSLSTSGMS VGWIRQPPGKALEWLADIWWDDKKDYNPSLKS RLTISKDTSKNQVVLKVTNMDPADTATYYCARS MITNWYFDVWGAGTTVTVSS	919
具有臼突變之 Pro1468 臂2輕鏈	DIQMTQSPSTLSASVGDRVTITCKSQLSVGYMH WYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSG TEFTLTISSLQPDDFATYYCFQGSGYPFTFGGGTK LEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	920
具有**C25S**突變之 帕利珠單抗輕鏈	DIQMTQSPSTLSASVGDRVTITCK**S**QLSVGYMH WYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSG TEFTLTISSLQPDDFATYYCFQGSGYPFTFGGGTK LEIK	921
人IgG4 CH1 結構域	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVE	922
CM	LSGRSNI	923

[實施例]

【0431】本發明進一步描述於下列實施例中，這些實施例並不用來限制申請專利範圍中描述之本發明的範圍。

實施例1：在活體外表徵示例性細胞介素構築體

【0432】藉由重組方法製備可經活化之細胞介素構築體ProC440。該ProC440之第一和第二個單體構築體係相同，各為具有SEQ ID NO：286之胺基酸序列且在其N端具有信號序列之多肽。該第一和第二單體構築體各自於N端至C端包含信號序列(例如SEQ ID NO：470)、對應於人干擾素α-2b(SEQ ID NO：1)之成熟細胞介素蛋白、具有SEQ ID NO：100之胺基酸序列的可裂解部分及對應於人IgG4 Fc，在Cys226(根據EU編號)(SEQ ID NO：3)處被截斷且包括S228P突變之二聚化結構域。

【0433】以具有SEQ ID NO：286之序列的多核苷酸將宿主細胞轉化，接著培養所產生之重組宿主細胞來製備多肽。將所產生之表現出的多肽二聚化可產生該細胞介素構築體ProC440。

【0434】使用IFN反應性HEK293細胞和Daudi細胞在活體外測試該ProC440之活性。分別參見圖7A和7B。

【0435】藉由使用人STAT2和IRF9基因進行穩定轉染來產生IFN反應性HEK293細胞，以獲得完整活性第I型IFN傳信路徑。該等細胞亦具有誘導型SEAP(分泌型胚胎鹼性磷酸酶)報告基因，該SEAP報告基因受該IFNα/β誘導型

ISG54啟動子控制。為了維持轉基因表現，將細胞培養在輔以10% FBS、Pen/Strep、30μg/mL之殺稻瘟素(blasticidin)、100μg/ml之博萊黴素(zeocin)和100μg/mL之normocin的DMEM GlutaMax培養基中。在這些細胞中添加第I型IFN可活化該JAK/STAT/ISGF3路徑並隨後誘導SEAP產生，該SEAP可使用Quanti-Blue溶液(用於鹼性磷酸酶活性之比色檢測法)輕易地在上清液中對其進行評估。

【0436】該Daudi細胞為源自人B細胞淋巴母細胞之細胞株。在輔以10% FBS之RPMI-1640培養基中製備濃度為2×10^5個細胞/mL的Daudi細胞並將50μL之等分試樣移液至白色平底96孔盤之孔中(10K/孔)。將測試之ProC440或對照組在輔以10% FBS之RPMI 1640培養基中稀釋。產生五倍系列稀釋液，一式二份，從該系列稀釋液中取出50μL加入每個孔中。在37℃下培育3天後，使用存活力套組測量細胞內ATP之水準作為對剩餘之活細胞數量的間接估算。將100μL之cell-titer go直接添加在該盤中，然後將該盤置於定軌振盪器上10分鐘。培育後，使用Envision分析儀直接測量該發光信號。產生劑量-反應曲線並使用Graph Pad Prism軟體，藉由S形擬合非線性回歸獲得EC50值。

【0437】在使用HEK293細胞和Daudi細胞之二種分析中，與Stem Cell IFNα-2b(人重組IFN-α2b，可從StemCell Technologies獲得，目錄編號78077.1)相比較，ProC440之活性至少降低1,000倍(圖7A和7B)。這表明對應於人IgG Fc之可裂解的二聚化結構域融合物可為該ProC440構築體中

之IFNα-2b提供空間掩蔽。使用uPa蛋白酶活化可將活性恢復至與該重組細胞介素相當之水準。從IFNα/β分析結果計算ProC440、ProC440+uPA和StemCell IFNα-2b之EC50值並提供於下列表8中。

表8. EC50：IFNα/β報告基因分析

	ProC440	ProC440 + uPA	Stem Cell IFNα-2b
EC50	7643	4.333	10.88

【0438】從Daudi細胞凋亡分析結果計算ProC440、ProC440+uPA和StemCell IFNα-2b之EC50值並提供於下列表9中。

表9. EC50：Daudi細胞凋亡分析

	ProC440	ProC440 + uPA	Stem Cell IFNα-2b
EC50	264.2	0.1842	0.3530

【0439】藉由電泳和質譜分析(圖6A和6B)確認使用uPa在可裂解部分之預期位點處的裂解。結果表明該uPa蛋白酶有效裂解該ProC440可經活化之細胞介素構築體中之可裂解部分。除了對uPa活化敏感外，ProC440亦被MMP14裂解(圖6A至6C)。圖6A描繪凝膠電泳結果；左列顯示未曾暴露於蛋白酶之ProC440，中間列顯示暴露於蛋白酶uPA之ProC440，而最右列顯示暴露於MMP14之ProC440。藉由質譜法之分析鑑定出MMP14裂解位點在IFNα-2b之最C端，靠近該可裂解部分(圖6B)。使用MMP14蛋白酶活化亦使活性恢復至與重組細胞介素相當之水準(圖6C)。該數

據表明ProC440在被蛋白酶(諸如uPa或MMP14)裂解內部和經工程處理之可裂解部分後恢復全部活性。

【0440】藉由重組方法製備可經活化之細胞介素構築體ProC732。該ACC之第一和第二單體構築體係相同，其各為具有圖8所示之胺基酸序列的多肽(SEQ ID NO：290，具有示例性可選擇之信號序列(QSGQ))。該第一和第二單體構築體各自於N端至C端包含信號序列、間隔子(QSGQ SEQ ID NO：480)序列、IFNα-2b掩蔽肽(SEQ ID NO：292)、連接子(SEQ ID NO：293)、具有胺基酸序列SEQ ID NO：41(LSGRSDNI)之可裂解部分、連接子(SEQ ID NO：227，其中n=1)、對應於人干擾素α-2b(SEQ ID NO：1)之成熟細胞介素蛋白、具有SEQ ID NO：41之胺基酸序列的可裂解部分和對應於人IgG4 S228PFc，在Cys226(根據EU編號)(SEQ ID NO：3)被截斷之DD。

【0441】藉由重組方法製備另一可經活化之細胞介素構築體ProC733。該ACC之第一和第二單體構築體係相同，其各為具有圖9所示之胺基酸序列的多肽(SEQ ID NO：291，具有示例性可選擇之信號序列)。該第一和第二單體構築體各自於N端至C端包含信號序列、間隔子(例如QSGQ)序列、IFNα-2b掩蔽肽(SEQ ID NO：292)、連接子(SEQ ID NO：293)，具有SEQ ID NO：41之胺基酸序列的可裂解部分、連接子(SEQ ID NO：227，其中n=1)、對應於人干擾素α-2b(SEQ ID NO：1)之成熟細胞介素蛋白及對應於人IgG4 S228P Fc，包括完整之鉸鏈序列(SEQ ID

NO：4)之DD。由於該ProC733構築體在介於該細胞介素序列與DD之間缺少可裂解部分，其僅能被部分活化(如下文中所討論者)。

【0442】使用分別編碼SEQ ID NO：290和291之序列的多核苷酸將宿主細胞轉化，隨後將所產生之重組宿主細胞進行培養以製備該經掩蔽之細胞介素構築體ProC732和ProC733。將所產生之表現出的多肽二聚化以分別產生該細胞介素構築體ProC732和ProC733。

【0443】依前述，在活體外使用IFN反應性HEK293細胞測試ProC732、ProC733和ProC440之活性。與ProC440相比較時，該ProC732和該ProC733之活性被進一步降低(圖10A和10B)。此表明添加肽掩蔽物提供額外之掩蔽強度，即使該ProC440之細胞介素活性已透過二聚化結構域藉由空間掩蔽顯著降低。令人驚訝的是，添加掩蔽肽(PM)似乎不會干擾由該DD提供之空間掩蔽，該DD亦似乎亦不會干擾由該PM造成之掩蔽。使用uPa蛋白酶活化可使該ProC732之活性水準恢復到與使用uPa蛋白酶活化後之ProC440的水準相當。這表明該ProC732在蛋白酶活化後恢復該未經掩蔽之IFNα-2b的全部活性強度。

【0444】ProC733含有經由可裂解部分連接至IFNα-2b之親和肽掩蔽物，該IFNα-2b之C端直接融合至人IgG Fc(在該細胞介素與該Fc區之間未插入可裂解部分)。使用uPa蛋白酶活化可使該ProC733之活性水準恢復到與未經活化之ProC440的水準相當。這進一步表明除了由該可裂解

之人IgG Fc提供之空間掩蔽或受IFNα-2b二聚化之限制外，可裂解之親和性肽掩蔽物對IFNα-2b提供額外之掩蔽強度。從IFNα/β分析結果計算ProC440、ProC440+uPa、ProC732、ProC732+uPa、ProC733和ProC733+uPa之EC50值，並提供於下列表10中。

表10. EC50：IFNα/β報告基因分析

	ProC440	ProC440 + uPA	ProC732	ProC732 + uPA	ProC733	ProC733 + uPA
EC50	0.6344	0.0004	40.69	0.0005	21.83	0.2977

【0445】在HEK報告基因分析中，該ACC之掩蔽效率(藉由比較該未裂解之ACC的EC50與該裂解之ACC的EC50來測量)如下：

ProC440：1358X

ProC732：7380X

ProC733：60X

【0446】因此，可在同時包括肽掩蔽物和透過二聚化結構域之空間掩蔽的ACC中實現高水準之掩蔽效率(例如>5,000x)。

【0447】如圖38A至38D所示，該肽掩蔽物(圖38A(無肽掩蔽物)相對於圖38B(肽掩蔽物))和該Fc掩蔽物(圖38C(無Fc掩蔽物)相對於38D(Fc掩蔽的))之每一者均影響該ACC與該受體之結合。鑑於該數據，協同活性已透過使用本發明之ACC的雙重掩蔽結構取得。依前述，在活體外使用IFN反應性HEK293細胞測試該重組IFNa2b、單體

IFNa2b/Fc、經活化之同二聚體IFNa2b/Fc和同二聚體IFNa2b/Fc的活性。依上述製備重組IFNa2b、單體IFNa2b/Fc、經活化之同二聚體IFNa2b/Fc和同二聚體IFNa2b/Fc。與重組IFNa2b相比較，該同二聚體IFNa2b/Fc之活性大隔降低，但藉由蛋白酶活化而恢復至與重組IFNa2b相當之水準(圖27)。圖31亦顯示單體IFNa2b/Fc顯現之活性水準近似在該經活化和未經活化之同二聚體IFNa2b/Fc所觀察到之活性之間的中點處。

【0448】此外，與經uPA處理之ProC440相比較，ProC440顯示出大幅降低之活性(圖35A)。該相同，但具有NSUB受質之分子對MMP反應時已恢復活性，此表明存在隱蔽之裂解位點(圖39A)。uPA恢復ProC732和ProC1299(L161缺失)二者之活性(圖39B)。L161(在MMP14裂解位點)缺失會防止ProC1301(NSUB受質)活化，即使是在MMP14或uPA之存在下(圖39C)。

【0449】與ProC440相比較，該ProC732和ProC733之活性被進一步降低(圖10A和10B)。此表明添加該肽掩蔽物提供額外之掩蔽強度，即使ProC440中之細胞介素活性已透過二聚化結構域之空間掩蔽而被大幅降低。令人驚訝的是，添加掩蔽肽(PM)似乎不會干擾該DD之空間掩蔽，該DD似乎也不會干擾該PM之掩蔽。使用uPa蛋白酶活化可將ProC732之活性恢復至與使用uPa蛋白酶活化後之ProC440水準相當的水準。此表明ProC732在蛋白酶活化後恢復該未經掩蔽之IFNα-2b的全部活性強度。

【0450】依前述，在活體外使用IFN反應性HEK293細胞測試該重組IFNa2b、單體IFNa2b/Fc、經活化之同二聚體IFNa2b/Fc和同二聚體IFNa2b/Fc之活性。依前述製備重組IFNa2b、單體IFNa2b/Fc、經活化之同二聚體IFNa2b/Fc和同二聚體IFNa2b/Fc。與重組IFNa2b相比較，該同二聚體IFNa2b/Fc之活性大幅降低，但藉由蛋白酶活化而恢復至與重組IFNa2b相當之水準(**圖27**)。圖27亦顯示單體IFNa2b/Fc顯現之活性在約介於該經活化和未經活化之同二聚體IFNa2b/Fc所觀察到之活性之間的中點處。

【0451】此外，使用IFN反應性HEK293細胞在活體外測試為未裂解狀態和蛋白酶活化後之經活化和未經活化之經掩蔽的IFNa2b以及經活化和未經活化之經雙重掩蔽的IFNa2b之活性(**圖32**)。依上述製備經活化和未經活化之經掩蔽的IFNa2b以及經活化和未經活化之經雙重掩蔽的IFNa2b。如圖32所示，與經蛋白酶活化之經掩蔽的IFNa2b相比較，經掩蔽之IFNa2b顯示活性低約700倍，而與經蛋白酶活化之經雙重掩蔽的IFNa2b相比較，經雙重掩蔽之IFNa2b顯示活性低約1400倍。

實施例2：細胞介素構築體之活體內耐受性

【0452】人IFNα-2b與倉鼠IFNα受體交叉反應且先前已證明在倉鼠中具有活性(Altrock et al, Journal of Interferon Research, 1986)。為了評估該含有IFNα-2b之細胞介素構築體的耐受性，給予敘利亞金倉鼠0.4 mg/kg之起

始劑量。動物接受一個測試物劑量並在給藥後繼續研究至多7天，除非鑑定出不可耐受之毒性。起始劑量(0.4mpk)代表IFNα-con(重組干擾素α，由Amgen以Infergen®之名稱製造之非天然存在的第I型干擾素)之等效劑量，預期其會導致倉鼠(125gr)體重減輕、食物攝入減少和骨髓抑制。在食蟹彌猴中，0.1 mg/kg/天之INFα-con(相當於125克倉鼠之1.25至2.5×10^7 U)與體重減輕、食物攝入減少和骨髓抑制有關。若起始劑量可被耐受，將動物提高至2 mg/kg之“中等劑量”並接受三個測試物劑量，除非不能耐受。若可耐受，則將動物提高至10 mg/kg之“高劑量”，並接受三個測試物劑量，除非不能耐受。若可耐受，則將動物提高至15 mg/kg之“更高劑量”。在每個階段，若該測試劑量不能被耐受，則將動物移至下一個較低之劑量。若不能耐受該起始劑量，則將動物降低至0.08 mg/kg之“較低劑量”。亦給予動物該未經掩蔽之INFα-2bFc融合構築體ProC286。作為陰性對照組，給予動物人IgG4劑量。如預期，該陰性對照組未在動物中引起任何毒性。

【0453】亦藉由重組方法製備ProC286(ChIgG4 5AA 1204DNIdL IFNa2b)。該第一和第二單體構築體係相同，其各為具有SEQ ID NO：295之胺基酸序列及在其N端具有信號序列之多肽。該第一和第二單體構築體之每一者於N端至C端包含信號序列、對應於人IgG4 S228P Fc之DD(包括該ESKYGPP鉸鏈序列(SEQ ID NO：4))、連接子(SEQ ID NO：296)、具有SEQ ID NO：100之胺基酸序列的可裂解

部分、連接子(SEQ ID NO：228)及對應於人干擾素α-2b(SEQ ID NO：1)之成熟細胞介素蛋白。

【0454】亦藉由重組方法製備ProC291(NhIgG4 5AA 1204DNIdL IFNa2b)。該第一和第二單體構築體係相同，其各為具有SEQ ID NO：463之胺基酸序列及在其N端之信號序列的多肽。該第一和第二單體構築體之每一者於N端至C端包含信號序列、對應於人干擾素α-2b(SEQ ID NO：1)之成熟細胞介素蛋白、連接子(SEQ ID NO：NO：459)、CM(SEQ ID NO：100)、連接子(GGGS SEQ ID NO：2)和包括ESKYGPP(SEQ ID NO：524)鉸鏈序列之人IgG4 Fc區(SEQ ID NO：4)。

【0455】在Daudi細胞凋亡分析中將該ProC286和ProC291之活性與Sylatron®(PEG-IFN-α2b)之活性相比較(圖11A至11B)。如圖11A所示，於該分析中，ProC286和Sylatron®顯示相似水準之活性。此表明ProC286與市售之聚乙二醇化IFNα-2b具有相似之活性且可作為替代之Sylatron對照組以在倉鼠研究中評估該IFNα-2b之耐受性。與ProC286和Sylatron®相比較，該ProC291顯示活性降低，此表明該IFN N端至該Fc的結構取向對活性降低很重要。亦即，當該DD為一對Fc結構域時，將該細胞介素N端定位至該DD(如ProC291中)可能使該細胞介素之活性的降低幅度大於將該細胞介素定位在該DD之C端(如ProC286中)。

【0456】在第1天給予動物0.4 mg/kg之起始劑量。除

非達到不可耐受之劑量(DLT)，否則繼續研究動物一週。在給藥前和給藥後6小時、24小時、72小時、7天對每隻動物進行臨床觀察、測量體重和體溫。在給藥後72小時、7天收集每隻動物之血液樣品以用於血液學和化學分析。採樣後立即進行血液學和化學分析。在血液學分析方面，評估血液塗片、白血球分類計數、血球容積比、血紅蛋白、平均紅血球血紅蛋白、平均紅血球體積、血小板計數、紅色血細胞(紅血球)計數、紅血球分佈寬度、網狀紅血球計數和白色血細胞(白血球)計數。臨床化學組包括測量丙胺酸胺基轉移酶、白蛋白、白蛋白/球蛋白比率、鹼性磷酸酶、天冬胺酸胺基轉移酶、鈣、氯化物、膽固醇、肌酸激酶、肌酸、γ麩胺醯胺轉移酶、球蛋白、葡萄糖、無機磷、鉀、鈉、總膽紅素、總蛋白、三酸甘油酯、尿素、氮和C反應蛋白。耐受性研究中之毒性證據總結於圖13A至13C、14和15中。

【0457】總括而言，接受ProC286構築體劑量之動物在接受2mpk(即2 mg/kg)之劑量時顯示出體重平均減輕5%，而在接受10mpk和15mpk劑量時顯示出體重平均減輕15%(圖13A至13C)。一隻接受15mpk之ProC286劑量的動物在給藥後7天(研究結束)顯示出體重減輕20%。此被視為非耐受之劑量。相對地，接受2mpk和10mpk之ProC440和ProC732劑量的動物未顯示出體重減輕(圖13A至13B)。接受15mpk之ProC440劑量的動物顯示出體重平均減輕5%(圖13A至13C)。接受15mpk之ProC732劑量的動物未顯示出體

重減輕(圖13C)。此表明在ProC440之背景下，IFNα-2b對其受體之掩蔽限制該由IFNα-2b介導之體重減輕。與接受經掩蔽和經雙重掩蔽之IFNa2b/Fc劑量的動物相比較，接受15mpk之未經掩蔽之IFNa2b/Fc劑量的動物顯示出ALP升高(且在0.4mpk時檢測到ALP增加)。該結果表明，經掩蔽之IFNa2b/Fc在倉鼠毒性模型中可被良好耐受，劑量可高達15 mg/kg。

【0458】不欲受理論束縛，咸信，在ProC440之背景下，將干擾素定位在DD之N端並使用相對較短之LR會抑制細胞介素活性，與聚乙二醇化之IFNα-2b(Sylatron®)或ProC286相比較，會降低干擾素的毒性。令人意外的是，在ProC732之背景下，在該細胞介素之N端添加肽親和性掩蔽物會完全消除在至少15mpk劑量下由IFNα-2b介導之體重減輕。因此，同時使用可裂解之肽掩蔽物和可裂解之二聚化結構域可降低毒性並允許給予較高水準之劑量，可能導致該細胞介素治療劑之治療窗口改善。

【0459】在臨床化學方面，接受ProC286劑量之動物在所有劑量(0.4mpk、2mpk、10mpk和15mpk)下顯示出在給藥後7天(研究結束)鹼性磷酸酶(ALP)顯著升高(圖14)。當給予動物10mpk或15mpk之ProC440或ProC73劑量時未測量到ALP顯著增加(圖14)。ALT升高為肝毒性之標誌。IFNα-2b已被證明會引起肝毒性。此表明在ProC440和ProC732之背景下，掩蔽IFNα-2b使其不與受體結合會限制由IFNa-2b介導之肝毒性。

【0460】在血液學方面，給藥後3天和給藥後7天(研究結束)，接受2mpk、10mpk和15mpk之ProC286劑量的動物顯示網狀紅血球計數、嗜中性粒細胞計數和白血球(WBC)計數顯著減少(圖15)。這些減少讓人聯想到由IFNa-2b介導之骨髓毒性。給藥後三天，接受ProC440和ProC732劑量之動物表現出網狀紅血球計數、嗜中性粒細胞計數和白血球(WBC)計數水準降低(圖15)。總括而言，在接受ProC440和ProC732劑量之動物中觀察到之造血細胞水準降低的程度不像在接受ProC286之動物中觀察到之水準降低的程度顯著。在給藥後7天(研究結束)，在接受ProC732和ProC440劑量之動物中，網狀紅血球計數、嗜中性粒細胞計數和白血球(WBC)計數之總體水準恢復到正常水準，或與接受陰性對照IgG4劑量之動物中所觀察到之水準相似(圖15)。在接受ProC286劑量之動物中，網狀紅血球計數、嗜中性粒細胞計數和白血球(WBC)計數維持在低水準。此表明在ProC440和ProC732之背景下，掩蔽IFNα-2b使受體不能與其結合會限制由IFNa-2b介導之骨髓毒性。

實施例3. 具有各種不同長度之連接子的細胞介素構築體在活體外對癌細胞之抗增殖作用

【0461】在活體外使用Daudi細胞測試在該IFNa-2b與該hIgG4 Fc之間具有各種不同連接子長度或沒有連接子之IFNa-2b-hIgG4 Fc融合構築體的抗增殖作用。依實施例1中之描述使用Daudi細胞分析進行該測試。

【0462】本實驗中測試之融合蛋白於N端至C端方向包括成熟IFNα-2b細胞介素序列、可選擇之連接子和/或可裂解部分及SEQ ID NO：4之人IgG4的Fc結構域(包括該完整鉸鏈區，使得該Fc序列之N端從胺基酸序列ESKYGPPCPPC(SEQ ID NO：926)…)開始。該ESKYGPP(SEQ ID NO：524)序列對該等構築體之“連接區”貢獻7個胺基酸。該第一構築體(連接區=7)構築體不具有連接子或可裂解部分；其序列於N至C端方向係由融合至SEQ ID NO：4之SEQ ID NO：1組成。該第二構築體(連接區=12)構築體具有5個胺基酸之連接子SGGGG(SEQ ID NO：459)且沒有CM；其序列於N至C端方向係由融合至SEQ ID NO：459之SEQ ID NO：1，該SEQ ID NO：459再融合至SEQ ID NO：4組成。該第三構築體(連接區=18)包括7個胺基酸之CM(SGRSDNI，SEQ ID NO：100)和4個胺基酸之連接子GGGS(SEQ ID NO：2)；其序列於N至C端方向係由融合至SEQ ID NO：100之SEQ ID NO：1，該SEQ ID NO：100再融合至SEQ ID NO：2組成。該第四構築體(連接區=23)包括5個胺基酸之連接子、7個胺基酸之CM和4個胺基酸之連接子；其序列於N至C端方向係由融合至SEQ ID NO：459之SEQ ID NO：1，該SEQ ID NO：459再融合至SEQ ID NO：100，該SEQ ID NO：100再融合至SEQ ID NO：2，該SEQ ID NO：2再融合至SEQ ID NO：4組成。該第五構築體(連接區=24)包括13個胺基酸之CM(ISSGLLSGRSDNI，SEQ ID NO：68)和4個胺基酸之連接

子；其序列於N至C端方向係由融合至SEQ ID NO：68之SEQ ID NO：1，該SEQ ID NO：68再融合至SEQ ID NO：2，該SEQ ID NO：2再融合至SEQ ID NO：4組成。

【0463】圖16顯示上述ACC在Daudi細胞中之活性。本實施例中測試之該ACC不具有連接至其上之肽親和性掩蔽物。該數據表明該彈性連接子之長度和介於該細胞介素與該Fc結構域之間的連接區(LR)之長度對該(未經裂解的)ACC之活性有影響。具有零連接子或短連接子及相對短之LR的構築體顯示出細胞介素活性降低，而具有較長之連接子且因此LR較長之構築體具有較高之細胞介素活性水準。

實施例4. 在活體外表徵另外之可經活化之細胞介素構築體

【0464】亦藉由重組方法製備沒有肽掩蔽物之另外的可經活化之細胞介素構築體。該等ACC之第1和第2單體構築體係相同。該第1和第2單體構築體各自於N端至C端包含信號序列、對應於人干擾素α-2b(SEQ ID NO：1)之成熟細胞介素蛋白、具有SEQ ID NO：100(SGRSDNI)之胺基酸序列的可裂解部分(CM)及對應於人IgG4 S228PFc(包含SEQ ID NO：3)之二聚化結構域。此外，該等ACC在該CP和該CM之間包括或不包括具有胺基酸序列SGGGG(SEQ ID NO：459)之連接子。該等ACC在該CM與該DD之間包括或不包括具有胺基酸序列GGGS之連接子。該等ACC亦含有

或不含有在半胱胺酸226(按EU編號)N端之該DD的鉸鏈部分。該等另外之可經活化之細胞介素構築體描述於表11中。

表11：具有不同連接區長度之可經活化的細胞介素

名稱	替代名稱	介於CP和CM之間的連接子	介於CM和DD之間的連接子	Fc鉸鏈N端殘基	連接區長度
ProC288	IFNa2b 1204DNI 0AA Fc	SGGGG (SEQ ID NO: 459)	不存在	不存在	12
ProC289	IFNa2b 1204DNI 3AA Fc	SGGGG (SEQ ID NO: 459)	不存在	GPP	15
ProC290	IFNa2b 1204DNI 7AA Fc	SGGGG (SEQ ID NO: 459)	不存在	ESKYGPP (SEQ ID NO: 524)	19
ProC291	IFNa2b 1204DNI 11AA Fc	SGGGG (SEQ ID NO: 459)	GGGS	ESKYGPP (SEQ ID NO: 524)	23
ProC440	N IFNa2b 0 1204DNIdL 0AA Fc	不存在	不存在	不存在	7
ProC441	N IFNa2b 0 1204DNIdL 3AA Fc	不存在	不存在	GPP	10
ProC442	N IFNa2b 0 1204DNIdL 7AA Fc	不存在	不存在	ESKYGPP (SEQ ID NO: 524)	14
ProC443	N IFNa2b 0 1204DNIdL 11AA Fc	不存在	GGGS	ESKYGPP (SEQ ID NO: 524)	18

【0465】依前述，使用IFN反應性HEK293細胞和Daudi細胞在活體外測試ProC440(不具有彈性連接子且IgG4 Fc區在Cys226被截斷(即，包含7個胺基酸之連接區)之ACC)之活性，以及含有各種不同彈性連接子和Fc區序列(即，包含具有超過7個胺基酸之連接子)之另外的ACC之活性。在二種分析中，與具有較長連接區之所有其他ACC相比較，ProC440之活性(例如抗增殖作用)降低，該具有較長連接區之其他ACC在該細胞介素與該將DD結合至該

對應之第二單體的第一胺基酸(即，根據EU編號之IgG4的Cys226)之間含有各種不同之額外序列。從該IFNα/β分析結果計算該ACC之EC50值，並提供於下列表12中。

表12. EC50：IFNα/β報告基因分析

	Pro C288	Pro C289	Pro C290	Pro C291	Pro C440	Pro C441	Pro C442	Pro C443
EC50	34.34	17.93	10.33	8.743	41.37	6.28	6.637	1.687

【0466】從該Daudi細胞凋亡分析結果計算該ACC之EC50值，並提供於下列表13中。

表13. EC50：Daudi細胞凋亡分析

	Pro C288	Pro C289	Pro C290	Pro C291	Pro C440	Pro C441	Pro C442	Pro C443
EC50	112.8	64.55	23.04	13.39	2078	1053	642.9	478

【0467】表7至8中之數據亦顯示該(未經裂解之)ACC之活性可藉由改變該連接區之長度來調節。

【0468】本實施例中測試之該ACC不包含肽掩蔽物。基於本文報告之比較ProC440與ProC732的實驗結果，該未經裂解之ACC的活性可能藉由對該細胞介素構築體之N端添加可裂解部分和肽掩蔽物而進一步降低。同樣地，基於本文比較ProC440和ProC732之數據，與不包含PM之ACC相比較，在N端進一步包含CM和PM之ACC可能具有增加之掩蔽效率。

實施例5. 通用之細胞介素構築體

【0469】藉由本文所描述之重組方法製備通用之可經

活化之細胞介素構築體。該通用ACC之通用干擾素序列(ProC859)對人和小鼠細胞均具有活性(如圖29所示)。該通用ACC為二聚體。該ACC之第一和第二單體構築體係相同，其各為具有SEQ ID NO：447之胺基酸序列，在其N端具有信號序列的多肽。該第一和第二單體構築體各自於N端至C端包含信號序列、成熟細胞介素蛋白(其對應於為IFNα1和IFNα2a之雜交體的通用干擾素分子(SEQ ID NO：488))、具有SEQ ID NO：100之胺基酸序列的可裂解部分和對應於人IgG Fc(SEQ ID NO：3)之二聚化結構域。

【0470】使用IFN反應性HEK293細胞和B16小鼠黑色素瘤細胞在活體外測試該通用細胞介素構築體之活性。與小鼠IFNa4相比較，該ProC859之活性降低至少150倍。如圖29所示，使用uPa蛋白酶活化可將活性恢復至與小鼠IFNa4相當之水準。從該分析結果計算ACC ProC859、ACC ProC859+uPa和小鼠IFNα4之EC50值並提供於圖29中。

EC50：B16 IFNα/β報告基因分析

	ProC859 (ACC)	ProC859 (ACC) + uPA	IFNa4
EC50	293.7	1.951	1.966

【0471】根據本發明之具有通用IFN和肽掩蔽物之ACC可藉由本文描述之重組方法來製備。該肽掩蔽物與通用干擾素偶聯以進一步相較於ProC859降低該ACC之細胞介素活性。該ACC之第一和第二單體構築體係相同，其各

為具有胺基酸序列之多肽。該第一和第二單體構築體各自於N端至C端包含信號序列(例如SEQ ID NO：468至470其中一者)、掩蔽肽(例如選自SEQ ID NO：292和297至446中之任一PM)、可選擇之連接子(例如選自SEQ ID NO：2或SEQ ID NO：210至236中之任一者)、可裂解部分(例如選自SEQ ID NO：5至100和237至252中之任一者)、可選擇之連接子(例如選自SEQ ID NO：2、210至236、293、294和296中之任一者)、成熟細胞介素蛋白(其對應於為IFNα1和IFNα2a之雜交體之通用干擾素分子(SEQ ID NO：448))、具有SEQ ID NO：100之胺基酸序列的可裂解部分和對應於人IgG Fc(SEQ ID NO：3)之二聚化結構域。使用IFN反應性HEK293細胞和B16小鼠黑色素瘤細胞活體外測試該通用ACC之活性。基於本文報告之實驗結果比較ProC440與ProC732，預期該親和性掩蔽物(PM)之存在將相對於ProC859進一步降低該未經裂解之ACC的細胞介素活性，但當該CM被蛋白酶裂解時將允許該細胞介素活性完全恢復，從而進一步降低毒性並改善該治療窗。

【0472】不欲受理論束縛，基於本文呈現之結果，本發明者設想除了使用在該細胞介素之C端具有非常短之LR的DD外，使用在該細胞介素之N端的親和性掩蔽物(PM)將為除了前述具體實施例中舉例說明的干擾素α細胞介素之外的細胞介素提供對細胞介素活性的顯著掩蔽。如上述，本文所描述之本發明包含可經活化之細胞介素構築體，該細胞介素構築體包括本文討論之各種不同的細胞介素蛋

白。作為非限制性實例，本發明之ACC中所使用之該CP可為SEQ ID NO：101至209中所列之任一者及其變體。特別是，單體細胞介素適合用於本文所描述之ACC。基於本文提供之結果，咸信本發明之ACC相對於該對應之野生型細胞將表現出降低之細胞介素活性，且當該ACC被相關蛋白酶裂解後，該裂解產物細胞介素活性將恢復至類似於該對應之野生型細胞介素的水準。

實施例6：在活體內表徵條件式活性之單獨的INFa-A/D或IFNa2b或與抗PD-L1之組合

【0473】依實施例1中之描述製備經雙重掩蔽之INFa-A/D(SEQ ID NO：493，ProC1023)及其可裂解性可能降低之經修飾的版本(SEQ ID NO：494，ProC1549)。CX-171(SEQ ID NO：504或505-HC，SEQ ID NO：506-LC)為單株抗體，其可與人和小鼠細胞表現之PD-L1(“PD-L1 mAb”)結合。CX-171具有小鼠IgG2a Fc部分以促進在活體內與小鼠免疫系統交互作用。表現後，該C端離胺酸可能存在或可能不存在於CX-171抗體中。

【0474】使用MC38腫瘤模型在活體內測試該經掩蔽之IFNa-A/D的抗腫瘤活性。經由皮下途徑為小鼠(每組N=5)植入在無血清培養基中之1.5×10^6個MC38細胞。在研究期間每週二次記錄體重和腫瘤測量值。當平均腫瘤體積達到80 mm^3時，每週二次經由皮下注射給予小鼠經掩蔽之IFNa-A/D(ProC1023)或經掩蔽之不可裂解的IFNa-

A/D(ProC1549)劑量或每週一次經由腹膜內給予小鼠PD-L1 mAb(CX-171)劑量，或給予小鼠指定之劑量水準之經掩蔽之IFNa-A/D與PD-L1的組合(ProC1023+CX-171)。

【0475】經掩蔽之IFNa-A/D在50至200μg之劑量水準下顯示抗腫瘤活性。投予50μg導致顯著之腫瘤生長抑制，而投予200μg亦導致該動物去除60%腫瘤(**圖18A**)。該經掩蔽之IFNa-A/D(ProC1023)的抗腫瘤作用依賴蛋白水解活化，因為該不可裂解之構築體(ProC1549)不介導類似之反應(**圖18B**)。

【0476】50μg/劑量之經掩蔽的IFNa-A/D與200μg/劑量之PD-L1 mAb的組合導致與任一單獨之分子相比較下增進的抗腫瘤作用(**圖18C**)。

【0477】經掩蔽之IFNa2b在漸增之劑量下減少腫瘤體積。依上述製備經掩蔽之IFNa2b。0.02 mg/kg之經掩蔽之IFNa2b/Fc的劑量會防止腫瘤進展並在0.1 mg/kg之劑量下誘導腫瘤消退(**圖28、51**)。如圖28和圖51所示，經掩蔽之IFNa2b/Fc表現出與聚乙二醇化干擾素和未經掩蔽之Fc-IFN-a2b對照組相似之抗腫瘤活性。

【0478】此外，與對照相比較，經掩蔽之IFNa2b在20μg和200μg時顯示出抗腫瘤活性(**圖33**)。依上述在第1、4、8、11和15天使用經掩蔽之IFNa-A/D劑量測試抗腫瘤活性。在圖23之圖形中指示之時間評估腫瘤體積。

【0479】如圖33所示，與不可裂解之版本相比較，在10、50和200μg劑量下之經雙重掩蔽之IFNa AD可減少腫瘤

體積(圖33A)。與劑量為10和50μg之單獨的經雙重掩蔽之IFNa AD或劑量為200μg之單獨的PD-L1單株抗體相比較，經雙重掩蔽之IFNa AD與PD-L1單株抗體的組合減少腫瘤體積(**圖33B**)。依上述方法在第1、4、7和11天給予劑量測試抗腫瘤活性。在第1天和第7天投予單獨之PD-L1單株抗體。

【0480】如**圖34A**所示，Pro IFNa A/D(ProC1023)以劑量依賴性方式抑制腫瘤體積生長。如**圖34B**)所示，該抑制需要活化，其中200μg之IFNa A/D NSUB(ProC1549)與相同劑量之Pro IFNa A/D(ProC1023)相比較顯示出抗腫瘤活性降低。

【0481】與PBS對照組相比較，10μg、50μg和200μg之Pro IFNa A/D(ProC1023)減少腫瘤體積生長(**圖35A**)。與Pro IFNa A/D(ProC1023)相比較，50和200μg之IFNa A/D NSUB(ProC1549)在相同期間內之抗腫瘤活性降低(圖35B)。依上述在第1、4、7、11和15天給予劑量來測試該經掩蔽之IFNa-A/D的抗腫瘤活性。在第1、7和15天給予CX-171劑量。在圖35A和35B之圖形中指示的時間評估腫瘤體積。

表14. 示例之序列

SEQ ID NO.	名稱	序列
924	單體 IFNa-2b/Fc 不具信號序列之 ProC657 第一單體(鈕突變)	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFP QEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDE TLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSI LAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKESGRSDNICPPCPAPEFEGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPCQEEMTK NQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH YTQKSLSLSLG
925	單體 IFNa-2b/Fc 不具信號序列之 ProC657 第二單體(孔突變)	SDNICPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSRLTVD KSRWQEGNVFSCSVMHEALHNRFTQKSLSLSLG

實施例7. 經IFNa-A/D治療之小鼠的免疫記憶.

【0482】在初次治療後第56天使用1.5x10^{6}個MC38細胞再次挑戰未曾接受治療之小鼠(N=5；圖19A)或使用200μg之ProC1023劑量進行IFNa-A/D治療後去除MC38腫瘤的小鼠(N=3；圖19B)。每週監測腫瘤生長二次。在初次治療後56天以MC38腫瘤再次挑戰使用200μg/劑量之IFNa-A/D治療後去除腫瘤之小鼠。在再挑戰期間不對小鼠投予任何治療。挑戰後，在所有五隻對照動物中逐漸長成MC38腫瘤(**圖19A**)，然而只有三分之一先前接受IFNa-A/D治療之

小鼠中發展出腫瘤，且該小鼠中之腫瘤表現出明顯生長較慢，此與先前曾使用200μg之ProC1023劑量進行治療之該等小鼠中形成抗腫瘤免疫記憶一致(**圖19B**)。

【0483】結果表明該經掩蔽之IFNa-A/D係以活化依賴性、免疫介導之方式抑制MC38腫瘤生長。IFNa-A/D與PD-L1 mAb之組合活性表明該二種治療之抗腫瘤作用的不重複機制。

實施例8：未經掩蔽之INF-a2b在活體外活化腫瘤免疫浸潤

【0484】依前述使用uPa處理來活化經雙重掩蔽之INFa-a2b(SEQ ID NO：290，ProC732)。自供應商購得聚乙二醇化之IFN-a2b(默克公司，美國)並作為對照組。於本實例中，CX-075(SEQ ID NO：496-HC，SEQ ID NO：497-LC)為與人免疫細胞和腫瘤細胞表現人PD-L1結合的單株mAb。CX-075具有人IgG4 Fc部分。

【0485】來自腎癌患者之經分離之腫瘤和PBMC係以經冷凍保存之單細胞懸浮液形式從供應商獲得，解凍後存活率至少50%。在0.1 ng/mL、10 ng/mL或1000 ng/mL之ProC732劑量下，使用經掩蔽之IFNa-2b(未經裂解之ProC732)、未經掩蔽之IFNa-2b(以uPa蛋白酶處理之ProC732)、Peg-IFN-a2b或未經掩蔽之IFN-a2b與PD-L1mAb(CX-075)之組合處理PBMC或經分離之腫瘤細胞持續24小時。藉由MSD多重分析測量干擾素γ釋放(由第I型IFN和PD-1：PD-L1軸阻斷誘導之敏感性生物標誌物)。

【0486】與未經處理之對照組相比較，以經掩蔽之IFN-a2b(未經裂解之ProC732)處理不會導致干擾素γ上清液濃度發生可測量之變化。以經活化之IFN-a2b(經uPA處理之ProC732)處理顯示由經分離之腫瘤和PBMC釋放的干擾素γ水準呈劑量依賴性增加(**圖20**)。該變化之特徵和幅度均與Peg-IFN-a2b基準對照組相似。雖然以PD-L1 mAb(CX-075)處理不會導致干擾素γ釋放水準增加，但經活化之IFN-a2b與PD-L1 mAb之組合會以劑量依賴性方式增加經分離之腫瘤細胞中之生物標誌物的釋放，但在PBMC中則否。

【0487】觀察到之結果與藉由經活化之IFN-a2b活化腫瘤免疫浸潤相一致。經活化之IFN-a2b與PD-L1 mA之組合活性表明免疫活化之不重複機制。經掩蔽和未經掩蔽形式之IFN-a2b的活性之間的差異表明其功能被該雙重掩蔽結構削弱。

【0488】此外，IFN之生物學效果和掩蔽在分離出之腫瘤中很明顯。依上述獲得來自患有腎癌之患者的分離出之腫瘤和PBMC。如圖31所示，IFN-γ釋放在10 ng/mL時飽和(PD-L1 mAb係以單劑量投予)。如圖31所示，與單獨之經活化之IFNa2b或PD-L1 mAb相比較，經活化之IFNa2b與PD-L1 mAb之組合會增加IFN-γ釋放。

實施例9：未經掩蔽之IFN-a2b以活化依賴方式誘導第I型干擾素特徵

【0489】依前述使用uPa處理來活化經雙重掩蔽之INFa-a2b(SEQ ID NO：290，ProC732)。聚乙二醇化之IFN-a2b(默克公司，美國)係購自供應商。

【0490】從供應商購買自來自四名健康供體之PBMC，該PBMC為冷凍保存形式之單細胞懸浮液，解凍後存活率至少為80%。在活體外使用1μg/mL(高劑量)之經掩蔽的IFN-a2b(未經裂解之ProC732)或10 ng/mL之經掩蔽的IFN-a2b(未經裂解之ProC732)、未經掩蔽之IFN-a2b(經uPA處理之ProC732)或Peg-IFN-a2b(Sylatron®-Merck，USA)處理來自各供體之PBMC 24小時。將來自經處理之細胞的大量mRNA進行雙端150c RNAseq高通量測序。使用Subread包v.1.5.2計算獨特基因命中數。使用DESeq2進行指定樣本組之間的基因表現比較。使用Wald試驗來產生p值和log2倍數變化。其調整後之p值<0.05且絕對log2倍數變化>1之基因稱為每次比較時差別表現之基因。

表15. 基因表現輪廓之成對比較

	未經處理的	**ProC732**	**ProC732** 高劑量	**ProC732 + uPA**	**Sylatron** (Peg-IFN-a2b)
未經處理的		↑1 ↓0	↑248 ↓ 36	↑418 ↓ 77	↑480 ↓ 86
ProC732			↑8 ↓1	↑71 ↓ 10	↑125 ↓ 17
ProC732 高劑量				↑1 ↓0	↑0 ↓0
ProC732 + uPA					↑0 ↓0

【0491】以經掩蔽之IFN-a2b處理的PBMC不會導致基因表現變化，而經活化之IFN-a2b在所有四個供體中一致地上調和下調大量基因(**圖21**)。結果表明418個基因之表現統計學上顯著地增加，而77個基因被下調(**表15**)。基因本體論分析揭露與第I型干擾素信號傳導活化相關之模式，包括已知之IFN-a2b標靶(諸如CXCL10、TRAIL和2'OAS)的表現增加。使用聚乙二醇化之IFN-a2b處理在所有供體中誘導和抑制相似數量之基因。直接比較使用經活化之IFN-a2b和Peg-IFN-a2b處理之PBMC的表現輪廓揭露出二種處理之間沒有差異。

【0492】此結果與在原代人免疫細胞中使用未經掩蔽之IFN-a2b以活化依賴方式誘導干擾素信號傳導一致。由高劑量之經掩蔽之IFN-a2b和未經掩蔽之干擾素誘導的基因表現之間的最小變化表明雙重掩蔽會降低該細胞介素之信號傳導潛力，而不會與受體產生新交互作用。

實施例10：經掩蔽之IFN-a2b 在嚙齒動物中之藥代動力學特性

【0493】依前述對金色敘利亞倉鼠投予經雙重掩蔽之INFa-a2b(SEQ ID NO：290，ProC732)、經空間掩蔽之IFN-a2b(SEQ ID NO：286，ProC440)、其不可裂解之對照組(SEQ ID NO：507，ProC659)或Fc-IFN-a2b融合分子(SEQ ID NO：295，ProC286)。在投予後6、24、72小時或7天取得血液樣品。使用ELISA(Mabtech，美國)測量IFN-

a2b之濃度。使用WinNonlin軟體(Certara，美國)進行非室藥代動力學分析。

【0494】所有測試分子之藥代動力學輪廓表明增加之血清濃度與投予之劑量成比例(**圖22**)。在每個劑量水準下，經掩蔽之IFN-a2b與對照蛋白之間的藥物暴露相當。非室分析揭露平均循環半衰期為4.3天-範圍在1.98至6.38天(**表16**)。

【0495】結果表明IFN-a2b在活體內之線性藥代動力學特性且與未經修飾之IFN-a2b(2.3小時)和與12kDa PEG分子結合之Peg-IFN-a2b(4.3小時)的公開數據相比較，其半衰期延長。

【0496】所有測試之分子的藥代動力學輪廓表明增加之血清濃度與投予之劑量成比例。

表16. IFN-a2b藥代動力學之非室分析的總結

測試_品項	劑量	Tmax	Cmax	AUClast	HL_λ_z (半衰期)
	mg/kg	day	ng/mL	day*ng/mL	day
ProC286	0.4	0.25	2913	10371	4.3499
ProC286	2	1	8225	30936	
ProC286	2	1	8863	39595	
ProC286	2	1	7685	29731	
ProC286	10	3	19443	104368	
ProC286	10	1	37673	79286	
ProC286	10	1	24036	118866	
ProC286	15	0.25	41340	187894	1.9774
ProC286	15	1	63075	250384	
ProC286	15	1	74989	259900	
ProC286	15	3	45546	219676	
ProC440	0.4	1	401	1791	4.3952
ProC440	2	1	4718	18986	
ProC440	2	1	7137	27274	
ProC440	2	1	8968	40329	
ProC440	10	1	36860	161885	
ProC440	10	1	31851	152170	
ProC440	15	0.25	53422	214393	5.1186
ProC440	15	1	44331	226428	
ProC440	15	0.25	37551	122954	4.5772
ProC440	15	1	18738	109485	
ProC659	0.4	1	686	3143	5.0481
ProC659	2	3	9842	48705	
ProC659	2	0.25	12284	44567	
ProC659	2	0.25	15715	36674	5.7591
ProC659	10	1	51601	303538	
ProC659	10	1	57389	315392	
ProC659	10	1	51022	241447	
ProC732	10	1	21019	128288	
ProC732	10	1	34498	182458	
ProC732	10	1	34191	179881	
ProC732	15	0.25	33121	186676	6.3841
ProC732	15	1	54723	164326	
ProC732	15	1	27760	157575	
ProC732	15	1	33898	177802	

【0497】以單次投予指定劑量之Pb-IFN-a2b來治療Beige/SCID小鼠(每組n=15)。在投予後1、2、3、6、24、48、72、120小時、7和14天收集用於PK研究之血漿。使用抗人IFN-α2b特異性捕獲和檢測抗體(Mabtech，美國)，

藉由MSD分析來分析樣品。

【0498】所有測試之分子的藥代動力學輪廓表明增加之濃度與投予之劑量成比例(**圖52**)。

實施例11：在活體外表徵示例性通用細胞介素構築體

【0499】藉由本文所描述之重組方法製備通用可經活化之細胞介素構築體。該通用ACC具有對人類和小鼠細胞均有活性之通用干擾素序列(ProC1023)。該通用ACC為二聚體。該ACC之第一和第二單體構築體係相同，其各為具有SEQ ID NO：493之胺基酸序列，在其N端具有信號序列的多肽。該第1和第2單體構築體各自於N端至C端包含信號序列、間隔子(QSGQ，SEQ ID NO：480)序列、IFNα-2b掩蔽肽(TDVDYYREWSWTQVS)(SEQ ID NO ：292)、連接子(GSSGGS)(SEQ ID NO：293)、具有SEQ ID NO：41(LSGRSDNI)之胺基酸序列的可裂解部分、連接子(GS)n、(GGS)n、(GSGGS)n(SEQ ID NO：227，其中n＝1)、成熟細胞介素蛋白(其對應於為IFNα1和IFNα2a之雜交體的通用干擾素分子(SEQ ID NO：448))、具有SEQ ID NO：41之胺基酸序列的可裂解部分及對應於人IgG4 S228P Fc，在Cys226(根據EU編號) (SEQ ID NO：3)截斷之DD。

【0500】藉由重組方法製備另一通用細胞介素構築體ProC1549。該ACC之第一和第二單體構築體係相同，其各為具有SEQ ID NO：494之胺基酸序列的多肽(具有示例性可選擇的信號序列)。該第一和第二單體構築體於N端至C

端包含信號序列、間隔子(例如QSGQ，SEQ ID NO：480)序列、IFNα-2b掩蔽肽(TDVDYYREWSWTQVS)(SEQ ID NO：292)、連接子(GSSGGS)(SEQ ID NO：293)、具有SEQ ID NO：211之胺基酸序列的不可裂解部分、連接子(GS)n、(GGS)n、(GSGGS)n(SEQ ID NO：227，其中n=1)、成熟細胞介素蛋白(其對應於為IFNα1和IFNα2a之雜交體的通用干擾素分子(SEQ ID NO：481))、具有(GGSGGGGS)SEQ ID NO：495之胺基酸序列的不可裂解部分和對應於人IgG4 S228P Fc，包括完整的鉸鏈序列(SEQ ID NO：3)之DD。如下文所討論，由於該ProC1549構築體在該掩蔽肽與該細胞介素之間以及該細胞介素序列與該DD之間缺少可裂解部分，所以其為不可經活化的。

【0501】藉由本文所描述之重組方法製備另一通用之可經活化之細胞介素構築體ProC859。ProC859具有對人類和小鼠細胞均有活性之通用干擾素序列。ProC859為二聚體。該ProC859之第一和第二單體構築體係相同，其各為具有SEQ ID NO：447之胺基酸序列，在其N端具有信號序列的多肽。該第1和第2單體構築體各自於N端至C端包含信號序列、成熟細胞介素蛋白(其對應於為IFNα1和IFNα2a之雜交體的通用干擾素分子(SEQ ID NO：448))、具有(SGRSDNI)SEQ ID NO：100之胺基酸序列的可裂解部分和對應於人IgG Fc(SEQ ID NO：3)的二聚化結構域。與ProC1023不同，ProC859不包含肽掩蔽部分。

【0502】在活體外使用B16小鼠黑色素瘤細胞測試通

用細胞介素構築體ProC1023(SEQ ID NO：493)和proC859(SEQ ID NO：447)之活性。與ProC859相比較，ProC1023之活性進一步降低(圖24A)。此表明添加肽掩蔽物提供額外之掩蔽強度，即使ProC859中之該細胞介素活性已透過二聚化結構域之空間掩蔽顯著降低。令人驚訝的是，添加掩蔽肽(PM)似乎不會干擾該DD之空間掩蔽，該DD似乎也不會干擾該PM之掩蔽。使用uPa蛋白酶活化將該ProC1023之活性水準恢復至相當於使用uPa蛋白酶活化後之ProC859的水準。此表明ProC1023在蛋白酶活化後恢復未經掩蔽之通用IFNα的全部活性強度。

【0503】ACC在HEK報告基因分析中之掩蔽效率(藉由比較該未經裂解之ACC的EC50與該經裂解之ACC的EC50來測量)如下：

ProC1023：1387X

ProC859：700X

【0504】在活體外使用B16小鼠黑色素瘤細胞測試該通用細胞介素構築體ProC1023和ProC1549之活性。在未經活化之狀態下，ProC1023和ProC1549顯示出類似之信號傳導活性降低(圖24B和24C)。在使用uPa或MMP14蛋白酶活化後，該不可裂解之ProC1549的活性維持很低且類似於無蛋白酶活化之ProC1549，而ProC1023之活性在蛋白酶活化後與沒有蛋白酶活化之ProC1023和ProC1549相較下顯著增加(圖24B和24C)。此表明ProC1549對蛋白酶活化具有抗性，且其可用來作對照組以證明通用之可經活化之細胞介

素構築體的蛋白酶依賴性活化。

實施例12：在活體外表徵另外之異二聚體ACC

【0505】亦藉由重組方法製備ACC ProC1239(Pro-IFN 49CS 1204 IFNa2b 0 1204 0 G4鈕 殘段 孔(Knob Stub Hole)。該ACC之第一單體構築體為具有ProC1239 Arm 1 SEQ ID NO：792之胺基酸序列，在其N端具有信號序列的多肽。該ACC之第一單體構築體於N端至C端包含信號序列、間隔子(QSGQ，SEQ ID NO：480)序列、IFNα-2b掩蔽肽(TDVDYYREWSWTQVS)(SEQ ID NO：292)、連接子(GSSGGS)(SEQ ID NO：293)、具有胺基酸序列SEQ ID NO：41(LSGRSDNI)之可裂解部分、連接子(GS)n、(GGS)n、(GSGGS)n(SEQ ID NO：227，其中n=1)、對應於人干擾素α-2b(SEQ ID NO：1)之成熟細胞介素蛋白、具有SEQ ID NO：41之胺基酸序列的可裂解部分和對應於人IgG Fc，具有鈕突變，在Cys226(根據EU編號)(SEQ ID NO：287)被截斷的DD。該ACC之第二單體構築體為具有ProC1239 Arm 2 SEQ ID NO：793之胺基酸序列且在其N端具有信號序列之多肽。該第二單體構築體於N端至C端具有信號序列、殘段部分(SDNI)(SEQ ID NO：289)和對應於人IgG Fc，具有孔突變(SEQ ID NO：288)之二聚化結構域。

【0506】依前述，使用IFN反應性HEK293細胞在活體外測試ProC1239和ProC732之活性。與ProC732相比較，該

ProC1239之活性適度地降低(圖25)。

實施例13：在活體外表徵具有各種不同可裂解之連接子的另外之ACC

【0507】亦藉由重組方法製備具有各種不同可裂解之連接子之另外的可經活化之細胞介素構築體。該等ACC之第一和第二單體構築體係相同。該第一和第二單體構築體於N端至C端各自包含信號序列、間隔子(QSGQ，SEQ ID NO：480)序列、IFNα-2b掩蔽肽(TDVDYYREWSWTQVS)(SEQ ID NO：292)、連接子(GSSGGS)(SEQ ID NO：293)、可裂解部分、連接子(GS)n、(GGS)n、(GSGGS)n(SEQ ID NO：227，其中n=1)、對應於人干擾素α-2b(SEQ ID NO：1)之成熟細胞介素蛋白、可裂解部分和對應於人IgG4 S228P Fc，在Cys226(根據EU編號)截斷(SEQ ID NO：3)的DD。下表中描述各種不同之可裂解連接子：

表17.介於下列部位之間的具有不同可裂解連接子之可經活化的細胞介素

名稱	替代名稱	介於CP與細胞介素部分之間的CM	介於細胞介素部分與DD之間的CM
ProC732	Pro-IFN 49CS 1204 IFNa2b 0 1204 0 (-ESKYGPP) G4	LSGRSDNI (SEQ ID NO: 41)	LSGRSDNI (SEQ ID NO: 41
ProC1550	Pro-IFN 49CS 1205 IFNa2b 0 1205 0 (-ESKYGPP) G4	LSGRSNI (SEQ ID NO: 799)	LSGRSNI (SEQ ID NO: 799)
ProC1552	Pro-IFN 49CS 559 IFNa2b 0 559 0 (-ESKYGPP) G4	QNQALRMA (SEQ ID NO: 16)	QNQALRMA (SEQ ID NO: 16)

【0508】使用IFN反應性HEK293細胞在活體外測試該ProC732、ProC1550和ProC1552之活性。使用uPa或MTSP1蛋白酶活化後，所有可經活化之細胞介素構築體均顯示出類似之活性增加，表明所有經活化之細胞介素構築體在蛋

白酶處理後恢復相同之活性水準，如圖26所示。

實施例14：經掩蔽之IFNa-A/D在CT26和B16同基因腫瘤模型中引起腫瘤生長延遲

【0509】使用B16和CT26腫瘤模型在活體內測試該經掩蔽之IFNa-A/D(ProC1023)的抗腫瘤活性。經由皮下為小鼠(每組N=6)植入在無血清培養基中之腫瘤細胞。在研究期間每週二次記錄體重和腫瘤測量值。當該平均腫瘤體積達到80 mm^3時，每週1次經由皮下注射給予小鼠經掩蔽之Pb-IFNa-A/D劑量和/或每週2次經由腹膜內給予小鼠PD-1或PD-L1 mAb劑量。

【0510】經掩蔽之IFNa-A/D在二種模型系統中均顯示在50μg劑量水準下具有抗腫瘤活性。投予Pb-IFNa-A/D導致統計學上顯著之腫瘤生長抑制，而PD-1和PD-L1 mAb並未顯著影響腫瘤生長。與單獨之任一分子相比較，經掩蔽之IFNa-A/D與200μg/劑量之PD-L1 mAb的組合導致增強之抗腫瘤效果(圖37)。在B16腫瘤模型中，Pb-IFNa-A/D與PD-L1之組合導致統計上顯著之存活率提高。

【0511】結果表明該經掩蔽之IFNa-A/D在多種腫瘤模型中抑制腫瘤生長。具Pb-IFNa-A/D之組合使PD-L1mAb在CPI抗性B16腫瘤模型中具有治療活性。

實施例15：經活化之Pb-IFN-a2b在活體外與干擾素α受體結合

【0512】在活體外使用uPa活化Pb-INF-a2b並藉由色層分析法純化該活性部分(ProC1640)。將人干擾素α受體1(ProC1822)和食蟹獼猴干擾素α受體1(ProC1824)，以及人IFNAR2(ProC1823)和食蟹獼猴IFNAR2(ProC1825)以重組蛋白形式表現出並純化之。使用表面等離子體共振方法在活體外進行結合。將配體捕獲在具有固定化之抗人Fc或抗組胺酸抗體塗層的晶片上。建立允許多周期測量動力學的再生條件。令不同濃度之分析物流過液配體捕獲晶片以產生多周期動力學傳感圖，使用1:1結合模型分析該動力學傳感圖以獲得該動力學速率常數和親和力常數。

【0513】ProC1640與人和食蟹彌猴IFNAR1結合，然而由於該分子之解離極其緩慢，目前的方法無法測定該交互作用之親和力和特異性。檢測該IFN-α2b之經活化部分與人IFNAR2和食蟹彌猴IFNAR2之結合。如圖40A至40D所示，ProC732以相似之親和力與人和食蟹彌猴干擾素α受體IFNAR2結合。圖40A顯示人類IFNAR1隨時間之反應。圖40B顯示食蟹彌猴IFNAR1隨時間之反應。圖40C顯示人類IFNAR2隨時間之反應。圖40D顯示食蟹彌猴IFNAR2隨時間之反應。

【0514】如下表所示，對hIFNAR2之親和力為2.7 nM，對cynoIFNAR2之親和力為9.3 nM：

表18 使用IFN-a2b分子之結合研究的總結

配體	分析物	ka (1/Ms)	kd (1/s)	KD (nM)
ProC1823	ProC1640	4.374E+06	1.195E-02	2.731
ProC1825	ProC1640	2.674E+06	2.501E-02	9.353
ProC1823	ProC1976	8.985E+04	1.175E-02	130.8
ProC1718	ProC1640	5.177E+06	1.214E-02	2.344
ProC440	ProC1718	2.055E+05	2.077E-02	101.1

【0515】在驗證研究方面，分析該經活化之Pb-IFN-a2b(ProC1640)與經Fc標記之二聚體FNAR2(ProC1718)的結合。ProC1640與ProC1718之交互作用的Kd為2.3 nM。

【0516】因此，人IFN-a2b以相似之親和力與人IFNAR2和食蟹彌猴IFNAR2結合。該配體之形式和價數不影響測量結果。

實施例16：經單掩蔽之Pb-IFN-a2b分子與IFNAR2之結合

【0517】依上述將經掩蔽之Pb-INF-a2b與人IFNAR2結合。將經肽掩蔽之IFN-a2b(ProC1976)與其未經掩蔽之版本(ProC1640)直接比較表明親和力差別~50x(分別為130.8 nM和2.7 nM)。此外，與該未經掩蔽之分子相比較，經空間掩蔽之分子(ProC440)與IFNAR2之結合親和力顯著降低(kD=101.1 nM)。如圖38A至38D所示，該肽掩蔽物(圖38A(無肽掩蔽物)相對於圖38B(經肽掩蔽的))和Fc掩蔽物(圖38C(無Fc掩蔽物)相對於圖38D(經Fc掩蔽的))的每一者均影響ACC與該受體之結合。鑑於該數據，協同活性已透過使用本發明之ACC的雙重掩蔽結構獲得。因此，親和力

和空間掩蔽二者均降低該IFN-a2b與IFNAR2之結合。

實施例17：由腫瘤組織活化ACC

【0518】如圖41A所示，依(Howng, B, Winter, MB, LePage, C, et al. Novel Ex Vivo Zymography Approach for Assessment of Protease Activity in Tissues with Activatable Antibodies. Pharmaceutics 2021;13:1390)中之描述將經螢光標記之ProC732與酶活性之腫瘤樣品或低活性對照組織在37℃下一起培育。分析培育2或16小時後回收之蛋白質的活化狀態(毛細管電泳)和生物活性(HEK-blue報告基因分析)。然後透過毛細管電泳分析回收之溶液以能夠量化活性分子或低活性對照組織(圖41B)或使用HEK-blue IFNA報告基因模型(圖41C)。使用酶無活性之樣品作對照組織。結果證明ProC732在腫瘤微環境中活化。

【0519】與乳癌腫瘤樣品一起培育，但無低活性對照組織導致出現對應於預期在空間(Fc片段)和親和力(CS49肽)掩蔽物釋放後產生之分子的蛋白質產物(圖41B)。肽掩蔽物之釋放較早被檢測到，而Fc掩蔽物之分離在較晚的時間點較為明顯。與該乳癌組織一起培育，但無對照組織之Pb-IFN-a2b樣品在IFN路徑活化分析中顯示效力增加(圖41C)。與2小時相比較，培育16小時導致較高之效力。

【0520】該觀察結果與Pb-IFN-a2b分子以時間倚賴方式釋放空間和肽掩蔽物一致，因此，腫瘤組織可導致Pb-IFN-a2b之蛋白水解性活化。

實施例18：與腫瘤組織一起培育後干擾素分子之生物活性的變化。

【0521】將經完全掩蔽之Pb-INF-a2b(ProC732)或在活體外活化之(ProC1640)IFN-a2b蛋白與腫瘤樣本一起培育。使用HEK-blue報告基因分析來分析培育2、6或24小時後回收之蛋白質的生物活性。

【0522】與酶活性之腫瘤組織一起培育導致Pb-IFN-a2b活化和生物活性增加。相反地，與腫瘤組織一起培育會降低該未經掩蔽之干擾素的生物活性，此可能由該分子之蛋白水解降解造成。Pb-IFN-a2b和未經掩蔽之IFN-a2b二者之對照樣品的生物活性在無腫瘤的情況下培育後沒有變化。如圖42A至42C所示，將ProC732或重組IFN-a2b在37℃下，在TNBC和頭頸(“H&N”)腫瘤組織切片上或在無腫瘤之玻璃區域中培育。然後，藉由HEK-blue IFNA報告基因模型分析回收之溶液。圖42A和42B顯示相對於0小時數值，計算出之10 ng/mL ProC732或1 ng/mL之重組IFN-a2b的生物活性之倍數變化。圖42C顯示在沒有腫瘤組織之情況下培育24小時之ProC732和IFN-a2b蛋白的生物活性。每一條線連接培育前和培育24小時後所分析之個別樣品(濃度範圍100至0.01 ng/mL)。

【0523】結果表明暴露於腫瘤組織可在活體外降解未經掩蔽之干擾素分子。經掩蔽之Pb-IFN-a2b在暴露於腫瘤後保持並增進其生物活性。

實施例19：經掩蔽之INF-a2b和對照分子在非人靈長類動物中之藥效動力學

【0524】為了解該Pb-IFN-a2b在食蟹彌猴中之PK/PD特性，經由皮下投予0.03、0.3、3或15 mg/kg之單一Pb-IFN-a2b劑量來處理動物(每組N=2)。在指定之時間點收集血漿樣品並分析總Pb-IFN-a2b濃度。藉由MesoScale Discovery MSD V-plex分析測量血清中之IP-10的濃度。

【0525】投予ProC732導致該藥物之血漿濃度從投予後24小時的第一次測量開始以劑量依賴性方式增加(圖43)。Pb-IFN-a2b之血漿濃度在投予後至少維持2週。

【0526】最早在投予後24小時在經處理之動物中檢測到IP-10之血清濃度升高(圖44A)。增加之幅度與劑量水準相關；投予15和3 mg/kg導致IP-10濃度分別高於8和4 ng/mL。投予後7天，除了接受最高劑量水準處理之猴子外，所有動物之IP-10的血清水準恢復到生理濃度。將投予後第1天和第7天之循環Pb-IFN-a2b和IP-10濃度相對於彼此作圖(圖44B)。

【0527】結果與Pb-IFN-a2b在非人靈長類動物中半衰期延長相一致。以高劑量之Pb-IFN-a2b處理後，IP-10瞬時增加表明該分子可活化非人靈長類動物中第I型IFN信號傳導路徑，再給予高劑量水準。

實施例20：非人靈長類動物中由Pb-INF-a2b誘導之基因表

現輪廓變化

【0528】依前述使用Pb-IFN-a2b處理食蟹彌猴。投予後24小時從全血中分離出PBMC。分析食蟹彌猴中由ProC732誘導之基因表現輪廓變化。經由皮下投予0.03、0.3、3或15 mg/kg之單一ProC732劑量來處理食蟹彌猴(每組N=2)。將來自經分離之細胞的大量mRNA進行雙端配對150c RNAseq高通量測序。使用Subread包v.1.5.2計算獨特基因命中數，使用DESeq2比較指定樣本組之間的基因表現。使用Wald測試來產生p值和log2倍數變化。每次比較時其調整後之p值<0.05且絕對倍數變化 > 3之基因稱為差別表現基因。

【0529】投予之所有劑量水準的Pb-IFN-a2b均與循環白血球中之35個基因的上調有關(圖45)。投予之Pb-IFN-a2b的劑量水準增加(0.3、3和15 mg/kg)會分別上調額外數量之基因(3、12和47)。許多上調之基因屬於被鑑定為ISG或經干擾素刺激之基因(已知係由第I型干擾素誘導)的組別。對個別上調之基因的分析表明劑量依賴性之誘導模式，其中最明顯的變化與該Pb-IFN-a2b之最高劑量水準相關。圖46顯示基因表現之劑量依賴性變化。若讀數變化之數量>3，則基因被稱為差別表現。

【0530】此結果與在活體內藉由Pb-IFN-a2b活化第I型IFN信號傳導一致。

實施例21：P活體內表徵b-INFa-A/D

【0531】使用MC38腫瘤模型在活體內測試該經掩蔽之IFNa-A/D(ProC1023)的抗腫瘤活性。經由皮下為小鼠(每組N=10)植入1.5x10^{6}個在不含血清之培養基中之MC38細胞。在研究期間每週二次記錄體重和腫瘤測量值。當平均腫瘤體積達到80 mm^{3}時，藉由單次皮下注射給予小鼠指定量之ProC1023劑量。先前我們已建立該經掩蔽之IFNa-A/D在50至200μg劑量水準下會表現出抗腫瘤活性。投予50μg會導致顯著之腫瘤生長抑制，而投予200μg亦會導致60%之動物排去除腫瘤。在此實驗中，在投予後6天將動物安樂死，收集腫瘤、腫瘤引流淋巴結和脾臟並加工成單細胞懸浮液。藉由流式細胞術，使用全部細胞進行腫瘤免疫浸潤液之組成和活化的分析，並將門控設在存活之CD45+CD3+亞群。

【0532】在使用Pb-IFNa-A/D處理之小鼠中，CD8+T細胞亞群在腫瘤微環境(TME)中，但不在外周組織中表現出活化增強，包括產生與殺腫瘤活性相關之效應分子(圖47)。顆粒酶B為細胞毒性T細胞之效應分子，其可由第I型干擾素信號傳導誘導。Pb-IFNa-A/D之投予與腫瘤中顆粒酶B陽性和CD69陽性CD8+ T細胞頻率顯著增加有關，但周圍組織(包括腫瘤引流淋巴結)中沒有重大變化。

【0533】因此，數據顯示Pb-IFNa-A/D介導腫瘤中免疫活化，但外周組織中則無。免疫活化之模式與已發表之第I型干擾素作用大致上一致。腫瘤優先之免疫活化方式顯示ACC係由腫瘤透過蛋白水解式裂解活化。該觀察結果

與Pb-IFNa-A/D之由免疫介導之抑制MC38腫瘤生長的機制一致。

實施例22：Pb-IFN-a2b在活體內之耐受性

【0534】人IFNα-2b與倉鼠IFNα受體交叉反應且之前已證明在倉鼠中具有活性(Altrock et al, Journal of Interferon Research, 1986)。如實施例2所示，在單次投予後與未經掩蔽之IFN-a2b-Fc融合物(ProC286)或經單(空間)掩蔽之IFN-a2b(ProC440)相比較，ProC732在倉鼠中之耐受性提高。於該實施例中，在多次投予後測定該Pb-IFNα-2b在敘利亞金倉鼠中之耐受性。

【0535】每週一次i.p.給予動物(每組N=5)15、30或60 mg/kg劑量水準之ProC732劑量或7.5或15 mg/kg劑量水準之未經掩蔽之IFN-a2b-Fc融合蛋白(ProC286)劑量，共投予3次。給藥前進行臨床觀察、測量體重和體溫，此後每週測量二次。接受未經掩蔽之IFN分子(ProC286)劑量的動物早在第一次投予後3天顯示出顯著之體重減輕(圖48)。接受15 mg/kg之ProC286劑量的第一隻動物在第10天因體重過度減輕(>25%)而被安樂死，而所有其他動物則或因體重過度減輕、不活動和嗜睡被安樂死，或被發現在第11天和第19天之間死亡。對使用較低劑量(7.5 mg/kg)之未經掩蔽之INF-a2b處理的動物進行類似觀察。相反地，使用高達30 mg/kg之ProC732處理之動物沒有一隻表現出明顯的體重減輕或發病。

表19. 動物之存活情況顯示於圖48和下表中

	3.75 mg/kg	7.5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
Pb-IFN-a2b (經掩蔽的)			耐受的	耐受的	耐受的
Fc-IFN-a2b (未經掩蔽的)	耐受的	3/5 存活的	0/5 存活的		

【0536】結果與由於使用本發明中使用之雙重掩蔽結構而增加之Pb-IFN-a2b的安全性一致。

實施例23. 經投予單一劑量之Pb-IFN-a2b處理的食蟹彌猴中細胞介素和趨化因子釋放減少

【0537】為了解Pb-IFN-a2b在食蟹彌猴中之掩蔽作用，經由皮下投予單劑量之1 mg/kg的Pb-IFN-a2b (ProC732)或1或0.1 mg/kg之未經掩蔽之對照分子ProC286來處理動物(每組N=2)。在指定之時間點收集血漿樣本，並使用多重MSD V-plex分析來分析IP-10、MIP-1b和IL-12p70濃度。

【0538】如圖49所示，投予ProC732導致投予後6小時血漿IP-10和MIP-1b水準升高。在使用高劑量和低劑量水準之未經掩蔽之分子處理之動物中，所有測量之分子的血漿濃度均較高。投予後24小時，在使用ProC732處理之動物中僅觀察到IP-10稍微升高。相反地，接受1 mg/kg ProC286之動物表現出IP-10之水準大為升高。在投予0.1 mg/kg ProC286後24小時所觀察到之IP-10升高程度較由高10倍之ProC732劑量所誘導者更高。

【0539】結果表明與未經掩蔽之細胞介素-Fc融合物相比較，使用ProC732處理之非人靈長類動物中第I型干擾素反應之生物標誌物的誘導減弱。該觀察結果與掩蔽效果一致。

實施例24：多次投予Pb-IFN-a2b在非人靈長類動物中之耐受性

【0540】本研究之目的係測定當每週一次藉由靜脈輸注或皮下注射投予Pb-IFN-a2b(ProC732)，共3週時對食蟹彌猴的潛在毒性(總共3個劑量)。此外，亦調查該測試品Pb-IFN-a2b之藥代動力學(參見實施例25)。

【0541】本研究設計如下：

表20

組別編號[c]	測試品	劑量水準 (mg/kg)[a]	劑量體積 (mL/kg)	劑量濃度 (mg/mL)	劑量投予路徑	動物數目[b]	
						雄性	雌性
1	ProC732	7.5	10	0.75	IV	2	2
2	ProC732	15	10	1.5	IV	2	2
3	ProC732	30	10	3	IV	2	2
4	ProC732	30	10	3	SC	1	1
5	ProC732	60	12	5	IV	2	2

IV=靜脈內輸注；SC=皮下注射。

[a] 基於最近之體重測量。

[b] 動物在第18天被安樂死。

[c] 在第1組和第2組之第1天後的7天給予第3組和第4組劑量。在第3組和第4組之第1天後的20天給予第5組劑量。

【0542】本研究評估下列參數和終點：死亡率、臨床觀察、體重、體溫、定性食物消耗、臨床病理學參數(血

液學和臨床化學)、外周血單核細胞收集、器官重量以及宏觀和微觀檢查。

【0543】觀察總結如下：

表21

	7.5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
不良反應	-	-	-	-
CRP 升高	+/-	+	++	++
WBC 減少	+	+/-	++	++
IP-10 升高	++	++	++	++

【0544】所有動物均存活到第18天之預定屍檢。體重、定性食物消耗或體溫均沒有與藥物相關之變化。沒有確定之與Pb-IFN-a2b相關之臨床觀察結果且食物消耗沒有變化。在所有劑量下，在各種不同時間點，在一或多隻動物中觀察到總WBC計數和/或一或多個WBC亞群減少，且沒有劑量反應。這些減少包括嗜中性粒細胞之最低至顯著減少(除了在30 mg/kg SC之雄性和雌性動物及在15 mg/kg IV之雌性動物外)，在個別動物中有嗜中性粒細胞加速成熟和釋放之證據(帶狀、Döhle小體和/或細胞質嗜鹼性粒細胞)，包括在7.5和30 mg/kg IV下一些雄性和雌性動物，以及在30 mg/kg SC下一些雄性動物中嗜中性粒細胞沒有減少且淋巴細胞最低至輕度減少。除了在30 mg/kg SC下之雌性動物外，在所有劑量下單核細胞和/或嗜酸性粒細胞亦減少。除了在7.5 mg/kg IV下之雌性動物外，在所有劑量下，雄性和雌性動物中CRP亦最低至輕度增加，此表明輕

度急性期反應可能促成白蛋白減少。

【0545】總之，經由IV輸注每週投予一次7.5、15、30和60 mg/kg水準之Pb-IFN-a2b或經由SC注射每週投予一次30 mg/kg劑量水準之Pb-IFN-a2b持續3週(總共3個劑量)在臨床上是食蟹彌猴可耐受的。在一或多個時間點觀察所有劑量下之臨床病理學變化，但它們缺乏劑量反應，大多數的幅度為最低至輕微，且經常係在個別動物中發現。這些變化通常在第11天和/或第18天有較高之幅度和發生率。在大多數評估之組織中以及在評估之所有劑量水準和二種劑量路徑下都觀察到與Pb-IFN-a2b相關之顯微研究結果。

實施例25：對非人靈長類動物多次投予該Pb-IFN-a2b期間Pb-IFN-a2b之藥代動力學

【0546】本研究之目的係測定每週一次藉由靜脈內輸注或皮下注射對食蟹彌猴投予Pb-IFN-a2b(ProC732)共3週(總共3個劑量)時Pb-IFN-a2b(ProC732)的藥代動力學。此外，調查測試品Pb-IFN-a2b之潛在毒性(參見實施例24)。

【0547】研究設計如下：

表22

組別編號[c]	測試品	劑量水準 (mg/kg)[a]	劑量體積 (mL/kg)	劑量濃度 (mg/mL)	劑量投予路徑	動物數目[b]	
						雄性	雌性
1	ProC732	7.5	10	0.75	IV	2	2
2	ProC732	15	10	1.5	IV	2	2
3	ProC732	30	10	3	IV	2	2
4	ProC732	30	10	3	SC	1	1
5	ProC732	60	12	5	IV	2	2

IV=靜脈內輸注；SC=皮下注射。
[a] 基於最近之體重測量。
[b] 動物在第18天被安樂死。
[c] 在第1組和第2組之第1天後的7天給予第3組和第4組劑量。在第3組和第4組之第1天後的20天給予第5組劑量。

【0548】本研究評估生物分析(藉由LC-MS調查之Pb-IFN-a2b的穩定性)和藥代動力學參數。

【0549】如圖53所示，Pb-IFN-a2b顯示延長的、與劑量成比例之PK輪廓。在皮下和靜脈內之間觀察到預期之差異。與靜脈內投予相比較，皮下投予後達到最大血漿濃度之時間延遲且峰值幅度降低。

【0550】檢測之Pb-IFN-a2b的總濃度和完整形式之間沒有顯著差異。該觀察結果與Pb-IFN-a2b在非人靈長類動物中之15天循環期間內保存其掩蔽特性一致。

實施例26：多次投予Pb-IFN-a2b在攜帶RPMI1846黑色素瘤之倉鼠中的抗腫瘤功效

【0551】人IFNα-2b與倉鼠IFNα受體交叉反應且先前

已證明在倉鼠中具有活性(Altrock et al, Journal of Interferon Research, 1986)。實施例2和22中證明與未經掩蔽之IFN-a2b-Fc融合物(ProC286)相比較，Pb-IFN-a2b(ProC732)在倉鼠中之耐受性提高。於該實施例中，使用RPMI1846倉鼠黑色素瘤模型測定Pb-IFNα-2b之抗腫瘤功效(Palencia et al, Journal of Experimental Therapeutics and Oncology, 2002)。

【0552】經由皮下為80隻9至11週齡之敘利亞雌性倉鼠在右下腹(靠近大腿背側區域)接種在0.1 mL無血清之McCoy's 5a培養基中的95%存活腫瘤細胞之單細胞懸浮液。植入右側之細胞總數為每隻倉鼠1000萬個細胞。在形成可觸知之腫瘤後，為倉鼠稱重並使用隨機化程序分配到治療組。由於腫瘤體積會影響任何給予之治療的有效性，因此將腫瘤在200至350 mm^3之間的倉鼠納入研究並根據腫瘤體積隨機分組。每週二次ip給予動物(每組N=10)劑量為5、10或20 mg/kg之Pb-IFN-a2b劑量，共投予8次。使用卡尺每週二次測量二維空間中之腫瘤，並使用下列公式以mm^3表示體積：$V=0.5(a\times b\times c)$，其中a、b和c分別為該腫瘤之長度、寬度和高度。

【0553】藉由腫瘤生長評估抗腫瘤功效。與對照動物相比較，使用20 mg/kg Pb-IFN-a2b處理之動物顯著延遲腫瘤生長(圖50)。此外，與對照組相比較，使用20 mg/kg劑量水準處理之組別的中位生存期顯著較長(如藉由Kaplan-Meier存活曲線和對數秩檢驗分析)。此外，與5和10 mg/kg

治療組相比較，治療組之中位存活期明顯較長。因此，20 mg/kg劑量水準之Pb-IFN-a2b與抗腫瘤功效相關，而5和10 mg/kg之劑量水準不顯示抗腫瘤功效。

【0554】這些結果應在實施例6中證明未經掩蔽和經掩蔽之INF-a2b 分子具同等功效和實施例22中證明該經掩蔽之分子耐受性增加的背景下進行。總之，與該未經掩蔽之基準對照組相比較，這些結果與該經雙掩蔽之Pb-IFN-a2b分子的治療間隔增加一致。

表23. 示例序列

SEQ ID NO.	名稱	序列
1	人干擾素-α-2b	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKE
2	連接子	GGGS
3	人IgG4, S228P 截短之Fc區	CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
4	人IgG4 Fc區，具有S228P突變和完整鉸鏈區	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSS IEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
5	CM	LSGRSDNH
6	CM	TGRGPSWV
7	CM	PLTGRSGG
8	CM	TARGPSFK
9	CM	NTLSGRSENHSG
10	CM	NTLSGRSGNHGS
11	CM	TSTSGRSANPRG
12	CM	TSGRSANP
13	CM	VHMPLGFLGP
14	CM	AVGLLAPP
15	CM	AQNLLGMV
16	CM	QNQALRMA
17	CM	LAAPLGLL
18	CM	STFPFGMF
19	CM	ISSGLLSS
20	CM	PAGLWLDP
21	CM	VAGRSMRP

22	CM	VVPEGRRS
23	CM	ILPRSPAF
24	CM	MVLGRSLL
25	CM	QGRAITFI
26	CM	SPRSIMLA
27	CM	SMLRSMPL
28	CM	ISSGLLSGRSDNH
29	CM	AVGLLAPPGGLSGRSDNH
30	CM	ISSGLLSSGGSGGSLSGRSDNH
31	CM	LSGRSGNH
32	CM	SGRSANPRG
33	CM	LSGRSDDH
34	CM	LSGRSDIH
35	CM	LSGRSDQH
36	CM	LSGRSDTH
37	CM	LSGRSDYH
38	CM	LSGRSDNP
39	CM	LSGRSANP
40	CM	LSGRSANI
41	CM	LSGRSDNI
42	CM	MIAPVAYR
43	CM	RPSPMWAY
44	CM	WATPRPMR
45	CM	FRLLDWQW
46	CM	ISSGL
47	CM	ISSGLLS
48	CM	ISSGLL
49	CM	ISSGLLSGRSANPRG
50	CM	AVGLLAPPTSGRSANPRG
51	CM	AVGLLAPPSGRSANPRG

52	CM	ISSGLLSGRSDDH
53	CM	ISSGLLSGRSDIH
54	CM	ISSGLLSGRSDQH
55	CM	ISSGLLSGRSDTH
56	CM	ISSGLLSGRSDYH
57	CM	ISSGLLSGRSDNP
58	CM	ISSGLLSGRSANP
59	CM	ISSGLLSGRSANI
60	CM	AVGLLAPPGGLSGRSDDH
61	CM	AVGLLAPPGGLSGRSDIH
62	CM	AVGLLAPPGGLSGRSDQH
63	CM	AVGLLAPPGGLSGRSDTH
64	CM	AVGLLAPPGGLSGRSDYH
65	CM	AVGLLAPPGGLSGRSDNP
66	CM	AVGLLAPPGGLSGRSANP
67	CM	AVGLLAPPGGLSGRSANI
68	CM	ISSGLLSGRSDNI
69	CM	AVGLLAPPGGLSGRSDNI
70	CM	GLSGRSDNHGGAVGLLAPP
71	CM	GLSGRSDNHGGVHMPLGFLGP
72	CM	LSGRSDNHGGVHMPLGFLGP
73	CM	ISSGLSS
74	CM	PVGYTSSL
75	CM	DWLYWPGI
76	CM	LKAAPRWA
77	CM	GPSHLVLT
78	CM	LPGGLSPW
79	CM	MGLFSEAG
80	CM	SPLPLRVP
81	CM	RMHLRSLG

82	CM	LLAPSHRA
83	CM	GPRSFGL
84	CM	GPRSFG
85	CM	SARGPSRW
86	CM	GGWHTGRN
87	CM	HTGRSGAL
88	CM	AARGPAIH
89	CM	RGPAFNPM
90	CM	SSRGPAYL
91	CM	RGPATPIM
92	CM	RGPA
93	CM	GGQPSGMWGW
94	CM	FPRPLGITGL
95	CM	SPLTGRSG
96	CM	SAGFSLPA
97	CM	LAPLGLQRR
98	CM	SGGPLGVR
99	CM	PLGL
100	CM	SGRSDNI
101	人干擾素-α-2b	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWD ETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDS ILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKE
102	大鼠干擾素-α-2	CDLPHTHNLRNKRAFTLLAQMRRLSPVSCLKDRKDFG FPLEKVDGQQIQKAQAIPVLHELTQQILSLFTSKESSTA WDASLLDSFCNDLQQQLSGLQACLMQQVGVQESPLTQ EDSLLAVREYFHRITVYLREKKHSPCAWEVVRAEVWR ALSSSANLLGRLREERNES
103	小鼠干擾素-α-2	CDLPHTYNLRNKRALKVLAQMRRLPFLSCLKDRQDFG

		FPLEKVDNQQIQKAQAIPVLRDLTQQTLNLFTSKASSA AWNATLLDSFCN DLHQQLNDLQ TCLMQQVGVQ EPPLTQEDAL LAVRKYFHRITVYLREKKHS PCAWEVVRAE VWRALSSSVN LLPRLSEEKE
104	人干擾素-α-2b	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWD ETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDS ILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKE
105	人干擾素-α-n3	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWD ETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDS ILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKECDLPQTHSLGSRRTLMLLAQMRRISLFS CLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLF STKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVG VTETPLMNEDSILAVRKYFQRITLYLKEKKYSPCAWEV VRAEIMRSFSLSTNLQESLRSKECDLPQTHSLGSRRTLM LLAQMRRISLFSCLKDRRDFGFPQEEFGNQFQKAETIPV LHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLN DLEACVIQGVGVTETPLMNEDSILAVRKYFQRITLYLKE KKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE
106	人干擾素-β-1a	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRM NFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSS TGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTR GKLMSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEIL RNFYFINRLTGYLRN
107	人干擾素-β-1b	SYNLLGFLQRSSNFQSQKLLWQLNGRLEYCLKDRMNF DIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSSTG WNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGK LMSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRN

		FYFINRLTGYLRN
108	小鼠干擾素-β	MNNRWILHAAFLLCFSTTALSINYKQLQLQERTNIRKC QELLEQLNGKINLTYRADFKIPMEMTEKMQKSYTAFAI QEMLQNVFLVFRNNFSSTGWNETIVVRLLDELHQQTV FLKTVLEEKQEERLTWEMSSTALHLKSYYWRVQRYLK LMKYNSYAWMVVRAEIFRNFLIIRRLTRNFQN
109	大鼠干擾素-β	MANRWTLHIAFLLCFSTTALSIDYKQLQFRQSTSIRTCQ KLLRQLNGRLNLSYRTDFKIPMEVMHPSQMEKSYTAF AIQVMLQNVFLVFRSNFSSTGWNETIVESLLDELHQQT ELLEIILKEKQEERLTWVTSTTTLGLKSYYWRVQRYLK DKKYNSYAWMVVRAEVFRNFSIILRLNRNFQN
110	人干擾素ω	MCDLPQNHGLLSRNTLVLLHQMRRISPFLCLKDRRDFR FPQEMVKGSQLQKAHVMSVLHEMLQQIFSLFHTERSS AAWNMTLLDQLHTGLHQQLQHLETCLLQVVGEGESA GAISSPALTLRRYFQGIRVYLKEKKYSDCAWEVVRMEI MKSLFLSTNMQERLRSKDRDLGSS
111	人 **IL-1 α**	MAKVPDMFEDLKNCYSENEEDSSSIDHLSLNQKSFYH VSYGPLHEGCMDQSVSLSISETSKTSKLTFKESMVVVA TNGKVLKKRRLSLSQSITDDDLEAIANDSEEEIIKPRSAP FSFLSNVKYNFMRIIKYEFILNDALNQSIIRANDQYLTA AALHNLDEAVKFDMGAYKSSKDDAKITVILRISKTQLY VTAQDEDQPVLLKEMPEIPKTITGSETNLLFFWETHGT KNYFTSVAHPNLFIATKQDYWVCLAGGPPSITDFQILE NQA
112	小鼠**IL-1 α**	MAKVPDLFEDLKNCYSENEDYSSAIDHLSLNQKSFYD ASYGSLHETCTDQFVSLRTSETSKMSNFTFKESRVTVS ATSSNGKILKKRRLSFSETFTEDDLQSITHDLEETIQPRS APYTYQSDLRYKLMKLVRQKFVMNDSLNQTIYQDVD KHYLSTTWLNDLQQEVKFDMYAYSSGGDDSKYPVTL KISDSQLFVSAQGEDQPVLLKELPETPKLITGSETDLIFF WKSINSKNYFTSAAYPELFIATKEQSRVHLARGLPSMT

		DFQIS
113	人 **IL-1 β**	MAEVPELASEMMAYYSGNEDDLFFEADGPKQMKCSF QDLDLCPLDGGIQLRISDHHYSKGFRQAASVVVAMDK LRKMLVPCPQTFQENDLSTFFPFIFEEEPIFFDTWDNEA YVHDAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQG QDMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLS CVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINN KLEFESAQFPNWYISTSQAENMPVFLGGTKGGQDITDF TMQFVSS
114	小鼠 **IL-1 β**	MATVPELNCEMPPFDSDENDLFFEVDGPQKMKGCFQT FDLGCPDESIQLQISQQHINKSFRQAVSLIVAVEKLWQL PVSFPWTFQDEDMSTFFSFIFEEEPILCDSWDDDDNLLV CDVPIRQLHYRLRDEQQKSLVLSDPYELKALHLNGQNI NQQVIFSMSFVQGEPSNDKIPVALGLKGKNLYLSCVM KDGTPTLQLESVDPKQYPKKKMEKRFVFNKIEVKSKV EFESAEFPNWYISTSQAEHKPVFLGNNSGQDIIDFTMES VSS
115	人 **IL-1RA**	MEICRGLRSHLITLLLFLFHSETICRPSGRKSSKMQAFRI WDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIE PHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSE NRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEAD QPVSLTNMPDEGVMVTKFYFQEDE
116	小鼠 **IL-1RA**	MEICWGPYSHLISLLLILLFHSEAACRPSGKRPCKMQAF RIWDTNQKTFYLRNNQLIAGYLQGPNIKLEEKIDMVPI DLHSVFLGIHGGKLCLSCAKSGDDIKLQLEEVNITDLSK NKEEDKRFTFIRSEKGPTTSFESAACPGWFLCTTLEADR PVSLTNTPEEPLIVTKFYFQEDQ
117	人 **IL-18**	MAAEPVEDNCINFVAMKFIDNTLYFIAEDDENLESDYF GKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRD NAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKI ISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKMQFESSS

		YEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNED
118	小鼠**IL-18**	MAAMSEDSCVNFKEMMFIDNTLYFIPEENGDLESDNF GRLHCTTAVIRNINDQVLFVDKRQPVFEDMTDIDQSAS EPQTRLIIYMYKDSEVRGLAVTLSVKDSKMSTLSCKNK IISFEEMDPPENIDDIQSDLIFFQKRVPGHNKMEFESSLY EGHFLACQKEDDAFKLILKKKDENGDKSVMFTLTNLH QS
119	人**IL-2**	MYRMQLLSCIALSLALVTNSAPTSSSTKKTQLQLEHLL LDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKH LQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVL ELKGSETTFMCEYADETATIVEFLNRWITFCQSIIS
120	小鼠**IL-2**	MYSMQLASCVTLTLVLLVNSAPTSSSTSSSTAEAQQQQ QQQQQQQQHLEQLLMDLQELLSRMENYRNLKLPRML TFKFYLPKQATELKDLQCLEDELGPLRHVLDLTQSKSF QLEDAENFISNIRVTVVKLKGSDNTFECQFDDESATVV DFLRRWIAFCQSIISTSPQ
121	人**IL-4**	MGLTSQLLPPLFFLLACAGNFVHGHKCDITLQEIIKTLN SLTEQKTLCTELTVTDIFAASKNTTEKETFCRAATVLR QFYSHHEKDTRCLGATAQQFHRHKQLIRFLKRLDRNL WGLAGLNSCPVKEANQSTLENFLERLKTIMREKYSKC SS
122	小鼠**IL-4**	MGLNPQLVVILLFFLECTRSHIHGCDKNHLREIIGILNE VTGEGTPCTEMDVPNVLTATKNTTESELVCRASKVLRI FYLKHGKTPCLKKNSSVLMELQRLFRAFRCLDSSISCT MNESKSTSLKDFLESLKSIMQMDYS
123	人**IL-7**	MFHVSFRYIFGLPPLILVLLPVASSDCDIEGKDGKQYES VLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKE GMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILL NCTGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLND LCFLKRLLQEIKTCWNKILMGTKEH

124	小鼠IL-7	MFHVSFRYIFGIPPLILVLLPVTSSECHIKDKEGKAYESV LMISIDELDKMTGTDSNCPNNEPNFFRKHVCDDTKEAA FLNRAARKLKQFLKMNISEEFNVHLLTVSQGTQTLVN CTSKEEKNVKEQKKNDACFLKRLLREIKTCWNKILKG SI
125	人IL-9	MLLAMVLTSALLLCSVAGQGCPTLAGILDINFLINKMQ EDPASKCHCSANVTSCLCLGIPSDNCTRPCFSERLSQMT NTTMQTRYPLIFSRVKKSVEVLKNNKCPYFSCEQPCNQ TTAGNALTFLKSLLEIFQKEKMRGMRGKI
126	小鼠IL-9	MLVTYILASVLLFSSVLGQRCSTTWGIRDTNYLIENLK DDPPSKCSCSGNVTSCLCLSVPTDDCTTPCYREGLLQL TNATQKSRLLPVFHRVKRIVEVLKNITCPSFSCEKPCNQ TMAGNTLSFLKSLLGTFQKTEMQRQKSRP
127	人IL-13	MHPLLNPLLLALGLMALLLTTVIALTCLGGFASPGPVP PSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGM YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFS SLHVRDTKIEVAQFVKDLLLHLKKLFREGRFN
128	小鼠IL-13	MALWVTAVLALACLGGLAAPGPVPRSVSLPLTLKELIE ELSNITQDQTPLCNGSMVWSVDLAAGGFCVALDSLTNI SNCNAIYRTQRILHGLCNRKAPTTVSSLPDTKIEVAHFI TKLLSYTKQLFRHGPF
129	人IL-15	MRISKPHLRSISIQCYLCLLLNSHFLTEAGIHVFILGCFS AGLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTESD VHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIIL ANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQ MFINTS
130	小鼠IL-15	MKILKPYMRNTSISCYLCFLLNSHFLTEAGIHVFILGCV SVGLPKTEANWIDVRYDLEKIESLIQSIHIDTTLYTDSDF HPSCKVTAMNCFLLELQVILHEYSNMTLNETVRNVLY LANSTLSSNKNVAESGCKECEELEEKTFTEFLQSFIRIV

		QMFINTS
131	人**IL-3**	MSRLPVLLLLQLLVRPGLQAPMTQTTPLKTSWVNCSN MIDEIITHLKQPPLPLLDFNNLNGEDQDILMENNLRRPN LEAFNRAVKSLQNASAIESILKNLLPCLPLATAAPTRHP IHIKDGDWNEFRRKLTFYLKTLENAQAQQTTLSLAIF
132	小鼠**IL-3**	MVLASSTTSIHTMLLLLLMLFHLGLQASISGRDTHRLT RTLNCSSIVKEIIGKLPEPELKTDDEGPSLRNKSFRRVNL SKFVESQGEVDPEDRYVIKSNLQKLNCCLPTSANDSAL PGVFIRDLDDFRKKLRFYMVHLNDLETVLTSRPPQPAS GSVSPNRGTVEC
133	人**IL-5**	MRMLLHLSLLALGAAYVYAIPTEIPTSALVKETLALLS THRTLLIANETLRIPVPVHKNHQLCTEEIFQGIGTLESQT VQGGTVERLFKNLSLIKKYIDGQKKKCGEERRRVNQF LDYLQEFLGVMNTEWIIES
134	小鼠**IL-5**	MRRMLLHLSVLTLSCVWATAMEIPMSTVVKETLTQLS AHRALLTSNETMRLPVPTHKNHQLCIGEIFQGLDILKN QTVRGGTVEMLFQNLSLIKKYIDRQKEKCGEERRRTR QFLDYLQEFLGVMSTEWAMEG
135	人 GM-CSF	MWLQSLLLLGTVACSISAPARSPSPSTQPWEHVNAIQE ARRLLNLSRDTAAEMNETVEVISEMFDLQEPTCLQTRL ELYKQGLRGSLTKLKGPLTMMASHYKQHCPPTPETSC ATQIITFESFKENLKDFLLVIPFDCWEPVQE
136	小鼠 GM-CSF	MWLQNLLFLGIVVYSLSAPTRSPITVTRPWKHVEAIKE ALNLLDDMPVTLNEEVEVVSNEFSFKKLTCVQTRLKIF EQGLRGNFTKLKGALNMTASYYQTYCPPTPETDCETQ VTTYADFIDSLKTFLTDIPFECKKPGQK
137	人**IL-6**	MNSFSTSAFGPVAFSLGLLLVLPAAFPAPVPPGEDSKD VAAPHRQPLTSSERIDKQIRYILDGISALRKETCNKSNM CESSKEALAENNLNLPKMAEKDGCFQSGFNEETCLVKI ITGLLEFEVYLEYLQNRFESSEEQARAVQMSTKVLIQFL

		QKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTT HLILRSFKEFLQSSLRALRQM
138	小鼠**IL-6**	MKFLSARDFHPVAFLGLMLVTTTAFPTSQVRRGDFTE DTTPNRPVYTTSQVGGLITHVLWEIVEMRKELCNGNS DCMNNDDALAENNLKLPEIQRNDGCYQTGYNQEICLL KISSGLLEYHSYLEYMKNNLKDNKKDKARVLQRDTET LIHIFNQEVKDLHKIVLPTPISNALLTDKLESQKEWLRT KTIQFILKSLEEFLKVTLRSTRQT
139	人**IL-11**	MNCVCRLVLVVLSLWPDTAVAPGPPPGPPRVSPDPRA ELDSTVLLTRSLLADTRQLAAQLRDKFPADGDHNLDS LPTLAMSAGALGALQLPGVLTRLRADLLSYLRHVQWL RRAGGSSLKTLEPELGTLQARLDRLLRRLQLLMSRLAL PQPPPDPPAPPLAPPSSAWGGIRAAHAILGGLHLTLDW AVRGLLLLKTRL
140	小鼠**IL-11**	MNCVCRLVLVVLSLWPDRVVAPGPPAGSPRVSSDPRA DLDSAVLLTRSLLADTRQLAAQMRDKFPADGDHSLDS LPTLAMSAGTLGSLQLPGVLTRLRVDLMSYLRHVQWL RRAGGPSLKTLEPELGALQARLERLLRRLQLLMSRLAL PQAAPDQPVIPLGPPASAWGSIRAAHAILGGLHLTLDW AVRGLLLLKTRL
141	人 G-CSF	MAGPATQSPMKLMALQLLLWHSALWTVQEATPLGPA SSLPQSFLLKCLEQVRKIQGDGAALQEKLVSECATYKL CHPEELVLLGHSLGIPWAPLSSCPSQALQLAGCLSQLHS GLFLYQGLLQALEGISPELGPTLDTLQLDVADFATTIW QQMEELGMAPALQPTQGAMPAFASAFQRRAGGVLVA SHLQSFLEVSYRVLRHLAQP
142	小鼠 G-CSF	MAQLSAQRRMKLMALQLLLWQSALWSGREAVPLVT VSALPPSLPLPRSFLLKSLEQVRKIQASGSVLLEQLCAT YKLCHPEELVLLGHSLGIPKASLSGCSSQALQQTQCLS QLHSGLCLYQGLLQALSGISPALAPTLDLLQLDVANFA TTIWQQMENLGVAPTVQPTQSAMPAFTSAFQRRAGGV

		LAISYLQGFLETARLALHHLA
143	人IL-12 α	MCPARSLLLVATLVLLDHLSLARNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITK DKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRK TSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKR QIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFY KTKIKLCILLHAFRIRAVTIDRVMSYLNAS
144	人IL-12 β	MCHQQLVISWFSLVFLASPLVAIWELKKDVYVVELDW YPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTL TIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIW STDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTIST DLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDNKEY EYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYT SSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWS TPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR KNASISVRAQDRYYSSSWSEWASVPCS
145	小鼠IL-12 β	MCPQKLTISWFAIVLLVSPLMAMWELEKDVYVVEVD WTPDAPGETVNLTCDTPEEDDITWTSDQRHGVIGSGKT LTITVKEFLDAGQYTCHKGGETLSHSHLLLHKKENGIW STEILKNFKNKTFLKCEAPNYSGRFTCSWLVQRNMDL KFNIKSSSSSPDSRAVTCGMASLSAEKVTLDQRDYEKY SVSCQEDVTCPTAEETLPIELALEARQQNKYENYSTSFF IRDIIKPDPPKNLQMKPLKNSQVEVSWEYPDSWSTPHS YFSLKFFVRIQRKKEKMKETEEGCNQKGAFLVEKTSTE VQCKGGNVCVQAQDRYYNSSCSKWACVPCRVRS
146	小鼠IL-12 α	MCQSRYLLFLATLALLNHLSLARVIPVSGPARCLSQSR NLLKTTDDMVKTAREKLKHYSCTAEDIDHEDITRDQT STLKTCLPLELHKNESCLATRETSSTTRGSCLPPQKTSL MMTLCLGSIYEDLKMYQTEFQAINAALQNHNHQQIIL DKGMLVAIDELMQSLNHNGETLRQKPPVGEADPYRV KMKLCILLHAFSTRVVTINRVMGYLSSA

147	人**LIF**	MKVLAAGVVPLLLVLHWKHGAGSPLPITPVNATCAIR HPCHNNLMNQIRSQLAQLNGSANALFILYYTAQGEPFP NNLDKLCGPNVTDFPPFHANGTEKAKLVELYRIVVYL GTSLGNITRDQKILNPSALSLHSKLNATADILRGLLSNV LCRLCSKYHVGHVDVTYGPDTSGKDVFQKKKLGCQL LGKYKQIIAVLAQAF
148	小鼠**LIF**	MKVLAAGIVPLLLLVLHWKHGAGSPLPITPVNATCAIR HPCHGNLMNQIKNQLAQLNGSANALFISYYTAQGEPFP NNVEKLCAPNMTDFPSFHGNGTEKTKLVELYRMVAY LSASLTNITRDQKVLNPTAVSLQVKLNATIDVMRGLLS NVLCRLCNKYRVGHVDVPPVPDHSDKEAFQRKKLGC QLLGTYKQVISVVVQAF
149	人**OSM**	MGVLLTQRTLLSLVLALLFPSMASMAAIGSCSKEYRVL LGQLQKQTDLMQDTSRLLDPYIRIQGLDVPKLREHCRE RPGAFPSEETLRGLGRRGFLQTLNATLGCVLHRLADLE QRLPKAQDLERSGLNIEDLEKLQMARPNILGLRNNIYC MAQLLDNSDTAEPTKAGRGASQPPTPTPASDAFQRKL EGCRFLHGYHRFMHSVGRVFSKWGESPNRSRRHSPHQ ALRKGVRRTRPSRKGKRLMTRGQLPR
150	小鼠**OSM**	MQTRLLRTLLSLTLSLLILSMALANRGCSNSSSQLLSQL QNQANLTGNTESLLEPYIRLQNLNTPDLRAACTQHSVA FPSEDTLRQLSKPHFLSTVYTTLDRVLYQLDALRQKFL KTPAFPKLDSARHNILGIRNNVFCMARLLNHSLEIPEPT QTDSGASRSTTTPDVFNTKIGSCGFLWGYHRFMGSVG RVFREWDDGSTRSRRQSPLRARRKGTRRIRVRHKGTR RIRVRRKGTRRIWVRRKGSRKIRPSRSTQSPTTRA
151	人**IL-10**	MHSSALLCCLVLLTGVRASPGQGTQSENSCTHFPGNLP NMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFK GYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSL GENLKTLRLRLRRCHRFLPCENKSKAVEQVKNAFNKL QEKGIYKAMSEFDIFINYIEAYMTMKIRN

152	小鼠IL-10	MPGSALLCCLLLLTGMRISRGQYSREDNNCTHFPVGQS HMLLELRTAFSQVKTFFQTKDQLDNILLTDSLMQDFK GYLGCQALSEMIQFYLVEVMPQAEKHGPEIKEHLNSL GEKLKTLRMRLRRCHRFLPCENKSKAVEQVKSDFNKL QDQGVYKAMNEFDIFINCIEAYMMIKMKS
153	人IL-20	MKASSLAFSLLSAAFYLLWTPSTGLKTLNLGSCVIATN LQEIRNGFSEIRGSVQAKDGNIDIRILRRTESLQDTKPAN RCCLLRHLLRLYLDRVFKNYQTPDHYTLRKISSLANSF LTIKKDLRLCHAHMTCHCGEEAMKKYSQILSHFEKLEP QAAVVKALGELDILLQWMEETE
154	小鼠IL-20	MKGFGLAFGLFSAVGFLLWTPLTGLKTLHLGSCVITAN LQAIQKEFSEIRDSVQAEDTNIDIRILRTTESLKDIKSLD RCCFLRHLVRFYLDRVFKVYQTPDHHTLRKISSLANSF LIIKKDLSVCHSHMACHCGEEAMEKYNQILSHFIELEL QAAVVKALGELGILLRWMEEML
155	人IL-14	MKNQDKKNGAAKQSNPKSSPGQPEAGPEGAQERPSQ AAPAVEAEGPGSSQAPRKPEGAQARTAQSGALRDVSE ELSRQLEDILSTYCVDNNQGGPGEDGAQGEPAEPEDAE KSRTYVARNGEPEPTPVVNGEKEPSKGDPNTEEIRQSD EVGDRDHRRPQEKKKAKGLGKEITLLMQTLNTLSTPE EKLAALCKKYAELLEEHRNSQKQMKLLQKKQSQLVQ EKDHLRGEHSKAVLARSKLESLCRELQRHNRSLKEEG VQRAREEEEKRKEVTSHFQVTLNDIQLQMEQHNERNS KLRQENMELAERLKKLIEQYELREEHIDKVFKHKDLQ QQLVDAKLQQAQEMLKEAEERHQREKDFLLKEAVES QRMCELMKQQETHLKQQLALYTEKFEEFQNTLSKSSE VFTTFKQEMEKMTKKIKKLEKETTMYRSRWESSNKAL LEMAEEKTVRDKELEGLQVKIQRLEKLCRALQTERND LNKRVQDLSAGGQGSLTDSGPERRPEGPGAQAPSSPRV TEAPCYPGAPSTEASGQTGPQEPTSARA
156	小鼠IL-14	MKNQDKKNGPAKHSNSKGSPGQREAGPEGAHGRPRQ

		TAPGAEAEGSTSQAPGKTEGARAKAAQPGALCDVSEE LSRQLEDILSTYCVDNNQGGPAEEGAQGEPTEPEDTEK SRTYAARNGEPEPGIPVVNGEKETSKGEPGTEEIRASDE VGDRDHRRPQEKKKAKGLGKEITLLMQTLNTLSTPEE KLAALCKKYAELLEEHRNSQKQMKLLQKKQSQLVQE KDHLRGEHSKAVLARSKLESLCRELQRHNRSLKEEGV QRAREEEEKRKEVTSHFQVTLNDIQLQMEQHNERNSK LRQENMELAERLKKLIEQYELREEHIDKVFKHKDLQQ QLVDAKLQQAQEMLKEAEERHQREKEFLLKEAVESQR MCELMKQQETHLKQQLALYTEKFEEFQNTLSKSSEVF TTFKQEMEKMTKKIKKLEKETTMYRSRWESSNKALLE MAEEKTVRDKELEGLQVKIQRLEKLCRALQTERNDLN KRVQDLTAGGITDIGSERRPEATTASKEQGVESPGAQP ASSPRATDAPCCSGAPSTGTAGQTGPGEPTPATA
157	人IL-16	MESHSRAGKSRKSAKFRSISRSLMLCNAKTSDDGSSPD EKYPDPFEISLAQGKEGIFHSSVQLADTSEAGPSSVPDL ALASEAAQLQAAGNDRGKTCRRIFFMKESSTASSREKP GKLEAQSSNFLFPKACHQRARSNSTSVNPYCTREIDFP MTKKSAAPTDRQPYSLCSNRKSLSQQLDCPAGKAAGT SRPTRSLSTAQLVQPSGGLQASVISNIVLMKGQAKGLG FSIVGGKDSIYGPIGIYVKTIFAGGAAAADGRLQEGDEI LELNGESMAGLTHQDALQKFKQAKKGLLTLTVRTRLT APPSLCSHLSPPLCRSLSSSTCITKDSSSFALESPSAPIST AKPNYRIMVEVSLQKEAGVGLGIGLCSVPYFQCISGIFV HTLSPGSVAHLDGRLRCGDEIVEISDSPVHCLTLNEVYT ILSHCDPGPVPIIVSRHPDPQVSEQQLKEAVAQAVENTK FGKERHQWSLEGVKRLESSWHGRPTLEKEREKNSAPP HRRAQKVMIRSSSDSSYMSGSPGGSPGSGSAEKPSSDV DISTHSPSLPLAREPVVLSIASSRLPQESPPLPESRDSHPP LRLKKSFEIVRKPMSSKPKPPPRKYFKSDSDPQKSLEER ENSSCSSGHTPPTCGQEARELLPLLLPQEDTAGRSPSAS

		AGCPGPGIGPQTKSSTEGEPGWRRASPVTQTSPIKHPLL KRQARMDYSFDTTAEDPWVRISDCIKNLFSPIMSENHG HMPLQPNASLNEEEGTQGHPDGTPPKLDTANGTPKVY KSADSSTVKKGPPVAPKPAWFRQSLKGLRNRASDPRG LPDPALSTQPAPASREHLGSHIRASSSSSSIRQRISSFETF GSSQLPDKGAQRLSLQPSSGEAAKPLGKHEEGRFSGLL GRGAAPTLVPQQPEQVLSSGSPAASEARDPGVSESPPP GRQPNQKTLPPGPDPLLRLLSTQAEESQGPVLKMPSQR ARSFPLTRSQSCETKLLDEKTSKLYSISSQVSSAVMKSL LCLPSSISCAQTPCIPKEGASPTSSSNEDSAANGSAETSA LDTGFSLNLSELREYTEGLTEAKEDDDGDHSSLQSGQS VISLLSSEELKKLIEEVKVLDEATLKQLDGIHVTILHKEE GAGLGFSLAGGADLENKVITVHRVFPNGLASQEGTIQK GNEVLSINGKSLKGTTHHDALAILRQAREPRQAVIVTR KLTPEAMPDLNSSTDSAASASAASDVSVESTAEATVCT VTLEKMSAGLGFSLEGGKGSLHGDKPLTINRIFKGAAS EQSETVQPGDEILQLGGTAMQGLTRFEAWNIIKALPDG PVTIVIRRKSLQSKETTAAGDS
158	小鼠IL-16	MEPHGHSGKSRKSTKFRSISRSLILCNAKTSDDGSSPDE KYPDPFETSLCQGKEGFFHSSMQLADTFEAGLSNIPDL ALASDSAQLAAAGSDRGKHCRKMFFMKESSSTSSKEK SGKPEAQSSSFLFPKACHQRTRSNSTSVNPYSAGEIDFP MTKKSAAPTDRQPYSLCSNRKSLSQQLDYPILGTARPT RSLSTAQLGQLSGGLQASVISNIVLMKGQAKGLGFSIV GGKDSIYGPIGIYVKSIFAGGAAAADGRLQEGDEILELN GESMAGLTHQDALQKFKQAKKGLLTLTVRTRLTTPPS LCSHLSPPLCRSLSSSTCGAQDSSPFSLESPASPASTAKP NYRIMVEVSLKKEAGVGLGIGLCSIPYFQCISGIFVHTL SPGSVAHLDGRLRCGDEIVEINDSPVHCLTLNEVYTILS HCDPGPVPIIVSRHPDPQVSEQQLKEAVAQAVEGVKFG KDRHQWSLEGVKRLESSWHGRPTLEKEREKHSAPPHR

		RAQKIMVRSSSDSSYMSGSPGGSPCSAGAEPQPSEREG STHSPSLSPGEEQEPCPGVPSRPQQESPPLPESLERESHP PLRLKKSFEILVRKPTSSKPKPPPRKYFKNDSEPQKKLE EKEKVTDPSGHTLPTCSQETRELLPLLLQEDTAGRAPC TAACCPGPAASTQTSSSTEGESRRSASPETPASPGKHPL LKRQARMDYSFDITAEDPWVRISDCIKNLFSPIMSENHS HTPLQPNTSLGEEDGTQGCPEGGLSKMDAANGAPRVY KSADGSTVKKGPPVAPKPAWFRQSLKGLRNRAPDPRR PPEVASAIQPTPVSRDPPGPQPQASSSIRQRISSFENFGSS QLPDRGVQRLSLQPSSGETTKFPGKQDGGRFSGLLGQG ATVTAKHRQTEVESMSTTFPNSSEVRDPGLPESPPPGQ RPSTKALSPDPLLRLLTTQSEDTQGPGLKMPSQRARSFP LTRTQSCETKLLDEKASKLYSISSQLSSAVMKSLLCLPS SVSCGQITCIPKERVSPKSPCNNSSAAEGFGEAMASDTG FSLNLSELREYSEGLTEPGETEDRNHCSSQAGQSVISLL SAEELEKLIEEVRVLDEATLKQLDSIHVTILHKEEGAGL GFSLAGGADLENKVITVHRVFPNGLASQEGTIQKGNEV LSINGKSLKGATHNDALAILRQARDPRQAVIVTRRTTV EATHDLNSSTDSAASASAASDISVESKEATVCTVTLEK TSAGLGFSLEGGKGSLHGDKPLTINRIFKGTEQGEMVQ PGDEILQLAGTAVQGLTRFEAWNVIKALPDGPVTIVIR RTSLQCKQTTASADS
159	人IL-17	MTPGKTSLVSLLLLLSLEAIVKAGITIPRNPGCPNSEDK NFPRTVMVNLNIHNRNTNTNPKRSSDYYNRSTSPWNL HRNEDPERYPSVIWEAKCRHLGCINADGNVDYHMNSV PIQQEILVLRREPPHCPNSFRLEKILVSVGCTCVTPIVHH VA
160	小鼠IL-17	MSPGRASSVSLMLLLLLSLAATVKAAAIIPQSSACPNTE AKDFLQNVKVNLKVFNSLGAKVSSRRPSDYLNRSTSP WTLHRNEDPDRYPSVIWEAQCRHQRCVNAEGKLDHH MNSVLIQQEILVLKREPESCPFTFRVEKMLVGVGCTCV

		ASIVRQAA
161	人CD154	MIETYNQTSPRSAATGLPISMKIFMYLLTVFLITQMIGS ALFAVYLHRRLDKIEDERNLHEDFVFMKTIQRCNTGER SLSLLNCEEIKSQFEGFVKDIMLNKEETKKENSFEMQK GDQNPQIAAHVISEASSKTTSVLQWAEKGYYTMSNNL VTLENGKQLTVKRQGLYYIYAQVTFCSNREASSQAPFI ASLCLKSPGRFERILLRAANTHSSAKPCGQQSIHLGGVF ELQPGASVFVNVTDPSQVSHGTGFTSFGLLKL
162	小鼠CD154	MIETYSQPSPRSVATGLPASMKIFMYLLTVFLITQMIGS VLFAVYLHRRLDKVEEEVNLHEDFVFIKKLKRCNKGE GSLSLLNCEEMRRQFEDLVKDITLNKEEKKENSFEMQR GDEDPQIAAHVVSEANSNAASVLQWAKKGYYTMKSN LVMLENGKQLTVKREGLYYVYTQVTFCSNREPSSQRP FIVGLWLKPSSGSERILLKAANTHSSSQLCEQQSVHLG GVFELQAGASVFVNVTEASQVIHRVGFSSFGLLKL
163	人LT-β	MGALGLEGRGGRLQGRGSLLLAVAGATSLVTLLLAVP ITVLAVLALVPQDQGGLVTETADPGAQAQQGLGFQKL PEEEPETDLSPGLPAAHLIGAPLKGQGLGWETTKEQAF LTSGTQFSDAEGLALPQDGLYYLYCLVGYRGRAPPGG GDPQGRSVTLRSSLYRAGGAYGPGTPELLLEGAETVTP VLDPARRQGYGPLWYTSVGFGGLVQLRRGERVYVNIS HPDMVDFARGKTFFGAVMVG
164	小鼠LT-β	MGTRGLQGLGGRPQGRGCLLLAVAGATSLVTLLLAVP ITVLAVLALVPQDQGRRVEKIIGSGAQAQKRLDDSKPS CILPSPSSLSETPDPRLHPQRSNASRNLASTSQGPVAQSS REASAWMTILSPAADSTPDPGVQQLPKGEPETDLNPEL PAAHLIGAWMSGQGLSWEASQEEAFLRSGAQFSPTHG LALPQDGVYYLYCHVGYRGRTPPAGRSRARSLTLRSA LYRAGGAYGRGSPELLLEGAETVTPVVDPIGYGSLWY TSVGFGGLAQLRSGERVYVNISHPDMVDYRRGKTFFG AVMVG

165	人TNF-α	STESMIRDVELAEEALPKKTGGPQGSRRCLFLSLFSFLI VAGATTLFCLLHFGVIGPQREEFPRDLSLISPLAQAVRS SSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLAN GVELRDNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLT HTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYE PIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGII AL
166	小鼠TNF-α	NHQVEEQLEWLSQRANALLANGMDLKDNQLVVPAD GLYLVYSQVLFKGQGCPDYVLLTHTVSRFAISYQEKV NLLSAVKSPCPKDTPEGAELKPWYEPIYLGGVFQLEKG DQLSAEVNLPKYLDFAESGQVYFGVIAL
167	人TNF-β	MTPPERLFLPRVCGTTLHLLLLGLLLVLLPGAQGLPGV GLTPSAAQTARQHPKMHLAHSTLKPAAHLIGDPSKQN SLLWRANTDRAFLQDGFSLSNNSLLVPTSGIYFVYSQV VFSGKAYSPKATSSPLYLAHEVQLFSSQYPFHVPLLSSQ KMVYPGLQEPWLHSMYHGAAFQLTQGDQLSTHTDGI PHLVLSPSTVFFGAFAL
168	人4-1BBL	MEYASDASLDPEAPWPPAPRARACRVLPWALVAGLLL LLLLAAACAVFLACPWAVSGARASPGSAASPRLREGP ELSPDDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYS DPGLAGVSLTGGLSYKEDTKELVVAKAGVYYVFFQLE LRRVVAGEGSGSVSLALHLQPLRSAAGAAALALTVDL PPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARAR HAWQLTQGATVLGLFRVTPEIPAGLPSPRSE
169	小鼠4-1BBL	MDQHTLDVEDTADARHPAGTSCPSDAALLRDTGLLAD AALLSDTVRPTNAALPTDAAYPAVNVRDREAAWPPAL NFCSRHPKLYGLVALVLLLLIAACVPIFTRTEPRPALTIT TSPNLGTRENNADQVTPVSHIGCPNTTQQGSPVFAKLL AKNQASLCNTTLNWHSQDGAGSSYLSQGLRYEEDKK ELVVDSPGLYYVFLELKLSPTFTNTGHKVQGWVSLVL QAKPQVDDFDNLALTVELFPCSMENKLVDRSWSQLLL

		LKAGHRLSVGLRAYLHGAQDAYRDWELSYPNTTSFGL FLVKPDNPWE
170	人APRIL	AVLTQKQKKQHSVLHLVPINATSKDDSDVTEVMWQP ALRRGRGLQAQGYGVRIQDAGVYLLYSQVLFQDVTFT MGQVVSREGQGRQETLFRCIRSMPSHPDRAYNSCYSA GVFHLHQGDILSVIIPRARAKLNLSPHGTFLGFVKL
171	小鼠 APRIL	MPASSPGHMGGSVREPALSVALWLSWGAVLGAVTCA VALLIQQTELQSLRREVSRLQRSGGPSQKQGERPWQSL WEQSPDVLEAWKDGAKSRRRRAVLTQKHKKKHSVLH LVPVNITSKADSDVTEVMWQPVLRRGRGLEAQGDIVR VWDTGIYLLYSQVLFHDVTFTMGQVVSREGQGRRETL FRCIRSMPSDPDRAYNSCYSAGVFHLHQGDIITVKIPRA NAKLSLSPHGTFLGFVKL
172	人 CD70	MPEEGSGCSVRRRPYGCVLRAALVPLVAGLVICLVVCI QRFAQAQQQLPLESLGWDVAELQLNHTGPQQDPRLY WQGGPALGRSFLHGPELDKGQLRIHRDGIYMVHIQVT LAICSSTTASRHHPTTLAVGICSPASRSISLLRLSFHQGC TIASQRLTPLARGDTLCTNLTGTLLPSRNTDETFFGVQ WVRP
173	小鼠 CD70	MPEEGRPCPWVRWSGTAFQRQWPWLLLVVFITVFCC WFHCSGLLSKQQQRLLEHPEPHTAELQLNLTVPRKDPT LRWGAGPALGRSFTHGPELEEGHLRIHQDGLYRLHIQV TLANCSSPGSTLQHRATLAVGICSPAAHGISLLRGRFGQ DCTVALQRLTYLVHGDVLCTNLTLPLLPSRNADETFFG VQWICP
174	人 CD153	MDPGLQQALNGMAPPGDTAMHVPAGSVASHLGTTSR SYFYLTTATLALCLVFTVATIMVLVVQRTDSIPNSPDN VPLKGGNCSEDLLCILKRAPFKKSWAYLQVAKHLNKT KLSWNKDGILHGVRYQDGNLVIQFPGLYFIICQLQFLV QCPNNSVDLKLELLINKHIKKQALVTVCESGMQTKHV YQNLSQFLLDYLQVNTTISVNVDTFQYIDTSTFPLENVL

		SIFLYSNSD
175	小鼠 CD153	MEPGLQQAGSCGAPSPDPAMQVQPGSVASPWRSTRP WRSTSRSYFYLSTTALVCLVVAVAIILVLVVQKKDSTP NTTEKAPLKGGNCSEDLFCTLKSTPSKKSWAYLQVSK HLNNTKLSWNEDGTIHGLIYQDGNLIVQFPGLYFIVCQ LQFLVQCSNHSVDLTLQLLINSKIKKQTLVTVCESGVQ SKNIYQNLSQFLLHYLQVNSTISVRVDNFQYVDTNTFP LDNVLSVFLYSSSD
176	人 CD178	MQQPFNYPYPQIYWVDSSASSPWAPPGTVLPCPTSVPR RPGQRRPPPPPPPPLPPPPPPPLPPLPLPPLKKRGNHST GLCLLVMFFMVLVALVGLGLGMFQLFHLQKELAELRE STSQMHTASSLEKQIGHPSPPPEKKELRKVAHLTGKSN SRSMPLEWEDTYGIVLLSGVKYKKGGLVINETGLYFV YSKVYFRGQSCNNLPLSHKVYMRNSKYPQDLVMMEG KMMSYCTTGQMWARSSYLGAVFNLTSADHLYVNVSE LSLVNFEESQTFFGLYKL
177	小鼠 CD178	MQQPMNYPCPQIFWVDSSATSSWAPPGSVFPCPSCGPR GPDQRRPPPPPPPVSPLPPPSQPLPLPPLTPLKKKDHNTN LWLPVVFFMVLVALVGMGLGMYQLFHLQKELAELRE FTNQSLKVSSFEKQIANPSTPSEKKEPRSVAHLTGNPHS RSIPLEWEDTYGTALISGVKYKKGGLVINETGLYFVYS KVYFRGQSCNNQPLNHKVYMRNSKYPEDLVLMEEKR LNYCTTGQIWAHSSYLGAVFNLTSADHLYVNISQLSLI NFEESKTFFGLYKL
178	人 GITRL	MTLHPSPITCEFLFSTALISPKMCLSHLENMPLSHSRTQ GAQRSSWKLWLFCSIVMLLFLCSFSWLIFIFLQLETAKE PCMAKFGPLPSKWQMASSEPPCVNKVSDWKLEILQNG LYLIYGQVAPNANYNDVAPFEVRLYKNKDMIQTLTNK SKIQNVGGTYELHVGDTIDLIFNSEHQVLKNNTYWGIIL LANPQFIS
179	小鼠 GITRL	MEEMPLRESSPQRAERCKKSWLLCIVALLLMLLCSLGT

		LIYTSLKPTAIESCMVKFELSSSKWHMTSPKPHCVNTTS DGKLKILQSGTYLIYGQVIPVDKKYIKDNAPFVVQIYK KNDVLQTLMNDFQILPIGGVYELHAGDNIYLKFNSKD HIQKTNTYWGIILMPDLPFIS
180	人 LIGHT	MEESVVRPSVFVVDGQTDIPFTRLGRSHRRQSCSVARV GLGLLLLLMGAGLAVQGWFLLQLHWRLGEMVTRLPD GPAGSWEQLIQERRSHEVNPAAHLTGANSSLTGSGGPL LWETQLGLAFLRGLSYHDGALVVTKAGYYYIYSKVQL GGVGCPLGLASTITHGLYKRTPRYPEELELLVSQQSPC GRATSSSRVWWDSSFLGGVVHLEAGEKVVVRVLDER LVRLRDGTRSYFGAFMV
181	小鼠 LIGHT	MESVVQPSVFVVDGQTDIPFRRLEQNHRRRRCGTVQV SLALVLLLGAGLATQGWFLLRLHQRLGDIVAHLPDGG KGSWEKLIQDQRSHQANPAAHLTGANASLIGIGGPLL WETRLGLAFLRGLTYHDGALVTMEPGYYYVYSKVQL SGVGCPQGLANGLPITHGLYKRTSRYPKELELLVSRRS PCGRANSSRVWWDSSFLGGVVHLEAGEEVVVRVPGN RLVRPRDGTRSYFGAFMV
182	人 OX40L	MERVQPLEENVGNAARPRFERNKLLLVASVIQGLGLL LCFTYICLHFSALQVSHRYPRIQSIKVQFTEYKKEKGFIL TSQKEDEIMKVQNNSVIINCDGFYLISLKGYFSQEVNIS LHYQKDEEPLFQLKKVRSVNSLMVASLTYKDKVYLN VTTDNTSLDDFHVNGGELILIHQNPGEFCVL
183	小鼠 OX40L	MEGEGVQPLDENLENGSRPRFKWKKTLRLVVSGIKGA GMLLCFIYVCLQLSSSPAKDPPIQRLRGAVTRCEDGQL FISSYKNEYQTMEVQNNSVVIKCDGLYIIYLKGSFFQEV KIDLHFREDHNPISIPMLNDGRRIVFTVVASLAFKDKVY LTVNAPDTLCEHLQINDGELIVVQLTPGYCAPEGSYHS TVNQVP
184	人 TALL-1	MDDSTEREQSRLTSCLKKREEMKLKECVSILPRKESPS VRSSKDGKLLAATLLLALLSCCLTVVSFYQVAALQGD

		LASLRAELQGHHAEKLPAGAGAPKAGLEEAPAVTAGL KIFEPPAPGEGNSSQNSRNKRAVQGPEETVTQDCLQLI ADSETPTIQKGSYTFVPWLLSFKRGSALEEKENKILVKE TGYFFIYGQVLYTDKTYAMGHLIQRKKVHVFGDELSL VTLFRCIQNMPETLPNNSCYSAGIAKLEEGDELQLAIPR ENAQISLDGDVTFFGALKLL
185	小鼠 TALL-1	MAMAFCPKDQYWDSSRKSCVSCALTCSQRSQRTCTDF CKFINCRKEQGRYYDHLLGACVSCDSTCTQHPQQCAH FCEKRPRSQANLQPELGRPQAGEVEVRSDNSGRHQGS EHGPGLRLSSDQLTLYCTLGVCLCAIFCCFLVALASFLR RRGEPLPSQPAGPRGSQANSPHAHRPVTEACDEVTASP QPVETCSFCFPERSSPTQESAPRSLGIHGFAGTAAPQPC MRATVGGLGVLRASTGDARPAT
186	人 TRAIL	MAMMEVQGGPSLGQTCVLIVIFTVLLQSLCVAVTYVY FTNELKQMQDKYSKSGIACFLKEDDSYWDPNDEESMN SPCWQVKWQLRQLVRKMILRTSEETISTVQEKQQNISP LVRERGPQRVAAHITGTRGRSNTLSSPNSKNEKALGRK INSWESSRSGHSFLSNLHLRNGELVIHEKGFYYIYSQTY FRFQEEIKENTKNDKQMVQYIYKYTSYPDPILLMKSAR NSCWSKDAEYGLYSIYQGGIFELKENDRIFVSVTNEHLI DMDHEASFFGAFLVG
187	小鼠 TRAIL	MPSSGALKDLSFSQHFRMMVICIVLLQVLLQAVSVAVT YMYFTNEMKQLQDNYSKIGLACFSKTDEDFWDSTDGE ILNRPCLQVKRQLYQLIEEVTLRTFQDTISTVPEKQLSTP PLPRGGRPQKVAAHITGITRRSNSALIPISKDGKTLGQKI ESWESSRKGHSFLNHVLFRNGELVIEQEGLYYIYSQTY FRFQEAEDASKMVSKDKVRTKQLVQYIYKYTSYPDPI VLMKSARNSCWSRDAEYGLYSIYQGGLFELKKNDRIF VSVTNEHLMDLDQEASFFGAFLIN
188	人 TWEAK	MAARRSQRRRGRRGEPGTALLVPLALGLGLALACLGL

		LLAVVSLGSRASLSAQEPAQEELVAEEDQDPSELNPQT EESQDPAPFLNRLVRPRRSAPKGRKTRARRAIAAHYEV HPRPGQDGAQAGVDGTVSGWEEARINSSSPLRYNRQI GEFIVTRAGLYYLYCQVHFDEGKAVYLKLDLLVDGVL ALRCLEEFSATAASSLGPQLRLCQVSGLLALRPGSSLRI RTLPWAHLKAAPFLTYFGLFQVH
189	小鼠 TWEAK	MASAWPRSLPQILVLGFGLVLMRAAAGEQAPGTSPCS SGSSWSADLDKCMDCASCPARPHSDFCLGCAAAPPAH FRLLWPILGGALSLVLVLALVSSFLVWRRCRRREKFTT PIEETGGEGCPGVALIQ
190	人 TRANCE	MRRASRDYTKYLRGSEEMGGGPGAPHEGPLHAPPPPA PHQPPAASRSMFVALLGLGLGQVVCSVALFFYFRAQM DPNRISEDGTHCIYRILRLHENADFQDTTLESQDTKLIP DSCRRIKQAFQGAVQKELQHIVGSQHIRAEKAMVDGS WLDLAKRSKLEAQPFAHLTINATDIPSGSHKVSLSSWY HDRGWAKISNMTFSNGKLIVNQDGFYYLYANICFRHH ETSGDLATEYLQLMVYVTKTSIKIPSSHTLMKGGSTKY WSGNSEFHFYSINVGGFFKLRSGEEISIEVSNPSLLDPDQ DATYFGAFKVRDID
191	小鼠 TRANCE	MRRASRDYGKYLRSSEEMGSGPGVPHEGPLHPAPSAP APAPPPAASRSMFLALLGLGLGQVVCSIALFLYFRAQM DPNRISEDSTHCFYRILRLHENADLQDSTLESEDTLPDS CRRMKQAFQGAVQKELQHIVGPQRFSGAPAMMEGSW LDVAQRGKPEAQPFAHLTINAASIPSGSHKVTLSSWYH DRGWAKISNMTLSNGKLRVNQDGFYYLYANICFRHHE TSGSVPTDYLQLMVYVVKTSIKIPSSHNLMKGGSTKN WSGNSEFHFYSINVGGFFKLRAGEEISIQVSNPSLLDPD QDATYFGAFKVQDID
192	人 TGF-β	MPPSGLRLLLLLLPLLWLLVLTPGRPAAGLSTCKTIDM ELVKRKRIEAIRGQILSKLRLASPPSQGEVPPGPLPEAVL ALYNSTRDRVAGESAEPEPEPEADYYAKEVTRVLMVE

		THNEIYDKFKQSTHSIYMFFNTSELREAVPEPVLLSRAE LRLLRLKLKVEQHVELYQKYSNNSWRYLSNRLLAPSD SPEWLSFDVTGVVRQWLSRGGEIEGFRLSAHCSCDSRD NTLQVDINGFTTGRRGDLATIHGMNRPFLLLMATPLER AQHLQSSRHRRALDTNYCFSSTEKNCCVRQLYIDFRKD LGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLAL YNQHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQL SNMIVRSCKCS
193	小鼠 TGF-β1	MPPSGLRLLPLLLPLPWLLVLTPGRPAAGLSTCKTIDM ELVKRKRIEAIRGQILSKLRLASPPSQGEVPPGPLPEAVL ALYNSTRDRVAGESADPEPEPEADYYAKEVTRVLMVD RNNAIYEKTKDISHSIYMFFNTSDIREAVPEPPLLSRAEL RLQRLKSSVEQHVELYQKYSNNSWRYLGNRLLTPTDT PEWLSFDVTGVVRQWLNQGDGIQGFRFSAHCSCDSKD NKLHVEINGISPKRRGDLGTIHDMNRPFLLLMATPLER AQHLHSSRHRRALDTNYCFSSTEKNCCVRQLYIDFRKD LGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLAL YNQHNPGASASPCCVPQALEPLPIVYYVGRKPKVEQLS NMIVRSCKCS
194	人TGF-β2	MHYCVLSAFLILHLVTVALSLSTCSTLDMDQFMRKRIE AIRGQILSKLKLTSPPEDYPEPEEVPPEVISIYNSTRDLLQ EKASRRAAACERERSDEEYYAKEVYKIDMPPFFPSENA IPPTFYRPYFRIVRFDVSAMEKNASNLVKAEFRVFRLQ NPKARVPEQRIELYQILKSKDLTSPTQRYIDSKVVKTRA EGEWLSFDVTDAVHEWLHHKDRNLGFKISLHCPCCTF VPSNNYIIPNKSEELEARFAGIDGTSTYTSGDQKTIKSTR KKNSGKTPHLLLMLLPSYRLESQQTNRRKKRALDAAY CFRNVQDNCCLRPLYIDFKRDLGWKWIHEPKGYNANF CAGACPYLWSSDTQHSRVLSLYNTINPEASASPCCVSQ DLEPLTILYYIGKTPKIEQLSNMIVKSCKCS
195	小鼠 TGF-β2	MHYCVLSTFLLLHLVPVALSLSTCSTLDMDQFMRKRIE

		AIRGQILSKLKLTSPPEDYPEPDEVPPEVISIYNSTRDLL QEKASRRAAACERERSDEEYYAKEVYKIDMPSHLPSE NAIPPTFYRPYFRIVRFDVSTMEKNASNLVKAEFRVFRL QNPKARVAEQRIELYQILKSKDLTSPTQRYIDSKVVKT RAEGEWLSFDVTDAVQEWLHHKDRNLGFKISLHCPCC TFVPSNNYIIPNKSEELEARFAGIDGTSTYASGDQKTIKS TRKKTSGKTPHLLLMLLPSYRLESQQSSRRKKRALDAA YCFRNVQDNCCLRPLYIDFKRDLGWKWIHEPKGYNAN FCAGACPYLWSSDTQHTKVLSLYNTINPEASASPCCVS QDLEPLTILYYIGNTPKIEQLSNMIVKSCKCS
196	人 TGF- β3	MKMHLQRALVVLALLNFATVSLSLSTCTTLDFGHIKK KRVEAIRGQILSKLRLTSPPEPTVMTHVPYQVLALYNS TRELLEEMHGEREEGCTQENTESEYYAKEIHKFDMIQG LAEHNELAVCPKGITSKVFRFNVSSVEKNRTNLFRAEF RVLRVPNPSSKRNEQRIELFQILRPDEHIAKQRYIGGKN LPTRGTAEWLSFDVTDTVREWLLRRESNLGLEISIHCPC HTFQPNGDILENIHEVMEIKFKGVDNEDDHGRGDLGRL KKQKDHHNPHLILMMIPPHRLDNPGQGGQRKKRALDT NYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYY ANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASPCC VPQDLEPLTILYYVGRTPKVEQLSNMVVKSCKCS
197	小鼠 TGF- β3	MHLQRALVVLALLNLATISLSLSTCTTLDFGHIKKKRV EAIRGQILSKLRLTSPPEPSVMTHVPYQVLALYNSTREL LEEMHGEREEGCTQETSESEYYAKEIHKFDMIQGLAEH NELAVCPKGITSKVFRFNVSSVEKNGTNLFRAEFRVLR VPNPSSKRTEQRIELFQILRPDEHIAKQRYIGGKNLPTR GTAEWLSFDVTDTVREWLLRRESNLGLEISIHCPCHTF QPNGDILENVHEVMEIKFKGVDNEDDHGRGDLGRLKK QKDHHNPHLILMMIPPHRLDSPGQGSQRKKRALDTNY CFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYANF CSGPCPYLRSADTTHSTVLGLYNTLNPEASASPCCVPQ

		DLEPLTILYYVGRTPKVEQLSNMVVKSCKCS
198	人 EPO	MGVHECPAWLWLLLSLLSLPLGLPVLGAPPRLICDSRV LERYLLEAKEAENITTGCAEHCSLNENITVPDTKVNFY AWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPP DAASAAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEA CRTGDR
199	小鼠 EPO	MGVPERPTLLLLLSLLLIPLGLPVLCAPPRLICDSRVLER YILEAKEAENVTMGCAEGPRLSENITVPDTKVNFYAW KRMEVEEQAIEVWQGLSLLSEAILQAQALLANSSQPPE TLQLHIDKAISGLRSLTSLLRVLGAQKELMSPPDTTPPA PLRTLTVDTFCKLFRVYANFLRGKLKLYTGEVCRRGD R
200	人 TPO	MELTELLLVVMLLLTARLTLSSPAPPACDLRVLSKLLR DSHVLHSRLSQCPEVHPLPTPVLLPAVDFSLGEWKTQM EETKAQDILGAVTLLLEGVMAARGQLGPTCLSSLLGQL SGQVRLLLGALQSLLGTQLPPQGRTTAHKDPNAIFLSF QHLLRGKVRFLMLVGGSTLCVRRAPPTTAVPSRTSLVL TLNELPNRTSGLLETNFTASARTTGSGLLKWQQGFRAK IPGLLNQTSRSLDQIPGYLNRIHELLNGTRGLFPGPSRRT LGAPDISSGTSDTGSLPPNLQPGYSPSPTHPPTGQYTLFP LPPTLPTPVVQLHPLLPDPSAPTPTPTSPLLNTSYTHSQN LSQEG
201	小鼠 TPO	MELTDLLLAAMLLAVARLTLSSPVAPACDPRLLNKLL RDSHLLHSRLSQCPDVDPLSIPVLLPAVDFSLGEWKTQ TEQSKAQDILGAVSLLLEGVMAARGQLEPSCLSSLLGQ LSGQVRLLLGALQGLLGTQLPLQGRTTAHKDPNALFLS LQQLLRGKVRFLLLVEGPTLCVRRTLPTTAVPSSTSQLL TLNKFPNRTSGLLETNFSVTARTAGPGLLSRLQGFRVKI TPGQLNQTSRSPVQISGYLNRTHGPVNGTHGLFAGTSL QTLEASDISPGAFNKGSLAFNLQGGLPPSPSLAPDGHTP

		FPPSPALPTTHGSPPQLHPLFPDPSTTMPNSTAPHPVTM YPHPRNLSQET
202	人 FLT-3L	MTVLAPAWSPTTYLLLLLLLSSGLSGTQDCSFQHSPISS DFAVKIRELSDYLLQDYPVTVASNLQDEELCGGLWRL VLAQRWMERLKTVAGSKMQGLLERVNTEIHFVTKCA FQPPPSCLRFVQTNISRLLQETSEQLVALKPWITRQNFS RCLELQCQPDSSTLPPPWSPRPLEATAPTAPQPPLLLLL LLPVGLLLLAAAWCLHWQRTRRRTPRPGEQVPPVPSP QDLLLVEH
203	小鼠 FLT-3L	MTVLAPAWSPNSSLLLLLLLLSPCLRGTPDCYFSHSPIS SNFKVKFRELTDHLLKDYPVTVAVNLQDEKHCKALW SLFLAQRWIEQLKTVAGSKMQTLLEDVNTEIHFVTSCT FQPLPECLRFVQTNISHLLKDTCTQLLALKPCIGKACQN FSRCLEVQCQPDSSTLLPPRSPIALEATELPEPRPRQLLL LLLLLLPLTLVLLAAAWGLRWQRARRRGELHPGVPLP SHP
204	人 SCF	MKKTQTWILTCIYLQLLLFNPLVKTEGICRNRVTNNVK DVTKLVANLPKDYMITLKYVPGMDVLPSHCWISEMV VQLSDSLTDLLDKFSNISEGLSNYSIIDKLVNIVDDLVE CVKENSSKDLKKSFKSPEPRLFTPEEFFRIFNRSIDAFKD FVVASETSDCVVSSTLSPEKDSRVSVTKPFMLPPVAASS LRNDSSSSNRKAKNPPGDSSLHWAAMALPALFSLIIGF AFGALYWKKRQPSLTRAVENIQINEEDNEISMLQEKER EFQEV
205	小鼠 SCF	MKKTQTWIITCIYLQLLLFNPLVKTKEICGNPVTDNVK DITKLVANLPNDYMITLNYVAGMDVLPSHCWLRDMVI QLSLSLTTLLDKFSNISEGLSNYSIIDKLGKIVDDLVLCM EENAPKNIKESPKRPETRSFTPEEFFSIFNRSIDAFKDFM VASDTSDCVLSSTLGPEKDSRVSVTKPFMLPPVAASSL RNDSSSSNRKAAKAPEDSGLQWTAMALPALISLVIGFA FGALYWKKKQSSLTRAVENIQINEEDNEISMLQQKERE

		FQEV
206	人M-CSF	MTAPGAAGRCPPTTWLGSLLLLVCLLASRSITEEVSEY CSHMIGSGHLQSLQRLIDSQMETSCQITFEFVDQEQLK DPVCYLKKAFLLVQDIMEDTMRFRDNTPNAIAIVQLQE LSLRLKSCFTKDYEEHDKACVRTFYETPLQLLEKVKNV FNETKNLLDKDWNIFSKNCNNSFAECSSQDVVTKPDC NCLYPKAIPSSDPASVSPHQPLAPSMAPVAGLTWEDSE GTEGSSLLPGEQPLHTVDPGSAKQRPPRSTCQSFEPPET PVVKDSTIGGSPQPRPSVGAFNPGMEDILDSAMGTNW VPEEASGEASEIPVPQGTELSPSRPGGGSMQTEPARPSN FLSASSPLPASAKGQQPADVTGTALPRVGPVRPTGQD WNHTPQKTDHPSALLRDPPEPGSPRISSLRPQGLSNPST LSAQPQLSRSHSSGSVLPLGELEGRRSTRDRRSPAEPEG GPASEGAARPLPRFNSVPLTDTGHERQSEGSFSPQLQES VFHLLVPSVILVLLAVGGLLFYRWRRRSHQEPQRADSP LEQPEGSPLTQDDRQVELPV
207	小鼠 M-CSF	MTARGAAGRCPSSTWLGSRLLLVCLLMSRSIAKEVSE HCSHMIGNGHLKVLQQLIDSQMETSCQIAFEFVDQEQL DDPVCYLKKAFFLVQDIIDETMRFKDNTPNANATERLQ ELSNNLNSCFTKDYEEQNKACVRTFHETPLQLLEKIKN FFNETKNLLEKDWNIFTKNCNNSFAKCSSRDVVTKPDC NCLYPKATPSSDPASASPHQPPAPSMAPLAGLAWDDS QRTEGSSLLPSELPLRIEDPGSAKQRPPRSTCQTLESTEQ PNHGDRLTEDSQPHPSAGGPVPGVEDILESSLGTNWVL EEASGEASEGFLTQEAKFSPSTPVGGSIQAETDRPRALS ASPFPKSTEDQKPVDITDRPLTEVNPMRPIGQTQNNTPE KTDGTSTLREDHQEPGSPHIATPNPQRVSNSATPVAQL LLPKSHSWGIVLPLGELEGKRSTRDRRSPAELEGGSASE GAARPVARFNSIPLTDTGHVEQHEGSSDPQIPESVFHLL VPGIILVLLTVGGLLFYKWKWRSHRDPQTLDSSVGRPE DSSLTQDEDRQVELPV

208	人MSP	MGWLPLLLLLTQCLGVPGQRSPLNDFQVLRGTELQHL LHAVVPGPWQEDVADAEECAGRCGPLMDCRAFHYNV SSHGCQLLPWTQHSPHTRLRRSGRCDLFQKKDYVRTCI MNNGVGYRGTMATTVGGLPCQAWSHKFPNDHKYTPT LRNGLEENFCRNPDGDPGGPWCYTTDPAVRFQSCGIKS CREAACVWCNGEEYRGAVDRTESGRECQRWDLQHPH QHPFEPGKFLDQGLDDNYCRNPDGSERPWCYTTDPQIE REFCDLPRCGSEAQPRQEATTVSCFRGKGEGYRGTAN TTTAGVPCQRWDAQIPHQHRFTPEKYACKDLRENFCR NPDGSEAPWCFTLRPGMRAAFCYQIRRCTDDVRPQDC YHGAGEQYRGTVSKTRKGVQCQRWSAETPHKPQFTFT SEPHAQLEENFCRNPDGDSHGPWCYTMDPRTPFDYCA LRRCADDQPPSILDPPDQVQFEKCGKRVDRLDQRRSKL RVVGGHPGNSPWTVSLRNRQGQHFCGGSLVKEQWILT ARQCFSSCHMPLTGYEVWLGTLFQNPQHGEPSLQRVP VAKMVCGPSGSQLVLLKLERSVTLNQRVALICLPPEW YVVPPGTKCEIAGWGETKGTGNDTVLNVALLNVISNQ ECNIKHRGRVRESEMCTEGLLAPVGACEGDYGGPLAC FTHNCWVLEGIIIPNRVCARSRWPAVFTRVSVFVDWIH KVMRLG
209	小鼠 MSP	MGLPLPLLQSSLLLMLLLRLSAASTNLNWQCPRIPYAA SRDFSVKYVVPSFSAGGRVQATAAYEDSTNSAVFVAT RNHLHVLGPDLQFIENLTTGPIGNPGCQTCASCGPGPH GPPKDTDTLVLVMEPGLPALVSCGSTLQGRCFLHELEP RGKALHLAAPACLFSANNNKPEACTDCVASPLGTRVT VVEQGHASYFYVASSLDPELAASFSPRSVSIRRLKSDTS GFQPGFPSLSVLPKYLASYLIKYVYSFHSGDFVYFLTVQ PISVTSPPSALHTRLVRLNAVEPEIGDYRELVLDCHFAP KRRRRGAPEGTQPYPVLQAAHSAPVDAKLAVELSISEG QEVLFGVFVTVKDGGSGMGPNSVVCAFPIYHLNILIEE GVEYCCHSSNSSSLLSRGLDFFQTPSFCPNPPGGEASGP

		SSRCHYFPLMVHASFTRVDLFNGLLGSVKVTALHVTR LGNVTVAHMGTVDGRVLQVEIARSLNYLLYVSNFSLG SSGQPVHRDVSRLGNDLLFASGDQVFKVPIQGPGCRHF LTCWRCLRAQRFMGCGWCGDRCDRQKECPGSWQQD HCPPEISEFYPHSGPLRGTTRLTLCGSNFYLRPDDVVPE GTHQITVGQSPCRLLPKDSSSPRPGSLKEFIQELECELEP LVTQAVGTTNISLVITNMPAGKHFRVEGISVQEGFSFVE PVLTSIKPDFGPRAGGTYLTLEGQSLSVGTSRAVLVNG TQCRLEQVNEEQILCVTPPGAGTARVPLHLQIGGAEVP GSWTFHYKEDPIVLDISPKCGYSGSHIMIHGQHLTSAW HFTLSFHDGQSTVESRCAGQFVEQQQRRCRLPEYVVR NPQGWATGNLSVWGDGAAGFTLPGFRFLPPPSPLRAG LVELKPEEHSVKVEYVGLGAVADCVTVNMTVGGEVC QHELRGDVVICPLPPSLQLGKDGVPLQVCVDGGCHILS QVVRSSPGRASQRILLIALLVLILLVAVLAVALIFNSRR RKKQLGAHSLSPTTLSDINDTASGAPNHEESSESRDGTS VPLLRTESIRLQDLDRMLLAEVKDVLIPHEQVVIHTDQ VIGKGHFGVVYHGEYTDGAQNQTHCAIKSLSRITEVQE VEAFLREGLLMRGLHHPNILALIGIMLPPEGLPRVLLPY MRHGDLLHFIRSPQRNPTVKDLVSFGLQVACGMEYLA EQKFVHRDLAARNCMLDESFTVKVADFGLARGVLDK EYYSVRQHRHARLPVKWMALESLQTYRFTTKSDVWS FGVLLWELLTRGAPPYPHIDPFDLSHFLAQGRRLPQPE YCPDSLYHVMLRCWEADPAARPTFRALVLEVKQVVA SLLGDHYVQLTAAYVNVGPRAVDDGSVPPEQVQPSPQ HCRSTSKPRPLSEPPLPT
210	連接子	GSSGGSGGSGG
211	連接子	GGGSGGGS
212	連接子	GGGSGGGSGGGS
213	連接子	GGGGSGGGGSGGGGS
214	連接子	GGGGSGGGGSGGGGSGGGGSGGGGS

215	連接子	GGGGSGGGGS
216	連接子	(GGGGS)n
217	連接子	GGGGSGS
218	連接子	GGGGSGGGGSGGGGSGS
219	連接子	GGSLDPKGGGGS
220	連接子	PKSCDKTHTCPPCPAPELLG
221	連接子	SKYGPPCPPCPAPEFLG
222	連接子	GKSSGSGSESKS
223	連接子	GSTSGSGKSSEGKG
224	連接子	GSTSGSGKSSEGSGSTKG
225	連接子	GSTSGSGKPGSGEGSTKG
226	連接子	GSTSGSGKPGSSEGST
227	連接子	(GSGGS)n
228	連接子	(GGGS)n
229	連接子	GGSG
230	連接子	GGSGG
231	連接子	GSGSG
232	連接子	GSGGG
233	連接子	GGGSG
234	連接子	GSSSG
235	連接子	GPQGTAGQ
236	連接子	YGAGLGW
237	CM	AQNLLGMY
238	CM	LSGRSDNHGGAVGLLAPP
239	CM	VHMPLGFLGPGGLSGRSDNH
240	CM	LSGRSDNHGGVHMPLGFLGP
241	CM	LSGRSDNHGGSGGSISSGLLSS

242	CM	ISSGLLSSGGSGGSLSGRSGNH
243	CM	LSGRSDNHGGSGGSQNQALRMA
244	CM	QNQALRMAGGSGGSLSGRSDNH
245	CM	LSGRSGNHGGSGGSQNQALRMA
246	CM	QNQALRMAGGSGGSLSGRSGNH
247	CM	ISSGLLSGRSGNH
248	CM	AVGLLAPPGGTSTSGRSANPRG
249	CM	TSTSGRSANPRGGGAVGLLAPP
250	CM	VHMPLGFLGPGGTSTSGRSANPRG
251	CM	TSTSGRSANPRGGGVHMPLGFLGP
252	CM	LSGRSGNHGGSGGSISSGLLSS
253	裂解序列	PRFKIIGG
254	裂解序列	PRFRIIGG
255	裂解序列	SSRHRRALD
256	裂解序列	RKSSIIIRMRDVVL
257	裂解序列	SSSFDKGKYKKGDDA
258	裂解序列	SSSFDKGKYKRGDDA
259	裂解序列	IEGR
260	裂解序列	IDGR
261	裂解序列	GGSIDGR
262	裂解序列	PLGLWA
263	裂解序列	GPQGIAGQ
264	裂解序列	GPQGLLGA
265	裂解序列	GIAGQ
266	裂解序列	GPLGIAGI
267	裂解序列	GPEGLRVG
268	裂解序列	YGAGLGVV
269	裂解序列	AGLGVVER
270	裂解序列	AGLGISST
271	裂解序列	EPQALAMS

272	裂解序列	QALAMSAI
273	裂解序列	AAYHLVSQ
274	裂解序列	MDAFLESS
275	裂解序列	ESLPVVAV
276	裂解序列	SAPAVESE
277	裂解序列	DVAQFVLT
278	裂解序列	VAQFVLT
279	裂解序列	VAQFVLTE
280	裂解序列	AQFVLTEG
281	裂解序列	PVQPIGPQ
282	IFN-α2b-1204dL-hIgG4, 具信號序列	*METDTLLLWVLLLWVPGSTG*CDLPQTHSLGSRRTLMLL AQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVL HEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLND LEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKE KKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKESGRSD NIGGGSESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLS
283	IFN-α-1204dL-hIgG4 (多核苷酸)	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTT TTGTGGGTGCCAGGATCCACAGGCTGTGATCTGCCT CAAACGCATTCATTGGGGTCCAGGCGCACGCTTATG TTGCTTGCACAGATGAGGAGAATATCACTTTTCTCTT GCTTGAAGGACCGCCACGATTTTGGCTTTCCGCAGG AAGAGTTCGGTAACCAGTTCCAAAAGGCAGAGACA ATCCCCGTTTTGCATGAGATGATCCAACAGATCTTTA ACCTGTTTTCAACCAAGGATAGCAGCGCAGCGTGGG

		ATGAGACACTGCTTGACAAGTTTTACACCGAGCTCT ATCAGCAACTTAATGATCTCGAAGCCTGCGTAATTC AAGGAGTAGGCGTTACAGAGACACCTTTGATGAAGG AGGATTCCATCCTTGCAGTAAGAAAATACTTCCAGA GGATCACCCTCTACCTCAAAGAAAAGAAATACTCCC CATGCGCGTGGGAAGTAGTGCGAGCTGAAATAATGC GGAGCTTTTCTTTGTCAACTAATCTCCAAGAATCTCT GAGAAGCAAGGAGTCAGGTAGGTCTGATAATATCG GGGGAGGTTCTGAATCTAAGTACGGCCCTCCTTGTC CTCCATGTCCTGCTCCAGAGTTTCTCGGAGGCCCCTC CGTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTG ATGATCAGCAGAACCCCTGAAGTGACCTGCGTGGTG GTCGACGTTTCACAAGAGGACCCCGAGGTGCAGTTC AATTGGTACGTGGACGGCGTGGAAGTGCACAACGCC AAGACCAAGCCTAGAGAGGAACAGTTCAACAGCAC CTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCA GGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGG TGTCCAACAAGGGCCTGCCTAGCAGCATCGAGAAAA CCATCAGCAAGGCCAAGGGCCAGCCAAGGGAACCC CAGGTTTACACACTGCCACCTAGCCAAGAGGAAATG ACCAAGAACCAGGTGTCCCTGACCTGCCTGGTCAAG GGCTTTTACCCCTCCGATATCGCCGTGGAATGGGAG AGCAATGGCCAGCCTGAGAACAACTACAAGACCAC ACCTCCTGTGCTGGACAGCGACGGCTCATTCTTCCTG TACAGCAGACTGACCGTGGACAAGAGCAGATGGCA GCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGA GGCCCTGCACAACCACTACACCCAGAAGTCTCTGAG CCTGAGCTGA
284	IFN-α2b-1490DNI-hIgG4, 具信號序列	*METDTLLLWVLLLWVPGSTG*CDLPQTHSLGSRRTLMLL AQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVL HEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLND

		LEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKE KKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKEISSGLL SGRSDNIGGGSESKYGPPCPPCPAPEFLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLS
285	IFN-α2b-1490DNI-hIgG4 (多核苷酸)	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTT TTGTGGGTGCCAGGATCCACAGGCTGTGATCTGCCT CAAACGCATTCATTGGGGTCCAGGCGCACGCTTATG TTGCTTGCACAGATGAGGAGAATATCACTTTTCTCTT GCTTGAAGGACCGCCACGATTTTGGCTTTCCGCAGG AAGAGTTCGGTAACCAGTTCCAAAAGGCAGAGACA ATCCCCGTTTTGCATGAGATGATCCAACAGATCTTTA ACCTGTTTTCAACCAAGGATAGCAGCGCAGCGTGGG ATGAGACACTGCTTGACAAGTTTTACACCGAGCTCT ATCAGCAACTTAATGATCTCGAAGCCTGCGTAATTC AAGGAGTAGGCGTTACAGAGACACCTTTGATGAAGG AGGATTCCATCCTTGCAGTAAGAAAATACTTCCAGA GGATCACCCTCTACCTCAAAGAAAAGAAATACTCCC CATGCGCGTGGGAAGTAGTGCGAGCTGAAATAATGC GGAGCTTTTCTTTGTCAACTAATCTCCAAGAATCTCT GAGAAGCAAGGAGATTAGTTCTGGCCTGCTGTCAGG TAGGTCTGATAATATCGGGGGAGGTTCTGAATCTAA GTACGGCCCTCCTTGTCCTCCATGTCCTGCTCCAGAG TTTCTCGGAGGCCCCTCCGTGTTCCTGTTTCCTCCAA AGCCTAAGGACACCCTGATGATCAGCAGAACCCCTG AAGTGACCTGCGTGGTGGTCGACGTTTCACAAGAGG ACCCCGAGGTGCAGTTCAATTGGTACGTGGACGGCG

		TGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAG GAACAGTTCAACAGCACCTACAGAGTGGTGTCCGTG CTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAA GAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCT AGCAGCATCGAGAAAACCATCAGCAAGGCCAAGGG CCAGCCAAGGGAACCCCAGGTTTACACACTGCCACC TAGCCAAGAGGAAATGACCAAGAACCAGGTGTCCCT GACCTGCCTGGTCAAGGGCTTTTACCCCTCCGATATC GCCGTGGAATGGGAGAGCAATGGCCAGCCTGAGAA CAACTACAAGACCACACCTCCTGTGCTGGACAGCGA CGGCTCATTCTTCCTGTACAGCAGACTGACCGTGGA CAAGAGCAGATGGCAGCAGGGCAACGTGTTCAGCT GCAGCGTGATGCACGAGGCCCTGCACAACCACTACA CCCAGAAGTCTCTGAGCCTGAGCTGA
286	ProC440	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGRSDNICPPCPAPEFLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLS
287	人 IgG Fc ，只有鈕突變	CPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPCQEEMTKNQVSLWCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG

288	人 IgG Fc，只有孔突變	CPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSRLTVD KSRWQEGNVFSCSVMHEALHNRFTQKSLSLSLG
289	殘段部分	SDNI
290	ProC732	QSGQTDVDYYREWSWTQVSGSSGGSLSGRSDNIGSGG SCDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFG FPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKELSGRSDNICPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLS
291	ProC733	QSGQTDVDYYREWSWTQVSGSSGGSLSGRSDNIGSGG SCDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFG FPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKEESKYGPPCPPCPAPEFLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLS

292	IFNa-2b 掩蔽肽	TDVDYYREWSWTQVS
293	連接子	GSSGGS
294	連接子	ESKY
295	ProC286	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSS IEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS SGGGGSGRSDNIGGGSCDLPQTHSLGSRRTLMLLAQM RRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMI QQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEAC VIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYS PCAWEVVRAEIMRSFSLSTNLQESLRSKE
296	連接子	SGGG
297	經截短之 IFNa-2b (胺基酸 **1-150)**	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRS
298	IFNa-2b L130P 突變體	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYPKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKE
299 至 446	PM 序列	(See Table 24 below for sequences)
447	ProC859 序列	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFTTKDSSAAW DEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMN

		VDSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRS LSLSTNLQERLRRKELSGRSDNICPPCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLS
448	通用IFN-α A/D序列	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFTTKDSSAAW DEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMN VDSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRS LSLSTNLQERLRRKE
449	干擾素 β， 鏈A, 人 (1AU1)	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRM NFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIF RQDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEK EDFTRGKLMSSLHLKRYYGRILHYLKAKEYSH CAWTIVRVEILRNFYFINRLTGYLRN
450	IFNB_CHICK Q90873.1	MTANHQSPGMHSILLLLLLPALTTTFSCNHLRHQDANF SWKSLQLLQNTAPPPPQPCPQQDVTFPFPETL LKSKDKKQAAITTLRILQHLFNMLSSPHTPKHWIDRTR HSLLNQIQHYIHHLEQCFVNQGTRSQRRGPRN AHLSINKYFRSIHNFLQHNNYSACTWDHVRLQARDCF RHVDTLIQWMKSRAPLTASSKRLNTQ
451	IFNA3_CANLF O97945.1	MALPCSFSVALVLLSCHSLCCLACHLPDTHSLRNWRV LTLLGQMRRLSASSCDHYTTDFAFPKELFDGQR LQEAQALSVVHVMTQKVFHLFCTNTSSAPWNMTLLEE LCSGLSEQLDDLDACPLQEAGLAETPLMHEDST LRTYFQRISLYLQDRNHSPCAWEMVRAEIGRSFFSLTIL QERVRRRK
452	IFN_ANAPL	MPGPSAPPPPAIYSALALLLLLTPPANAFSCSPLRLHDS

	P51526.1	AFAWDSLQLLRNMAPSPTQPCPQQHAPCSFP DTLLDTNDTQQAAHTALHLLQHLFDTLSSPSTPAHWL HTARHDLLNQLQHHIHHLERCFPADAARLHRRG PRNLHLSINKYFGCIQHFLQNHTYSPCAWDHVRLEAH ACFQRIHRLTRTMR
453	IFNAH_BOVIN P49878.1	MAPAWSFLLALLLLSCNAICSLGCHLPHTHSLPNRRVL TLLRQLRRVSPSSCLQDRNDFAFPQEALGGSQ LQKAQAISVLHEVTQHTFQLFSTEGSAAAWDESLLDKL RAALDQQLTDLQACLRQEEGLRGAPLLKEDAS LAVRKYFHRLTLYLREKRHNPCAWEVVRAEVMRAFS SSTNLQERFRRKD
454	IFNA1_CHICK P42165.1	MAVPASPQHPRGYGILLLTLLLKALATTASACNHLRPQ DATFSHDSLQLLRDMAPTLPQLCPQHNASCSF NDTILDTSNTRQADKTTHDILQHLFKILSSPSTPAHWND SQRQSLLNRIHRYTQHLEQCLDSSDTRSRTR WPRNLHLTIKKHFSCLHTFLQDNDYSACAWEHVRLQA RAWFLHIHNLTGNTRT
455	IFNA_FELCA P35849.1	MALPSSFLVALVALGCNSVCSLGCDLPQTHGLLNRRA LTLLGQMRRLPASSCQKDRNDFAFPQDVFGGDQ SHKAQALSVVHVTNQKIFHFFCTEASSSAAWNTTLLEE FCTGLDRQLTRLEACVLQEVEEGEAPLTNEDI HPEDSILRNYFQRLSLYLQEKKYSPCAWEIVRAEIMRSL YYSSTALQKRLRSEK
456	干擾素-β-1 [野豬] AAA31056.1	MANKCILQIALLMCFSTTALSMSYDVLRYQQRSSNLA CQKLLGQLPGTPQYCLEDRMNFEVPEEIMQPPQ FQKEDAVLIIHEMLQQIFGILRRNFSSTGWNETVIKTILV ELDGQMDDLETILEEIMEEENFPRGDMTIL HLKKYYLSILQYLKSKEYRSCAWTVVQVEILRNFSFLN RLTDYLRN
457	IFNB2_BOVIN P01576.1	MTHRCLLQMVLLLCFSTTALSRSYSLLRFQQRRSLALC QKLLRQLPSTPQHCLEARMDFQMPEEMKQAQQ

		FQKEDAILVIYEMLQQIFNILTRDFSSTGWSETIIEDLLE ELYEQMNHLEPIQKEIMQKQNSTMGDTTVL HLRKYYFNLVQYLKSKEYNRCAWTVVRVQILRNFSFL TRLTGYLRE
458	A鏈A, 干擾素-α 2B 1RH2	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTK DSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTE TPLMNEDSILAVRKYFQRITLYLKEKKYSPCAW EVVRAEIMRSFSLSTNLQESLRSKE
459	連接子	SGGGG
460	ProC288	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWD ETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDS ILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKESGGGGSGRSDNI**CPPC**PAPEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLS
461	ProC289	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGGGGSGRSDNIGPP**CPPC**PAPEFL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQGNV

		FSCSVMHEALHNHYTQKSLSLS
462	ProC290	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGGGGSGRSDNIESKYGPPCPPCPA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLS
463	ProC291	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGGGGSGRSDNIGGGSESKYGPPCP PCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLS
464	ProC441	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGRSDNIGPPCPPCPAPEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNA
465	ProC442	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF

		PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGRSDNIESKYGPPCPPCPAPEFLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLS
466	ProC443	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGRSDNIGGGSESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLS
467	CM	GLSGRSDNHG
468	信號序列	MRAWIFFLLCLAGRALA
469	信號序列	MALTFALLVALLVLSCKSSCSVG
470	信號序列	METDTLLLWVLLLWVPGSTG
471	間隔子	QGQSGS
472	間隔子	GQSGS
473	間隔子	QSGS
474	間隔子	QGQSGQG
475	間隔子	GQSGQG

476	間隔子	QSGQG
477	間隔子	SGQG
478	間隔子	QGQSGQ
479	間隔子	GQSGQ
480	間隔子	QSGQ
481	間隔子	QGQSG
482	間隔子	QGQS
493	ProC1023	QSGQTDVDYYREWSWTQVSGSSGGSLSGRSDNIGSGG SCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFG FPQEEFGNQFQKAETIPVLHEMIQQIFNLFTTKDSSAAW DEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMNV DSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLS LSTNLQERLRRKELSGRSDNICPPCPAPEFLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLS
494	ProC1549	QSGQTDVDYYREWSWTQVSGSSGGSGGGSGGGSGSG GSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDF GFPQEEFGNQFQKAETIPVLHEMIQQIFNLFTTKDSSAA WDEDLLDKFCTELYQQLNDLEACVMQEERVGETPLM NVDSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMR SLSLSTNLQERRRKEGGSGGGGSCPPCPAPEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVM

		HEALHNHYTQKSLSLS
495	不可裂解之連接子	GGSGGGGS
507	ProC659 (不可裂解之經空間掩蔽的 IFN-a2b)	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKEGGGSGGSCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLS
504	CX-171-HC = C5H9-mIgG2a	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSSIWRNGIVTVYADSVKGRFTISRDNS KNTLYLQMNSLRAEDTAVYYCAKWSAAFDYWGQGT LVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGY FPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVT SSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVS EDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVS ALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGS VRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYV EWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK NWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
505	CX-171-HC = C5H9-mIgG2a (無C端離胺酸)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSSIWRNGIVTVYADSVKGRFTISRDNS KNTLYLQMNSLRAEDTAVYYCAKWSAAFDYWGQGT LVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGY FPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVT

		SSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVS EDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVS ALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGS VRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYV EWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK NWVERNSYSCSVVHEGLHNHHTTKSFSRTPG
506	CX-171-LC = C5H9v2-mCk	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQDNGYPSTFGGGTKVEIKRADAAPTV SIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSE RQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNS YTCEATHKTSTSPIVKSFNRNEC

表24. 適當細胞介素相關之掩蔽肽(PM)的實例

可與該PM偶聯之細胞介素	PM 序列	SEQ ID NO.
IFN	IAYLEYYEHLHMAYG	299
IFN	TDVDYYREWCWTQVS	300
IFN	FPLNTFDLVHELLSR	301
IFN	FLNDIHRFLHWTDLM	302
IFN	PYTFVEQVEYWLHAT	303
IFN	ACVIHFLDRISNILE	304
IFN	FCYIAAFSAMQRQSC	305
IFN	PLYLPEIGWMFGLPT	306
IFN	TVLVIPDLHYLYVDR	307
IFN	FINNVETALDTIYNL	308
IFN	SAKHLHPGRLPPMTK	309
IFN	ATMYAYLERLEAILS	310
IFN	IYPLDALLRHLNSLC	311
IFN	CFPTVVWRELYNLYG	312
IFN	NLDFYLNHLYNTLAG	313

IFN	DFINSMRSHLQSSDQ	314
IFN	EPKCSFCSPLIVPSP	315
IFN	PNCIESFLSSIHDSL	316
IFN	TDNALFLETVQHYLY	317
IFN	CYPSISWLFADAPRN	318
IFN	ELTQLLNALVDVRNC	319
IFN	LLSSFVETMSSILTC	320
IFN	YLLRLPSLEELWGPS	321
IFN	ATCYIINHWVERYII	322
IFN	IAYLEYYEHLHMAY	323
IFN	RVTCDDYYYGFGCNKFGRPA	324
IFN	MLAVVGAAALVLVAGAPWVLPSAAGGENLKPPENIDVYIID DNYTLKWSSHGESMGSVTFSAEYRTKDEAKWLKVPECQHTT TTKCEFSLLDTNVYIKTQFRVRAEEGNSTSSWNEVDPFIPFYT AHMSPPEVRLEAEDKAILVHISPPGQDGNMWALEKPSFSYTIR IWQKSSSDKKTINSTYYVEKIPELLPETTYCLEVKAIHPSLKKH SNYSTVQCISTTVANKMPVPGNLQVDAQGKSYVLKWDYIAS ADVLFRAQWLPGYSKSSSGSRSDKWKPIPTCANVQTTHCVFS QDTVYTGTFFLHVQASEGNHTSFWSEEKFIDSQKHILPPPPVIT VTAMSDTLLVYVNCQDSTCDGLNYEIIFWENTSNTKISMEKD GPEFTLKNLQPLTVYCVQARVLFRALLNKTSNFSEKLCEKTR PGSFST	325
IFN	MLLSQNAFIFRSLNLVLMVYISLVFGISYDSPDYTDESCTFKIS LRNFRSILSWELKNHSIVPTHYTLLYTIMSKPEDLKVVKNCAN TTRSFCDLTDEWRSTHEAYVTVLEGFSGNTTLFSCSHNFWLAI DMSFEPPEFEIVGFTNHINVMVKFPSIVEEELQFDLSLVIEEQSE GIVKKHKPEIKGNMSGNFTYIIDKLIPNTNYCVSVYLEHSDEQ AVIKSPLKCTLLPPGQESESAESAK	326

IFN	MMVVLLGATTLVLVAVAPWVLSAAAGGKNLKSPQKVEVDII DDNFILRWNRSDESVGNVTFSFDYQKTGMDNWIKLSGCQNIT STKCNFSSLKLNVYEEIKLRIRAEKENTSSWYEVDSFTPFRKA QIGPPEVHLEAEDKAIVIHISPGTKDSVMWALDGLSFTYSLVI WKNSSGVEERIENIYSRHKIYKLSPETTYCLKVKAALLTSWKI GVYSPVHCIKTTVENELPPPENIEVSVQNQNYVLKWDYTYAN MTFQVQWLHAFLKRNPGNHLYKWKQIPDCENVKTTQCVFP QNVFQKGIYLLRVQASDGNNTSFWSEEIKFDTEIQAFLLPPVF NIRSLSDSFHIYIGAPKQSGNTPVIQDYPLIYEIIFWENTSNAER KIIEKKTDVTVPNLKPLTVYCVKARAHTMDEKLNKSSVFSDA VCEKTKPGNTSK	327
IFN	MRSRCTVSAVGLLSLCLVVSASLETITPSAFDGYPDEPCTINITI RNSRLILSWELENKSGPPANYTLWYTVMSKDENLTKVKNCS DTTKSSCDVTDKWLEGMESYVVAIVIVHRGDLTVCRCSDYIV PANAPLEPPEFEIVGFTDHINVTMEFPPVTSKIIQEKMKTTPFVI KEQIGDSVRKKHEPKVNNVTGNFTFVLRDLLPKTNYCVSLYF DDDPAIKSPLKCIVLQPGQESGLSESA	328
IFN-α	TDVDYYREWXXXXXXXX (X可為任何胺基酸)	329
IFN-α 和 IFN-β	GSGTDVDYYREWSWTQV	330
IFN-α 和 IFN-β	GSGTDVDYYREWSWTQVS	331
IFN-α 和 IFN-β	TDVDYYREWSWTQV	332
IFN-α 和 IFN-β	TDVDYYREWSWTQVS	292
IFN-γ	ALTSTEDPEPPSVPVPTNVLIKSYNLNPVVCWEYQNMSQTPIF TVQVKVYSGSWTDSCTNISDHCCNIYEQIMYPDVSAWARVK AKVGQKESDYARSKEFLMCLKGKVGPPGLEIRRKKEEQLSVL VFHPEVVVNGESQGTMFGDGSTCYTFDYTVYVEHNRSGEILH TKHTVEKEECNETLCELNISVSTLDSRYCLSVDGISSFWQVRT EKSKDVCIPPFHDDRKDS	333

IFN-γ	ASSPDSFSQLAAPLNPRLHLYNDEQILTWEPSPSSNDPRPVVY QVEYSFIDGSWHRLLEPNCTDITETKCDLTGGGRLKLFPHPFT VFLRVRAKRGNLTSKWVGLEPFQHYENVTVGPPKNISVTPGK GSLVIHFSPPFDVFHGATFQYLVHYWEKSETQQEQVEGPFKS NSIVLGNLKPYRVYCLQTEAQLILKNKKIRPHGLLSNVSCHET TANASARLQQVILIPLGIFALLLGLTGACFTLFLKYQSRVKYW FQAPPNIPEQIEEYLKDPDQFILEVLDKDGSPKEDSWDSVSIISS PEKERDDVLQTP	334
IFN-γ	EMGTADLGPSSVPTPTNVTIESYNMNPIVYWEYQIMPQVPVF TVEVKNYGVKNSEWIDACINISHHYCNISDHVGDPSNSLWVR VKARVGQKESAYAKSEEFAVCRDGKIGPPKLDIRKEEKQIMI DIFHPSVFVNGDEQEVDYDPETTCYIRVYNVYVRMNGSEIQY KILTQKEDDCDEIQCQLAIPVSSLNSQYCVSAEGVLHVWGVT TEKSKEVCITIFNSSIKG	335
IFN-γ	SQLPAPQHPKIRLYNAEQVLSWEPVALSNSTRPVVYQVQFKY TDSKWFTADIMSIGVNCTQITATECDFTAASPSAGFPMDFNVT LRLRAELGALHSAWVTMPWFQHYRNVTVGPPENIEVTPGEG SLIIRFSSPFDIADTSTAFFCYYVHYWEKGGIQQVKGPFRSNSIS LDNLKPSRVYCLQVQAQLLWNKSNIFRVGHLSNISCYETMAD ASTELQQ	336
IL-12	CRTSECCFQDPPYPDADSGSASGPRDLRCYRISSDRYECSWQ YEGPTAGVSHFLRCCLSSGRCCYFAAGSATRLQFSDQAGVSV LYTVTLWVESWARNQTEKSPEVTLQLYNSVKYEPPLGDIKVS KLAGQLRMEWETPDNQVGAEVQFRHRTPSSPWKLGDCGPQ DDDTESCLCPLEMNVAQEFQLRRRQLGSQGSSWSKWSSPVC VPPENPPQPQVRFSVEQLGQDGRRRLTLKEQPTQLELPEGCQ GLAPGTEVTYRLQLHMLSCPCKAKATRTLHLGKMPYLSGAA YNVAVISSNQFGPGLNQTWHIPADTHTEPVALNISVGTNGTT MYWPARAQSMTYCIEWQPVGQDGGLATCSLTAPQDPDPAG MATYSWSRESGAMGQEKCYYITIFASAHPEKLTLWSTVLSTY HFGGNASAAGTPHHVSVKNHSLDSVSVDWAPSLLSTCPGVL KEYVVRCRDEDSKQVSEHPVQPTETQVTLSGLRAGVAYTVQ VRADTAWLRGVWSQPQRFSIEVQVSDWLIFFASLGSFLSILLV	337

	GVLGYLGLNRAARHLCPPLPTPC AS S AIEFPGGKETW QWINP VDF QEEASLQEAL VVEMS WDKGERTEPLEKTELPEGAP ELALDTELSLEDGDRCKAKM	
IL-12	KIDACKRGDVTVKPSHVILLGSTVNITCSLKPRQGCFHYSRRN KLILYKFDRRINFHHGHSLNSQVTGLPLGTTLFVCKLACINSD EIQICGAEIFVGVAPEQPQNLSCIQKGEQGTVACTWERGRDTH LYTEYTLQLSGPKNLTWQKQCKDIYCDYLDFGINLTPESPESN FTAKVTAVNSLGSSSSLPSTFTFLDIVRPLPPWDIRIKFQKASV SRCTLYWRDEGLVLLNRLRYRPSNSRLWNMVNVTKAKGRH DLLDLKPFTEYEFQISSKLHLYKGSWSDWSESLRAQTPEEEPT GMLDVWYMKRHIDYSRQQISLFWKNLSVSEARGKILHYQVT LQELTGGKAMTQNITGHTSWTTVIPRTGNWAVAVSAANSKG SSLPTRINIMNLCEAGLLAPRQVSANSEGMDNILVTWQPPRK DPSAVQEYVVEWRELHPGGDTQVPLNWLRSRPYNVSALISE NIKSYICYEIRVYALSGDQGGCSSILGNSKHKAPLSGPHINAIT EEKGSILISWNSIPVQEQMGCLLHYRIYWKERDSNSQPQLCEI PYRVSQNSHPINSLQPRVTYVLWMTALTAAGESSHGNEREFC LQGKANWMAFVAPSICIAIIMVGIFSTHYFQQKVFVLLAALRP QWCSREIPDPANSTCAKKYPIAEEKTQLPLDRLLIDWPTPEDP EPLVISEVLHQVTPVFRHPPCSNWPQREKGIQGHQASEKDMM HSASSPPPPRALQAESRQLVDLYKVLESRGSDPKPENPACPWT VLPAGDLPTHDGYLPSNIDDLPSHEAPLADSLEELEPQHISLSV FPSSSLHPLTFSCGDKLTLDQLKMRCDSLML	338
IL-12	NIDVCKLGTVTVQPAPVIPLGSAANISCSLNPKQGCSHYPSSN ELILLKFVNDVLVENLHGKKVHDHTGHSSTFQVTNLSLGMTL FVCKLNCSNSQKKPPVPVCGVEISVGVAPEPPQNISCVQEGEN	339

	GTVACSWNSGKVTYLKTNYTLQLSGPNNLTCQKQCFSDNRQ NCNRLDLGINLSPDLAESRFIVRVTAINDLGNSSSLPHTFTFLDI VIPLPPWDIRINFLNASGSRGTLQWEDEGQVVLNQLRYQPLNS TSWNMVNATNAKGKYDLRDLRPFTEYEFQISSKLHLSGGSW SNWSESLRTRTPEEEPVGILDIWYMKQDIDYDRQQISLFWKSL NPSEARGKILHYQVTLQEVTKKTTLQNTTRHTSWTRVIPRTG AWTASVSAANSKGASAPTHINIVDLCGTGLLAPHQVSAKSEN MDNILVTWQPPKKADSAVREYIVEWRALQPGSITKFPPHWLR IPPDNMSALISENIKPYICYEIRVHALSESQGGCSSIRGDSKHK APVSGPHITAITEKKERLFISWTHIPFPEQRGCILHYRIYWKER DSTAQPELCEIQYRRSQNSHPISSLQPRVTYVLWMTAVTAAG ESPQGNEREFCPQGKANWKAFVISSICIAIITVGTFSIRYFRQK AFTLLSTLKPQWYSRTIPDPANSTWVKKYPILEEKIQLPTDNL LMAWPTPEEPEPLIIHEVLYHMIPVVRQPYYFKRGQGFQGYST SKQDAMYIANPQATGTLTAETRQLVNLYKVLESRDPDSKLA NLTSPLTVTPVNYLPSHEGYLPSNIEDLSPHEADPTDSFDLEHQ HISLSIFASSSLRPLIFGGERLTLDRLKMGYDSLMSNEA	
IL-12	QLGASGPGDGCCVEKTSFPEGASGSPLGPRNLSCYRVSKTDY ECSWQYDGPEDNVSHVLWCCFVPPNHTHTGQERCRYFSSGP DRTVQFWEQDGIPVLSKVNFWVESRLGNRTMKSQKISQYLY NWTKTTPPLGHIKVSQSHRQLRMDWNVSEEAGAEVQFRRRM PTTNWTLGDCGPQVNSGSGVLGDIRGSMSESCLCPSENMAQE IQIRRRRRLSSGAPGGPWSDWSMPVCVPPEVLPQALVPRGS	340

IL-12	QLGASGPGDGCCVEKTSFPEGASGSPLGPRNLSCYRVSKTDY ECSWQYDGPEDNVSHVLWCCFVPPNHTHTGQERCRYFSSGP DRTVQFWEQDGIPVLSKVNFWVESRLGNRTMKSQKISQYLY NWTKTTPPLGHIKVSQSHRQLRMDWNVSEEAGAEVQFRRRM PTTNWTLGDCGPQVNSGSGVLGDIRGSMSESCLCPSENMAQE IQIRRRRRLSSGAPGGPWSDWSMPVCVPPEVLPQAKIKFLVEP LNQGGRRRLTMQGQSPQLAVPEGCRGRPGAQVKKHLVLVR MLSCRCQAQTSKTVPLGKKLNLSGATYDLNVLAKTRFGRSTI QKWHLPAQELTETRALNVSVGGNMTSMQWAAQAPGTTYCL EWQPWFQHRNHTHCTLIVPEEEDPAKMVTHSWSSKPTLEQE ECYRITVFASKNPKNPMLWATVLSSYYFGGNASRAGTPRHVS VRNQTGDSVSVEWTASQLSTCPGVLTQYVVRCEAEDGAWES EWLVPPTKTQVTLDGLRSRVMYKVQVRADTARLPGAWSHP QRFSFEVQISRLSIIFASLGSFASVLLVGSLGYIGLNRAAWHLC PPLPTPCGSTAVEFPGSQGKQAWQWCNPEDFPEVLYPRDALV VEMPGDRGDGTESPQAAPECALDTRRPLETQRQRQVQALSE ARRLGLAREDCPRGDLAHVTLPLLLGGVTQGASVLDDLWRT HKTAEPGPPTLGQEA	341
IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDT	342
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT ECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPP	343
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT ECVLNKATNVAHWTTPSLKCIRDP	344
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT ECVLNKATNVAHWTTPSLKCIR	345
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT ECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTVTTAGV TPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPS	346

	TGTTEISSHESSHGTPSQTTAKNWELTASASHQPPGVYPQGHS DTT	
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT ECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTVTTAGV TPQPESLSPSGKEPAAS	347
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT ECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPS	348
IL-15	MAPRRARGCRTLGLPALLLLLLLRPPATRGITCPPPMSVEHAD IWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAH WTTPSLKCIRDPALVHQRPAPPSTVTTAGVTPQPESLSPSGKE PAASSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESSH GTPSQTTAKNWELTASASHQPPGVYPQGHSDTTVAISTSTVL LCGLSAVSLLACYLKSRQTPPLASVEMEAMEALPVTWGTSSR DEDLENCSHHL	349
IL-2	AVKNCSHLECFYNSRANVSCMWSHEEALNVTTCHVHAKSNL RHWNKTCELTLVRQASWACNLILGSFPESQSLTSVDLLDINV VCWEEKGWRRVKTCDFHPFDNLRLVAPHSLQVLHIDTQRCN ISWKVSQVSHYIEPYLEFEARRRLLGHSWEDASVLSLKQRQQ WLFLEMLIPSTSYEVQVRVKAQRNNTGTW SPW SQPLTFRTRPADPMKE	350
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CL ETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAALG KDT	351
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEF QVRVKPLQ	352
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR	353

	RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDF	
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKD	354
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRSNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWIS LETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAAL GKD	355
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRSNIS WEISQASHYFEDHLEFEARTLSPGHTWEEAPLLTLKWKQEWI SLATLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKD	356
IL-2	CGGHQYERRGGC	357
IL-2	CGGHYFERHGGC	358
IL-2	CQKLTTVDIC	359
IL-2	CSFHQYERHEGC	360
IL-2	CSGHQYERREGC	361
IL-2	CSGHYFERHEGC	362
IL-2	CSHYFERC	363
IL-2	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQ KPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKLISRVEAE DVGVYYCMQALQTPLTFGGGTKVEIKR	364

IL-2	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLSWLQQ RPGQPPRLLIYKISNRFSGVPDRFSGSGAGTDFTLKISRVEAED VGVYYCMQATQFPTFGQGTKVEIKR	365
IL-2	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLSWLQQ RPGQPPRLLIYKISNRFSGVPDRFSGSGAGTDFTLKISRVEAED VGVYYCMQTSQFPTFGQGTKVEIKR	366
IL-2	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLSWLQQ RPGQPPRLLIYKISNRFSGVPDRFSGSGAGTDFTLKISRVEAED VGVYYCMQTTQFPTFGQGTKVEIKR	367
IL-2	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLSWLQQ RPGQPPRLLIYKISNRFSGVPDRFSGSGAGTDFTLKISRVEAED VGVYYCMQVTQFPTFGQGTKVEIKR	368
IL-2	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQ APRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVY YCQQYGSSPLTFGGGTKVEIKR	369
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSLY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	370
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSLY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSC	371
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSLY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKP	372

IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSVY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	373
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSVY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSC	374
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSVY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKP	375
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKELVY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	376
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKELVY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSC	377
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKELVY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKP	378
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL	379

	YMLCTGNSSHSSWDNQCQCTS	
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG E	380
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	381
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSC	382
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKP	383
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	384
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG	385

IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICT	386
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METS	387
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGSSSHSSWDNQCQCTSSATRSTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG E	388
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSV YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	389
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSV YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSC	390
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSV YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKP	391

IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSLY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	392
IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSLY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSC	393
IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSVY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	394
IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSVY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSC	395
IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKSGSVY MLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERK TTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKP	396
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	397

IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSC	398
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSL YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKP	399
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSV YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAAT METSIFTTEYQ	400
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSV YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKPQASPEGRPESETSC	401
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSV YMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKER KTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQ MVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTG EMETSQFPGEEKP	402
IL-2	ELCLYDPPEVPNATFKALSYKNGTILNCECKRGFRRLKELVY MRCLGNSWSSNCQCTS	403
IL-2	ELCLYDPPEVPNATFKALSYKNGTILNCECKRGFRRLKELVY MRCLGNSWSSNCQCTSNSHDKSRKQVTAQLEHQKEQQTTTD MQKPTQSMHQENLTGHCREPPPWKHEDSKRIYHFVEGQSVH YECIPGYKALQRGPAISICKMKCGKTGWTQPQLTCVDEREHH RFLASEESQGSRNSSPESETSCPITTTDFPQPTETTAMTETFVLT	404

	MEYK	
IL-2	ELCLYDPPEVPNATFKALSYKNGTILNCECKRGFRRLKELVY MRCLGNSWSSNCQCTSNSHDKSRKQVTAQLEHQKEQQTTTD MQKPTQSMHQENLTGHCREPPPWKHEDSKRIYHFVEGQSVH YECIPGYKALQRGPAISICKMKCGKTGWTQPQLTCVDEREHH RFLASEESQGSRNS SPESETSCPITTTDFPQPTETTAMTETFVLTMEYK	405
IL-2	ELCLYDPPEVPNATFKALSYKNGTILNCECKRGFRRLKELVY MRCLGNSWSSNCQCTSSATRNTTKQVTPQPEEQKERKTTEM QSPMQPVDQASLPGHCREPPPWENEATERIYHFVVGQMVYY QCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTGEMETS QFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAATMETSIF TTEYQ	406
IL-2	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMP GKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWS SLKASDTAMYYCARQQVAGMLDYWGQGTTVTVSS	407
IL-2	GMLSLAVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVH AWPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDI VTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVET HRCNISWEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQ KQEWICLETLTPDTQYEFQVRVKPLQAFRTLTGH	408
IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTTKQVTPQPEE QKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHF VVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQ LICTGE	409

IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTTKQVTPQPEE QKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHF VVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQ LICTGEAS	410
IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTTKQVTPQPEE QKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHF VVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQ LICTGEASGGGGHHHHHH	411
IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTTKQVTPQPEE QKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHF VVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQ LICTGEAS	412
IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTTKQVTPQPEE QKERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHF VVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQ LICTGEASGGGGHHHHHH	413
IL-2	LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFN VEYMNCTWNSSSEPQPTNLTLHYWYKNSDNDKVQKCSHYL FSEEITSGCQLQKKEIHLYQTFVVQLQDPREPRRQATQMLKL QNLVIPWAPENLTLHKLSESQLELNWNNRFLNHCLEHLVQYR TDWDHSWTEQSVDYRHKFSLPSVDGQKRYTFRVRSRFNPLC GSAQHWSEWSHPIHWGSNTSKENPFLFALEAV	414
IL-2	MDSYLLMWGLLTFIMVPGCQAELCDDDPPEIPHATFKAMAY KEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSWDNQCQC TSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGH CREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAE SVCKMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGRP ESETSCLVTTTDFQIQTEMAATMETSIFTTEYQVAVAGCVFLL	415

	ISVLLLSGLTWQRRQRKSRRTI	
IL-2	MLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIK SGSLYMLCTGSSSHSSWDNQCQCTSSATRSTTKQVTPQPEEQ KERKTTEMQSPMQPVDQASLPGHCREPPPWENEATERIYHFV VGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLI CTGE	416
IL-2	QKLTTVDI	417
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAREDWLGEADYGMDVWGQGTTVTVS S	418
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDGEQWRGFDYWGQGTTVTVSS	419
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDQEQWRLAFDYWGQGTTVTVSS	420
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGAVAGTGRDYYYYGMDVWGQGTT VTVSS	421
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGSYYDSSGYYYGEDFDYWGQGTTV TVSS	422
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAREEWELEDYGMDVWGQGTTVTVSS	423

IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDNWGSDAFDIWGQGTTVTVSS	424
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDDWFGEADYGMDVWGQGTTVTVS S	425
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARRISITPFDYWGQGTTVTVSS	426
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDDFWSDYPFDYWGQGTTVTVSS	427
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAREEWFGEADYGMDVWGQGTTVTVSS	428
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGSYYDSSGYYFGEDFDYWGQGTTV TVSS	429
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWVRQAP GKGLEWVTVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGTVAGTGRDYYYYGMDVWGQGTT VTVSS	430
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAREDFDSHYGMDVWGQGTTVTVSS	431
IL-2	SHYFER	432
IL-2	TLPLPEVQCFVFNVEYMNCTWNSSSEPQPTNLTLHYWYKNS DNDKVQKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDPR EPRRQATQMLKLQNLVIPWAPENLTLHKLSESQLELNWNNRF LNHCLEHLVQYRTDWDHSWTEQSVDYRHKFSLPSVDGQKR YTFRVRSRFNPLCGSAQHWSEWSHPIHWGSNT	433

IL-2	TLPLPEVQCFVFNVEYMNCTWNSSSEPQPTNLTLHYWYKNS DNDKVQKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDPR EPRRQATQMLKLQNLVI	434
IL-2	WSSKVLMSSANEDIKADLILTSTAPEHLSAPTLPLPEVQCFVF NIEYMNCTWNSSSEPQATNLTLHYRYKVSDNNTFQECSHYLF SKEITSGCQIQKEDIQLYQTFVVQLQDPQKPQRRAVQKLNLQ NLVIPRAPENLTLSNLSESQLELRWKSRHIKERCLQYLVQYRS NRDRSWTELIVNHEPRFSLPSVDELKRYTFRVRSRYNPICGSS QQWSKWSQPVHWGSHTVEENPSLFALEA	435
IL-2 和 IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDTGGGGSGGGGSGGGGSISSGLLSSGGSGGSLSGRSDNH GGGGSGGGGSLNTTILTPNGNEDTTADFFLTTMPTDSLSVSTL PLPEVQCFVFNVEYMNCTWNSSSEPQPTNLTLHYWYKNSDN DKVKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDPREPRR QATQMLKLQNLVIPWAPENLTLHKLSESQLELNWNNRFLNH CLEHLVQYRTDWDHSWTEQSVDYRHKFSLPSVDGQKRYTFR VRSRFNPLCGSAQHWSEWSHPIHWGSNTSKENPFLFALEA	436
IL-2 和 IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDTGGGGSGGGGSGGGGSISSGLLSSGGSGGSLSGRSDNH GGGGSGGGGSAVNGTSQFTCFYNSRANISCVWSQDGALQDT SCQVHAWPDRRRWNQTCELLPVSQASWACNLILGAPDSQKL TTVDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISLQV VHVETHRCNISWEISQASHYFERHLEFEARTLSPGHTWEEAPL LTLKQKQEWICLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQ PLAFRTKPAALGKDT	437

IL-2 和 IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPESQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDT	438
IL-2 和 IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDHQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDT	439
IL-2 和 IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTQDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDT	440
IL-2 和 IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTFDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDT	441
IL-2 和 IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFQRHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDT	442

IL-2 和 IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFQRRLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDT	443
IL-2 和 IL-15	AVNGTSQFTCFYNSYANISCVWSQDGALQDTSCQVHAWPDR RRWNQTCELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVL CREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNIS WEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWI CLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAA LGKDT	444
IL-2, IL-15, 和 IL-21	LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFN VEYMNCTWNSSSEPQPTNLTLHYWYKNSDNDKVQKCSHYL FSEEITSGCQLQKKEIHLYQTFVVQLQDPREPRRQATQMLKL QNLVIPWAPENLTLHKLSESQLELNWNNRFLNHCLEHLVQYR TDWDHSWTEQSVDYRHKFSLPSVDGQKRYTFRVRSRFNPLC GSAQHWSEWSHPIHWGSNTSKENPFLFALEA	445
IL-21	CPDLVCYTDYLQTVICILEMWNLHPSTLTLTWQDQYEELKDE ATSCSLHRSAHNATHATYTCHMDVFHFMADDIFSVNITDQSG NYSQECGSFLLAESIKPAPPFNVTVTFSGQYNISWRSDYEDPA FYMLKGKLQYELQYRNRGDPWAVSPRRKLISVDSRSVSLLPL EFRKDSSYELQVRAGPMPGSSYQGTWSEWSDPVIFQTQSEEL KE	446

表25. PD-1/PD-L1路徑抑制劑之實例

PD-L1 抗體 (CX-072(可經活化的) 和 CX-075 (不可經活化的))		
肽	序列	SEQ ID NO.
重鏈 (抗- PD-L1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSW VRQAPGKGLEWVSSIWRNGIVTVYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYCAKWSAAFDYW	485

	GQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG	
輕鏈 (CX- 072- 抗 -PD-L1)	QGQSGSGIALCPSHFCQLPQTGGGSSGGSGGSGGISS GLLSGRSDNHGGSDIQMTQSPSSLSASVGDRVTITCR ASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTF GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC	496
輕鏈 (CX- 075, 抗 -PD-L1- 不具有掩蔽物和受質)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQDNGYPSTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	497
PD-1 抗體 (CX-188)		
肽	序列	SEQ ID NO.
VL CDR1	RASESVDAYGISFMN	490

VL CDR2	AASNQGS	491
VL CDR3	QQSKDVPWT	492
可變輕鏈	DIQLTQSPSSLSASVGDRVTITCRASESVDAYGISFM NWFQQKPGKAPKLLIYAASNQGSGVPSRFSGSGSGT DFTLTISSMQPEDFATYYCQQSKDVPWTFGQGTKLE IK	484
掩蔽部分 (MM)	TSYCSIEHYPCNTHH	486
可裂解部分 (CM)	ISSGLLSGRSDNP	57
間隔子	QGQSGQG	474
完整輕鏈: 間隔子 -MM-GGGSSGGS 連接子 -CM-GGGS 連接子 - VL	QGQSGQGTSYCSIEHYPCNTHHGGGSSGGSISSGLLS GRSDNPGGGSDIQLTQSPSSLSASVGDRVTITCRASE SVDAYGISFMNWFQQKPGKAPKLLIYAASNQGSGV PSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVP WTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	498
VH CDR1	GFTFSGYAMS	487
VH CDR2	YISNSGGNAH	488
VH CDR3	EDYGTSPFVY	489
可變重鏈	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMS WVRQAPGKGLEWVAYISNSGGNAHYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSP FVYWGQGTLVTVSS	483
IgG4	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPC PAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV	499

	SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGF YPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	
完整重鏈 (VH + IgG4)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMS WVRQAPGKGLEWVAYISNSGGNAHYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSP FVYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLG	500
完整輕鏈: (不具有間隔子) MM-GGGSSGGS	TSYCSIEHYPCNTHHGGGSSGGSISSGLLSGRSDNPG GGSDIQLTQSPSSLSASVGDRVTIT CRASESVDAYGISFMNWFQQKPGKAPKLLIYAASNQ GSGVPSRFSGSGSGTDFTLTISSM QPEDFATYYCQQSKDVPWTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC	501
具"1.4版CDR組 之輕鏈 : VL CDR1	QGQSGQGAMSGCSWSAFCPYLAGGGSSGGSISSGLL SGRSDNHGGGSDIQLTQSPSSLSA SVGDRVTITCRASESVDSYGISFMNWFQQKPGKAPK	502

[+ 相同 VL CDR2 和1.5版之 VL CDR3]	LLIYAASNQGSGVPSRFSGSGSGT DFTLTISSMQPEDFATYYCQQSKDVPWTFGQGTKLE IK	
全長重鏈，IgG4 具有與 CX-188 重鏈相同之序列 (SEO ID NO:927), 但具有C端離胺酸	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMS WVRQAPGKGLEWVAYISNSGGNAHYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSP FVYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLGK	503
ProC1301	QSGQTDVDYYREWSWTQVSGSSGGSGGGSGGGSGS GGSCDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDR HDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTK DSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGV TETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWE VVRAEIMRSFSLSTNLQESRSKEGGSGGGGSCPPCPA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKA KGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS	508
ProC1640	DNIGSGGSCDLPQTHSLGSRRTLMLLAQMRRISLFSC LKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNL FSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQG	509

	VGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPC AWEVVRAEIMRSFSLSTNLQESLRSKELSGRS	
ProC1823	ISYDSPDYTDESCTFKISLRNFRSILSWELKNHSIVPT HYTLLYTIMSKPEDLKVVKNCANTTRSFCDLTDEW RSTHEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEP PEFEIVGFTNHINVMVKFPSIVEEELQFDLSLVIEEQS EGIVKKHKPEIKGNMSGNFTYIIDKLIPNTNYCVSVY LEHSDEQAVIKSPLKCTLLPPGQESESAESAKPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	510
ProC1976	DNIGSGGSCDLPQTHSLGSRRTLMLLAQMRRISLFSC LKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNL FSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQG VGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPC AWEVVRAEIMRSFSLSTNLQESLRSKELSGRS	511
ProC1718	ISYDSPDYTDESCTFKISLRNFRSILSWELKNHSIVPT HYTLLYTIMSKPEDLKVVKNCANTTRSFCDLTDEW RSTHEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEP PEFEIVGFTNHINVMVKFPSIVEEELQFDLSLVIEEQS EGIVKKHKPEIKGNMSGNFTYIIDKLIPNTNYCVSVY LEHSDEQAVIKSPLKCTLLPPGQESESAESAKGGGGS HHHHHHHH	512
ProC1824	KNLKSPQKVEVDVIDDNFILRWNRSEESVGNVTFSF DYQKPEMDNWIKLPGCQNMTSTKCNFSSLKLNIYD EIKLRIRAEKENTSSWCEVDSFTPFRKAQIGPPEVHLE AEDKAIVIYISPPGTEDSVMWALDRSSFTYSLVIWKN	513

	SSSVEERIENIYSRHKISKLSPETTYCLKVKAALLTSR KIGVYGPVHCIKTTVENELPPPENIEVIVQNQNYVLK WDYTYANMTFQVQWLHAFLKRKPGNHLYKWKQIP DCENVTTTQCVFPPNTFQKGIYLLRVQASDGNNTSF WSEEIKFDTEIQASLLPPVFNIRSLSDSLHISIGAPKWS ENKPVIQDYPLIYEILFWENTSKAERKIIKKKTDVTIP NLKPLTVYCVKARAHSMDEKLNKSSVFSDVVCEET KSGNTSKPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPG	
ProC1825	ISHDLPDYTSESCTFKISLRNFRSILSWELKNHSIVAT HYKLLYTIMSKPEDLKIVKNCANTTRSFCDLTDEWR STHEAYVTSLEGFSGNTTLFNCSHNFWLDIDMSFEPP EFEIVGFTNHINVIVKFPSIVEEELQFDLSLVIEEQSEG IVKKHKPTIKGNMSGNFTYIIDKLIPNTNYCVSVYFD HNDEQAVIKSPLKCTLLQPGQESESAESAKPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPG	514
ProC1822	KNLKSPQKVEVDIIDDNFILRWNRSDESVGNVTFSFD YQKTGMDNWIKLSGCQNITSTKCNFSSLKLNVYEEI KLRIRAEKENTSSWYEVDSFTPFRKAQIGPPEVHLEA EDKAIVIHISPGTKDSVMWALDGLSFTYSLVIWKNSS	515

	GVEERIENIYSRHKIYKLSPETTYCLKVKAALLTSWK IGVYSPVHCIKTTVENELPPPENIEVSVQNQNYVLKW DYTYANMTFQVQWLHAFLKRNPGNHLYKWKQIPD CENVKTTQCVFPQNVFQKGIYLLRVQASDGNNTSF WSEEIKFDTEIQAFLLPPVFNIRSLSDSFHIYIGAPKQS GNTPVIQDYPLIYEIIFWENTSNAERKIIEKKTDVTVP NLKPLTVYCVKARAHTMDEKLNKSSVFSDAVCEKT KPGNTSKPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPG	

【0555】本揭示之分子亦可包括IgG1重鏈(SEQ ID NO：517)、IgG4重鏈(SEQ ID NO：520)、IgG4 S228P重鏈(SEQ ID NO：516)、突變之IgG1 N297A重鏈(SEQ ID NO：518)或突變之IgG1 N297Q重鏈(SEQ ID NO：519)。

【0556】IgG4 S228P重鏈(Hc)胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
YWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV
ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLSLGK (SEQ ID NO: 516).

【0557】IgG1重鏈(Hc)胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
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VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPG (SEQ ID NO: 517).

【0558】IgG1NA Hc胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
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【0559】IgG1NQ Hc胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
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【0560】IgG4 Hc胺基酸序列：

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
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GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV
ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
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SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLSLG (SEQ ID NO: 520).

【0561】輕鏈(Lc)胺基酸序列：
AMSGCSWSAFCPYLA[X1]nLSGRSDNH[X2]nDIQLTQSPSSLSASVGDRVTITCRA
SESVDNYGISFMNWFQQKPGKAPKLLIYAASNQGSGVPSRFSGSGSGTDFTLTISS
MQPEDFATYYCQQSKDVPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC

【0562】其中[X1]n和[X2]n可各自獨立為具有0至20個胺基酸之連接肽(SEQ ID NO：521)。

其他實施態樣

【0563】應理解的是，雖然已經結合本發明之詳細描述來描述本發明，但前述描述旨在說明而非限制本發明之範圍，本發明之範圍係由所附之申請專利範圍限定。其他態樣、優點和修飾在下列申請專利範圍內。

【符號說明】

【0564】

110:第一單體構築體

111:DD1

112:連接子

113:CM1

114:連接子

115:CP1

116:連接子

117:CM3

118:連接子

119:PM1

120:第二單體構築體

121:DD2

122:連接子

123:CM2

124:連接子

125:CP2

126:連接子

127:CM4

128:連接子

129:PM2

210:第一單體構築體

211:DD1

212:連接子

213:CM1

214:連接子

215:CP1

216:連接子

217:CM3

218:連接子

219:PM1

220:第二單體構築體

221:DD2

222:連接子

223:CM2

224:連接子

225:CP2

226:連接子

227:CM4

228:連接子

229:PM2

310:第一單體構築體

311:DD1

312:連接子

313:CM1

314:連接子

315:CP1

316:連接子

317:CM3

318:連接子

319:PM1

320:第二單體構築體

321:DD2

322:連接子

323:CM2

324:連接子

325:CP2

326:連接子

327:CM4

328:連接子

329:PM2

410:第一單體構築體

411:DD1

412:連接子

413:CM1

414:連接子

415:CP1

416:連接子

417:CM3

418:連接子

419:PM1

420:第二單體構築體

421:DD2

422:連接子

423:CM2

424:連接子

425:CP2

426:連接子

427:CM4

428:連接子

429:PM2

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【發明申請專利範圍】

【請求項1】一種治療有此需要之個體之方法，其包含對該個體投予可經活化之細胞介素構築體(ACC)和PD-1/PD-L1路徑抑制劑的組合，其中該ACC包含第一單體構築體和第二單體構築體，其中：

(a)該第一單體構築體包含第一肽掩蔽物(PM1)、第一成熟細胞介素蛋白(CP1)、第一和第三可裂解部分(CM1和CM3)及第一二聚化結構域(DD1)，其中該CM1位於該CP1與該DD1之間且該CM3位於該PM1與該CP1之間；且

(b)該第二單體構築體包含第二成熟細胞介素蛋白(CP2)、第二可裂解部分(CM2)及第二二聚化結構域(DD2)，其中該CM2位於該CP2與該DD2之間；

其中該DD1與該DD2彼此結合從而形成該第一單體構築體和該第二單體構築體之二聚體。

【請求項2】如請求項1之方法，其中該第二單體構築體進一步包含第二肽掩蔽物(PM2)和第四可裂解部分(CM4)，其中該CM4位於該PM2與該CP2之間。

【請求項3】如請求項1或2之方法，其中該第一單體構築體包含第一多肽，該第一多肽包含該PM1、該CM3、該CP1、該CM1和該DD1。

【請求項4】如請求項1至3中任一項之方法，其中該第二單體構築體包含第二多肽，該第二多肽包含該CP2、該CM2和該DD2。

【請求項5】如請求項2之方法，其中該第二單體構築

體包含第二多肽，該第二多肽包含該PM2、該CM4、該CP2、該CM2和該DD2。

【請求項6】如請求項1至5中任一項之方法，其中該CP1和/或該CP2各自單獨地選自由下列組成之群組：干擾素、介白素、GM-CSF、G-CSF、LIF、OSM、CD154、LT-β、TNF-α、TNF-β、4-1BBL、APRIL、CD70、CD153、CD178、GITRL、LIGHT、OX40L、TALL-1、TRAIL、TWEAK、TRANCE、TGF-β1、TGF-β1、TGF-β3、Epo、Tpo、Flt-3L、SCF、M-CSF和MSP，可選擇地其中該CP1和/或該CP2係獨立地選自IL-2、IL-7、IL-8、IL-10、IL-12、IL-15、IL-21、IFNα、IFNβ、IFNγ、GM-CSF、TGF-β、LIGHT、GITR-L、CD40L、CD27L、4-1BB-L、OX40和OX40L。

【請求項7】如請求項1至6中任一項之方法，其中：

該PM1包含選自SEQ ID NO：297、298、292和299至336之序列，且該CP1為干擾素；

該PM1包含選自SEQ ID NO：297、298、292和299至332之序列，且該CP1為干擾素α；

該PM1包含選自SEQ ID NO：299至328和330至332之序列，且該CP1為干擾素β；

該PM1包含選自SEQ ID NO：299至328和333至336之序列，且該CP1為干擾素γ；

該PM1包含選自SEQ ID NO：337至341之序列，且該CP1為IL-12；

該PM1包含選自SEQ ID NO：342至349、436至444和478之序列，且該CP1為IL-15；

該PM1包含選自SEQ ID NO：350至435和436至445之序列，且該CP1為IL-2；或

該PM1包含選自SEQ ID NO：445和446之序列，且該CP1為IL-21。

【請求項8】如請求項2至7中任一項之方法，其中：

該PM2包含選自SEQ ID NO：297、298、292和299至336之序列，且該CP2為干擾素；

該PM2包含選自SEQ ID NO：297、298、292和299至332之序列，且該CP2為干擾素α；

該PM2包含選自SEQ ID NO：299至328和330至332之序列，且該CP2為干擾素β；

該PM2包含選自SEQ ID NO：299至328和333至336之序列，且該CP2為干擾素γ；

該PM2包含選自SEQ ID NO：337至341之序列，且該CP2為IL-12；

該PM2包含選自SEQ ID NO：342至349、436至444和478之序列，且該CP2為IL-15；

該PM2包含選自SEQ ID NO：350至435和436至445之序列，且該CP2為IL-2；或

該PM2包含選自SEQ ID NO：445和446之序列，且該CP2為IL-21。

【請求項9】如請求項1至8中任一項之方法，其中該

DD1和該DD2為選自由下列所組成之群組的一對：一對Fc結構域；源自人IL-15受體之α鏈(IL15Rα)的sushi結構域和可溶性IL-15；barnase和barnstar；PKA和AKAP；基於突變之RNase I片段之適配體構件/對接標籤構件；表位和sdAb；表位和scFv；基於蛋白突觸融合蛋白(syntaxin)、突觸結合蛋白(synaptotagmin)、突觸小蛋白(synaptobrevin)和SNAP25之交互作用的SNARE構件；及抗原結合結構域和表位。

【請求項10】如請求項9之方法，其中該DD1和該DD2為一對Fc結構域。

【請求項11】如請求項10之方法，其中該對Fc結構域為一對人Fc結構域。

【請求項12】如請求項11之方法，其中該人Fc結構域為人IgG1 Fc結構域、人IgG2 Fc結構域、人IgG3 Fc結構域或人IgG4 Fc結構域。

【請求項13】如請求項12之方法，其中該人Fc結構域為人IgG4 Fc結構域。

【請求項14】如請求項11之方法，其中該人Fc結構域包含與SEQ ID NO：3具有至少80%同一性之序列。

【請求項15】如請求項14之方法，其中該人Fc結構域包含與SEQ ID NO：3具有至少90%同一性之序列。

【請求項16】如請求項15之方法，其中該人Fc結構域包含SEQ ID NO：3。

【請求項17】如請求項9之方法，其中該DD1和該DD2

分別包含SEQ ID NO：287和288。

【請求項18】如請求項1至16中任一項之方法，其中該DD1和該DD2係相同。

【請求項19】如請求項9之方法，其中該DD1包含抗原結合結構域且該DD2包含對應之表位。

【請求項20】如請求項19之方法，其中該抗原結合結構域為抗His標籤抗原結合結構域且其中該DD2包含His標籤。

【請求項21】如請求項19之方法，其中該抗原結合結構域為單鏈可變片段(scFv)。

【請求項22】如請求項19之方法，其中該抗原結合結構域為單結構域抗體(sdAb)。

【請求項23】如請求項9之方法，其中該DD1和該DD2中至少一者包含選自由非多肽聚合物和小分子所組成之群組的二聚化結構域取代基。

【請求項24】如請求項23之方法，其中該DD1和該DD2包含彼此共價結合之非多肽聚合物。

【請求項25】如請求項24之方法，其中該非多肽聚合物為含硫聚乙二醇，且其中該DD1和該DD2彼此係經由一或多個二硫鍵共價結合。

【請求項26】如請求項23之方法，其中該DD1和該DD2中至少一者包含小分子。

【請求項27】如請求項26之方法，其中該小分子為生物素。

【請求項28】如請求項27之方法，其中該DD1包含生物素且該DD2包含抗生物素蛋白。

【請求項29】如請求項1至28中任一項之方法，其中該CP1和該CP2為成熟細胞介素。

【請求項30】如請求項1至28中任一項之方法，其中該CP1和該CP2包含信號肽。

【請求項31】如請求項1至30中任一項之方法，其中該CP1和該CP2係相同。

【請求項32】如請求項1至30中任一項之方法，其中該CP1和該CP2係不同。

【請求項33】如請求項1至30中任一項之方法，其中該CP1和/或該CP2為干擾素。

【請求項34】如請求項33之方法，其中該CP1和該CP2為干擾素。

【請求項35】如請求項33之方法，其中該CP1和該CP2為不同的干擾素。

【請求項36】如請求項33之方法，其中該CP1和該CP2為相同之干擾素。

【請求項37】如請求項33至36中任一項之方法，其中該干擾素為人野生型成熟干擾素。

【請求項38】如請求項33至37中任一項之方法，其中該干擾素係選自由下列所組成之群組：干擾素α、干擾素β、干擾素ω和干擾素τ。

【請求項39】如請求項38之方法，其中該干擾素為干

擾素α。

【請求項40】如請求項39之方法，其中該干擾素係選自由下列所組成之群組：干擾素α-2a、干擾素α-2b和干擾素α-n3。

【請求項41】如請求項40之方法，其中該干擾素為干擾素α-2b。

【請求項42】如請求項41之方法，其中該CP1和/或該CP2包含與SEQ ID NO：1具有至少80%同一性之序列。

【請求項43】如請求項42之方法，其中該CP1和/或該CP2包含與SEQ ID NO：1具有至少90%同一性之序列。

【請求項44】如請求項43之方法，其中該CP1和/或該CP2包含SEQ ID NO：1之序列。

【請求項45】如請求項38之方法，其中該干擾素為干擾素β。

【請求項46】如請求項45之方法，其中該干擾素β係選自由干擾素β-1a和干擾素β-1b所組成之群組。

【請求項47】如請求項1至46中任一項之方法，其中該CP1和/或該CP2包含IFab結構域。

【請求項48】如請求項1至33中任一項之方法，其中該CP1和/或該CP2包含介白素。

【請求項49】如請求項48之方法，其中該介白素係選自由下列所組成之群組：IL-1α、IL-1β、IL-1RA、IL-18、IL-2、IL-4、IL-7、IL-9、IL-13、IL-15、IL-3、IL-5、IL-6、IL-11、IL-12、IL-10、IL-20、IL-21、IL-14、IL-16和

IL-17。

【請求項50】如請求項1至49中任一項之方法，其中該CM1和該CM2之每一者包含共約3個胺基酸至約15個胺基酸。

【請求項51】如請求項1至50中任一項之方法，其中該CM1、該CM2、該CM3和該CM4中一或多者包含不同蛋白酶之受質。

【請求項52】如請求項1至51中任一項之方法，其中該CM1、該CM2和該CM3包含相同蛋白酶之受質。

【請求項53】如請求項1至52中任一項之方法，其中該蛋白酶係選自由下列所組成之群組：ADAM8、ADAM9、ADAM10、ADAM12、ADAM15、ADAM17/TACE、ADAMDEC1、ADAMTS1、ADAMTS4、ADAMTS5、BACE、腎素(Renin)、組織蛋白酶(Cathepsin)D、組織蛋白酶E、凋亡蛋白酶(Caspase)1、凋亡蛋白酶2、凋亡蛋白酶3、凋亡蛋白酶4、凋亡蛋白酶5、凋亡蛋白酶6、凋亡蛋白酶7、凋亡蛋白酶8、凋亡蛋白酶9、凋亡蛋白酶10、凋亡蛋白酶14、組織蛋白酶B、組織蛋白酶C、組織蛋白酶K、組織蛋白酶L、組織蛋白酶S、組織蛋白酶V/L2、組織蛋白酶X/Z/P、Cruzipain、天冬醯胺內肽酶(Legumain)、Otubain-2、KLK4、KLK5、KLK6、KLK7、KLK8、KLK10、KLK11、KLK13、KLK14、Meprin、腦啡肽酶(Neprilysin)、PSMA、BMP-1、MMP-1、MMP-2、MMP-3、MMP-7、MMP-9、MMP-10、MMP-11、MMP-12、

MMP-13、MMP-14、MMP-15、MMP-16、MMP-17、MMP-19、MMP-20、MMP-23、MMP-24、MMP-26、MMP-27、活化之蛋白C、組織蛋白酶A、組織蛋白酶G、凝乳酶(Chymase)、FVIIa、FIXa、FXa、FXIa、FXIIa、彈性蛋白酶、顆粒酶B、胍基苯甲酸酶、HtrA1、人嗜中性粒細胞裂解酶(lyase)、乳鐵蛋白、marapsin、NS3/4A、PACE4、纖溶酶、PSA、tPA、凝血酶、類胰蛋白酶(tryptase)、uPA、DESC1、DPP-4、FAP、Hepsin、膜型絲胺酸蛋白酶(Matriptase)-2、MT-SP1/Matripase、TMPRSS2、TMPRSS3和TMPRSS4。

【請求項54】如請求項53之方法，其中該蛋白酶係選自由下列所組成之群組：uPA、天冬醯胺內肽酶、MT-SP1、ADAM17、BMP-1、TMPRSS3、TMPRSS4、MMP-2、MMP-9、MMP-12、MMP-13和MMP-14。

【請求項55】如請求項1至52中任一項之方法，其中該CM1、該CM2、該CM3和/或該CM4包含選自由下列所組成之群組的序列：LSGRSDNH(SEQ ID NO：5)、TGRGPSWV(SEQ ID NO：6)、PLTGRSGG(SEQ ID NO：7)、TARGPSFK(SEQ ID NO：8)、NTLSGRSENHSG(SEQ ID NO：9)、NTLSGRSGNHGS(SEQ ID NO：10)、TSTSGRSANPRG(SEQ ID NO：11)、TSGRSANP(SEQ ID NO：12)、VHMPLGFLGP(SEQ ID NO：13)、AVGLLAPP(SEQ ID NO：14)、AQNLLGMV(SEQ ID NO：15)、QNQALRMA(SEQ ID NO：16)、LAAPLGLL(SEQ ID

NO：17)、STFPFGMF(SEQ ID NO：18)、ISSGLLSS(SEQ ID NO：19)、PAGLWLDP(SEQ ID NO：20)、VAGRSMRP(SEQ ID NO：21)、VVPEGRRS(SEQ ID NO：22)、ILPRSPAF(SEQ ID NO：23)、MVLGRSLL(SEQ ID NO：24)、QGRAITFI(SEQ ID NO：25)、SPRSIMLA(SEQ ID NO：26)、SMLRSMPL(SEQ ID NO：27)、ISSGLLSGRSDNH(SEQ ID NO：28)、AVGLLAPPGGLSGRSDNH(SEQ ID NO：29)、ISSGLLSSGGSGGSLSGRSDNH(SEQ ID NO：30)、LSGRSGNH(SEQ ID NO：31)、SGRSANPRG(SEQ ID NO：32)、LSGRSDDH(SEQ ID NO：33)、LSGRSDIH(SEQ ID NO：34)、LSGRSDQH(SEQ ID NO：35)、LSGRSDTH(SEQ ID NO：36)、LSGRSDYH(SEQ ID NO：37)、LSGRSDNP(SEQ ID NO：38)、LSGRSANP(SEQ ID NO：39)、LSGRSANI(SEQ ID NO：40)、LSGRSDNI(SEQ ID NO：41)、MIAPVAYR(SEQ ID NO：42)、RPSPMWAY(SEQ ID NO：43)、WATPRPMR(SEQ ID NO：44)、FRLLDWQW(SEQ ID NO：45)、ISSGL(SEQ ID NO：46)、ISSGLLS(SEQ ID NO：47)、ISSGLL(SEQ ID NO：48)、ISSGLLSGRSANPRG(SEQ ID NO：49)、AVGLLAPPTSGRSANPRG(SEQ ID NO：50)、AVGLLAPPSGRSANPRG(SEQ ID NO：51)、ISSGLLSGRSDDH(SEQ ID NO：52)、ISSGLLSGRSDIH(SEQ ID NO：53)、

ISSGLLSGRSDQH(SEQ ID NO：54)、

ISSGLLSGRSDTH(SEQ ID NO：55)、

ISSGLLSGRSDYH(SEQ ID NO：56)、

ISSGLLSGRSDNP(SEQ ID NO：57)、

ISSGLLSGRSANP(SEQ ID NO：58)、

ISSGLLSGRSANI(SEQ ID NO：59)、

AVGLLAPPGGLSGRSDDH(SEQ ID NO：60)、

AVGLLAPPGGLSGRSDIH(SEQ ID NO：61)、

AVGLLAPPGGLSGRSDQH(SEQ ID NO：62)、

AVGLLAPPGGLSGRSDTH(SEQ ID NO：63)、

AVGLLAPPGGLSGRSDYH(SEQ ID NO：64)、

AVGLLAPPGGLSGRSDNP(SEQ ID NO：65)、

AVGLLAPPGGLSGRSANP(SEQ ID NO：66)、

AVGLLAPPGGLSGRSANI(SEQ ID NO：67)、

ISSGLLSGRSDNI(SEQ ID NO：68)、

AVGLLAPPGGLSGRSDNI(SEQ ID NO：69)、

GLSGRSDNHGGAVGLLAPP(SEQ ID NO：70)、

GLSGRSDNHGGVHMPLGFLGP(SEQ ID NO：71)、

LSGRSDNHGGVHMPLGFLGP(SEQ ID NO：72)、

ISSGLSS(SEQ ID NO：73)、PVGYTSSL(SEQ ID NO：74)、DWLYWPGI(SEQ ID NO：75)、LKAAPRWA(SEQ ID NO：76)、GPSHLVLT(SEQ ID NO：77)、LPGGLSPW(SEQ ID NO：78)、MGLFSEAG(SEQ ID NO：79)、SPLPLRVP(SEQ ID NO：80)、RMHLRSLG(SEQ ID NO：81)、

LLAPSHRA(SEQ ID NO：82)、GPRSFGL(SEQ ID NO：83)、GPRSFG(SEQ ID NO：84)、SARGPSRW(SEQ ID NO：85)、GGWHTGRN(SEQ ID NO：86)、HTGRSGAL(SEQ ID NO：87)、AARGPAIH(SEQ ID NO：88)、RGPAFNPM(SEQ ID NO：89)、SSRGPAYL(SEQ ID NO：90)、RGPATPIM(SEQ ID NO：91)、RGPA(SEQ ID NO：92)、GGQPSGMWGW(SEQ ID NO：93)、FPRPLGITGL(SEQ ID NO：94)、SPLTGRSG(SEQ ID NO：95)、SAGFSLPA(SEQ ID NO：96)、LAPLGLQRR(SEQ ID NO：97)、SGGPLGVR(SEQ ID NO：98)、PLGL(SEQ ID NO：99)和SGRSDNI(SEQ ID NO：100)。

【請求項56】如請求項55之方法，其中該CM1、該CM2、該CM3和/或該CM4包含選自由下列所組成之群組的序列：ISSGLLSGRSDNH(SEQ ID NO：28)、LSGRSDDH(SEQ ID NO：33)、ISSGLLSGRSDQH(SEQ ID NO：54)、SGRSDNI(SEQ ID NO：100)和ISSGLLSGRSDNI(SEQ ID NO：68)。

【請求項57】如請求項1至56中任一項之方法，其中該蛋白酶係由個體之腫瘤產生。

【請求項58】如請求項57之方法，其中該個體已被診斷或鑑定為患有癌症。

【請求項59】如請求項1至58中任一項之方法，其中該CP1與該CM1在該第一單體構築體中彼此直接鄰接。

【請求項60】如請求項1至59中任一項之方法，其中

該CM1與該DD1在該第一單體構築體中彼此直接鄰接。

【請求項61】如請求項1至60中任一項之方法，其中該CP2與該CM2在該第二單體構築體中彼此直接鄰接。

【請求項62】如請求項1至61中任一項之方法，其中該CM2與該DD2在該第二單體構築體中彼此直接鄰接。

【請求項63】如請求項1至58中任一項之方法，其中該第一單體構築體包含至少一個連接子。

【請求項64】如請求項63之方法，其中該至少一個連接子為位於該PM1與該CM3之間的連接子L1和/或位於該CM3與該CP1之間的連接子L2。

【請求項65】如請求項63之方法，其中該第二單體構築體包含至少一個連接子。

【請求項66】如請求項65之方法，其中該至少一個連接子為位於該PM2與該CM4之間的連接子L3和/或位於該CM4與該CP2之間的連接子L4。

【請求項67】如請求項66之方法，其中該第一單體構築體包含連接子L1且該第二單體構築體包含連接子L3。

【請求項68】如請求項67之方法，其中L1和L3係相同。

【請求項69】如請求項66之方法，其中該第一單體構築體包含連接子L2且該第二單體構築體包含連接子L4。

【請求項70】如請求項69之方法，其中L2和L4係相同。

【請求項71】如請求項63至70中任一項之方法，其中

各連接子之總長度為1個胺基酸至約15個胺基酸。

【請求項72】如請求項71之方法，其中各連接子之總長度為至少5個胺基酸。

【請求項73】如請求項63之方法，其中該第一單體構築體包含至少一個連接子，其中各連接子係獨立選自由下列所組成之群組：GSSGGSGGSGG(SEQ ID NO：210)；GGGS(SEQ ID NO：2)；GGGSGGGS(SEQ ID NO：211)；GGGSGGGSGGGS(SEQ ID NO：212)；GGGGSGGGGSGGGGS(SEQ ID NO：213)；GGGGSGGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)；GGGGSGGGGS(SEQ ID NO：215)；GGGGS(SEQ ID NO：216)；GS；GGGGSGS(SEQ ID NO：217)；GGGGSGGGGSGGGGSGS(SEQ ID NO：218)；GGSLDPKGGGGS(SEQ ID NO：219)；PKSCDKTHTCPPCPAPELLG(SEQ ID NO：220)；SKYGPPCPPCPAPEFLG(SEQ ID NO：221)；GKSSGSGSESKS(SEQ ID NO：222)；GSTSGSGKSSEGKG(SEQ ID NO：223)；GSTSGSGKSSEGSGSTKG(SEQ ID NO：224)；GSTSGSGKPGSGEGSTKG(SEQ ID NO：225)；GSTSGSGKPGSSEGST(SEQ ID NO：226)；(GS)n、(GGS)n、(GSGGS)n(SEQ ID NO：227)、(GGGS)n(SEQ ID NO：228)、(GGGGS)n(SEQ ID NO：216)，其中各個n為至少1之整數；GGSG(SEQ ID NO：229)；GGSGG(SEQ ID

NO：230)；GSGSG(SEQ ID NO：231)；GSGGG(SEQ ID NO：232)；GGGSG(SEQ ID NO：233)；GSSSG(SEQ ID NO：234)；GGGGSGGGGSGGGGS(SEQ ID NO：213)；GGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)；GSTSGSGKPGSSEGST(SEQ ID NO：226)；SGGG(SEQ ID NO：296)；和SGGGG(SEQ ID NO：459)。

【請求項74】如請求項73之方法，其中該連接子包含GGGS(SEQ ID NO：2)之序列。

【請求項75】如請求項1至74中任一項之方法，其中該第一單體構築體於N端至C端之方向包含該PM1、該CM3、該CP1、該CM1和該DD1。

【請求項76】如請求項1至74中任一項之方法，其中該第一多肽於C端至N端之方向包含該PM1、該CM3、該CP1、該CM1和該DD1。

【請求項77】如請求項1至76中任一項之方法，其中該第二多肽於N端至C端之方向包含該CP2、該CM2和該DD2。

【請求項78】如請求項1至77中任一項之方法，其中該第二多肽於C端至N端之方向包含該CP2、該CM2和該DD2。

【請求項79】如請求項1至31、33、34及36至78中任一項之方法，其中該第一單體構築體和該第二單體構築體係相同。

【請求項80】如請求項1至74中任一項之方法，其中

該第一單體構築體於N端至C端之方向包含該PM1、可選擇之連接子、該CM3、可選擇之連接子、該CP1、該CM1和該DD1，其中該CP1與該CM1彼此直接鄰接，其中該CM1與該DD1彼此直接鄰接，其中該CM1為不超過10個胺基酸之肽，其中該第二單體構築體與該第一單體構築體係相同，且其中該第一和第二單體構築體係經由至少二個二硫鍵彼此共價結合。

【請求項81】如請求項80之方法，其中該DD1和該DD2各自為在根據EU編號的半胱胺酸216處具有N端之人Fc結構域。

【請求項82】如請求項80或81之方法，其中該CM1為不超過7個胺基酸之肽。

【請求項83】如請求項80至82中任一項之方法，其中該CP1和該CP2包含與SEQ ID NO：1具有至少90%同一性之胺基酸序列。

【請求項84】如請求項1至83中任一項之方法，其中該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，該至少一種CP1和/或CP2活性之水準降低。

【請求項85】如請求項84之方法，其中該CP1和該CP2活性中至少一者為淋巴瘤細胞之增殖水準。

【請求項86】如請求項84之方法，其中該CP1和該CP2活性中至少一者為淋巴瘤細胞中JAK/STAT/ISGF3路徑活化之水準。

【請求項87】如請求項84之方法，其中該至少一種活

性為淋巴瘤細胞中SEAP產生之水準。

【請求項88】如請求項84之方法，其中該ACC之特徵在於與該對照水準相比較，該CP1和該CP2活性中至少一者降低至少2倍。

【請求項89】如請求項88之方法，其中該ACC之特徵在於與該對照水準相比較，該CP1和/或該CP2活性中至少一者降低至少5倍。

【請求項90】如請求項89之方法，其中該ACC之特徵在於與該對照水準相比較，該CP1和/或該CP2活性中至少一者降低至少10倍。

【請求項91】如請求項90之方法，其中該ACC的特徵在於與該對照水準相比較，該CP1和/或該CP2活性中至少一者降低至少500倍。

【請求項92】如請求項84至91中任一項之方法，其中該CP1和/或該CP2活性中至少一者之該對照水準為該ACC暴露於該蛋白酶後該ACC之該CP1和/或該CP2的活性。

【請求項93】如請求項84至92中任一項之方法，其中該CP1和/或該CP2活性中至少一者之該對照水準為對應之野生型成熟細胞介素的對應CP1和/或CP2活性。

【請求項94】如請求項84至93中任一項之方法，其中該ACC之特徵在於暴露於該蛋白酶後產生裂解產物，其中該裂解產物包含該CP1和/或CP2活性中至少一者。

【請求項95】如請求項94之方法，其中該至少一種CP1和/或CP2活性為抗增殖活性。

【請求項96】如請求項95之方法，其中該對照水準為EC50值，且其中EC50(裂解產物)與EC50(對照水準)之比率小於約10、或小於約9、或小於約8、或小於約7、或小於約6、或小於約5、或小於約4、或小於約3、或小於約2、或小於約1.5、或小於約1.0。

【請求項97】如請求項84至96中任一項之方法，其中該CP1和該CP2活性中至少一者為如使用表面等離子共振所測定之該CP1和/或該CP2對其同源受體之結合親和力。

【請求項98】一種治療有此需要之個體之方法，其包含對該個體投予可經活化之細胞介素構築體(ACC)和PD-1/PD-L1路徑抑制劑之組合，其中該ACC包含第一單體構築體和第二單體構築體，其中：

(a)該第一單體構築體為多肽，該多肽包含第一肽掩蔽物(PM1)、第一成熟細胞介素蛋白(CP1)、第一和第三可裂解部分(CM1和CM3) 及第一二聚化結構域(DD1)；

(b)該第二單體構築體為多肽，該多肽包含第二肽掩蔽物(PM2)、第二成熟細胞介素蛋白(CP2)、第二和第四可裂解部分(CM2和CM4)及第二二聚化結構域(DD2)；

(c)該第一單體構築體於N端至C端之方向包含該PM1、該CM3、該CP1、該CM1及該DD1；

且

(d)該ACC之特徵在於與對應野生型干擾素或對應聚乙二醇化干擾素相比較，具有降低之干擾素活性水準。

【請求項99】如請求項98之方法，其中該ACC進一步

之特徵在於下列至少一者：

(i) 該PM1包含不超過20個胺基酸並與該CP1結合；

(ii) 該CM1與該DD1彼此直接鄰接；

(iii) 該CP1與該CM1彼此直接鄰接；

(iv) 該CM1包含不超過12個胺基酸；

(v) 該CM1和該CM3各自作為蛋白酶之受質；和

(vi) 該CP1為成熟干擾素。

【請求項100】如請求項98或99之方法，其中

(i) 該DD1和該DD2為一對人IgG Fc結構域；

(ii) 該DD1與該DD2經由至少一個二硫鍵彼此結合，從而形成該第一單體構築體與該第二單體構築體之同源二聚體；或

(iii) (i)和(ii)二者。

【請求項101】如請求項98至100中任一項之方法，其中該CP1為成熟干擾素α且該PM1包含與SEQ ID NO：292具有至少85%同一性之序列。

【請求項102】如請求項98至101中任一項之方法，其中該CM1和該CM3各自獨立地作為尿激酶(uPa)和/或基質金屬蛋白酶(MMP)之受質。

【請求項103】如請求項102之方法，其中該CM1和該CM3各自獨立地作為尿激酶(uPa)和/或MMP-14之受質。

【請求項104】如請求項99至103中任一項之方法，其中該成熟干擾素為成熟人干擾素α。

【請求項105】如請求項99至104中任一項之方法，其

中該成熟干擾素α為成熟干擾素α-2b。

【請求項106】如請求項99至105中任一項之方法，其中該成熟干擾素α為野生型成熟干擾素α-2b之截短形式。

【請求項107】如請求項99至106中任一項之方法，其中該成熟干擾素包含與SEQ ID NO：1具有至少95%同一性之序列。

【請求項108】如請求項99至107中任一項之方法，其中該成熟干擾素包含SEQ ID NO：1之序列。

【請求項109】如請求項99至108中任一項之方法，其中該CM1和該CM3各自包含不超過8個胺基酸。

【請求項110】如請求項99至109中任一項之方法，其中該CM1和該CM3係相同。

【請求項111】如請求項99至110中任一項之方法，其中該CM1和該CM3各自包含與SEQ ID NO：41具有至少85%同一性之序列。

【請求項112】如請求項99至111中任一項之方法，其中該CM1和該CM3各自包含選自由下列所組成之群組的序列：SEQ ID NO：41、SEQ ID NO：68和SEQ ID NO：100。

【請求項113】如請求項99至112中任一項之方法，其中該DD1和該DD2為一對人IgG4 Fc結構域。

【請求項114】如請求項113之方法，其中該DD1和該DD2為一對人IgG4 Fc結構域，該對人IgG4 Fc結構域在N端被截短至根據EU編號之半胱胺酸226。

【請求項115】如請求項113或114之方法，其中該人IgG4 Fc結構域包含根據EU編號之S228P突變。

【請求項116】如請求項99至115中任一項之方法，其中該DD1和該DD2各自包含與SEQ ID NO：3具有至少95%同一性之序列。

【請求項117】如請求項99至116中任一項之方法，其中該DD1和該DD2各自包含SEQ ID NO：3之序列。

【請求項118】如請求項99至117中任一項之方法，其中該第一和第二單體構築體係經由至少二個二硫鍵彼此共價結合。

【請求項119】如請求項118之方法，其中該第一和第二單體構築體係經由至少三個二硫鍵彼此共價結合。

【請求項120】如請求項99至119中任一項之方法，其中：

該第一單體構築體進一步包含在N端之第一信號序列，且該第二單體構築體進一步包含在N端之第二信號序列。

【請求項121】如請求項120之方法，其中該第一和第二信號序列各自包含與SEQ ID NO：470具有至少95%同一性之序列。

【請求項122】如請求項121之方法，其中該第一和第二信號序列各自包含SEQ ID NO：470之序列。

【請求項123】如請求項120至122中任一項之方法，其中：

該第一單體構築體進一步包含位於該第一信號序列與該PM1之間的第一間隔子，且該第二單體構築體進一步包含位於該第二信號序列與該PM2之間的第二間隔子。

【請求項124】如請求項123之方法，其中該第一和第二間隔子各自包含與SEQ ID NO：480具有至少80%同一性之序列。

【請求項125】如請求項124之方法，其中該第一和第二間隔子各自包含SEQ ID NO：480之序列。

【請求項126】如請求項99至125中任一項之方法，其進一步包含位於該PM1與該CM3之間的連接子L1和/或位於該CM3與該CP1之間的連接子L2，其中L1和L2各自獨立地包含與SEQ ID NO：27(其中n=1)具有至少80%同一性之序列、與SEQ ID NO：293具有至少80%同一性之序列、或不存在序列。

【請求項127】如請求項126之方法，其中該L1包含序列SEQ ID NO：27(其中n=1)且該L2包含序列SEQ ID NO：293。

【請求項128】如請求項99至127中任一項之方法，其包含連接區，該連接區包含不超過12個胺基酸。

【請求項129】如請求項128之方法，其中該連接區包含7至12個胺基酸。

【請求項130】如請求項129之方法，其中該連接區包含7個胺基酸。

【請求項131】如請求項99至130中任一項之方法，其

中該ACC之特徵在於與野生型干擾素α相比較，干擾素α活性降低至少2000倍。

【請求項132】如請求項131之方法，其中該ACC之特徵在於與野生型干擾素α相比較，干擾素α活性降低至少4000倍。

【請求項133】如請求項132之方法，其中該ACC之特徵在於與野生型干擾素α相比較，干擾素α活性降低至少5000倍。

【請求項134】如請求項99至130中任一項之方法，其中該ACC之特徵在於與聚乙二醇化干擾素α相比較，干擾素α活性降低至少2000倍。

【請求項135】如請求項99至134中任一項之方法，其中該干擾素活性降低係藉由在淋巴瘤細胞之抗增殖分析中比較該ACC之EC50與該野生型干擾素或該聚乙二醇化干擾素之EC50測定。

【請求項136】如請求項99至135中任一項之方法，其中該干擾素活性降低係藉由在干擾素反應性HEK293細胞之誘導分泌型胚胎鹼性磷酸酶產生的分析中比較該ACC之EC50與該野生型干擾素或該聚乙二醇化干擾素之EC50測定。

【請求項137】如請求項99至136中任一項之方法，其中該ACC之進一步特徵在於暴露於該CM1和該CM3作為受質的蛋白酶之後產生裂解產物，其中該對應野生型干擾素之干擾素活性對該裂解產物之干擾素活性的比率小於約

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【請求項138】如請求項137之方法，其中該裂解產物之EC50與該對應野生型干擾素之EC50大約相同。

【請求項139】如請求項99之方法，其中該第一和第二單體構築體各自包含與SEQ ID NO：290具有至少95%同一性之序列，其中該ACC之特徵在於與野生型干擾素α-2b相比較，干擾素活性降低至少1000倍，且其中該ACC之進一步特徵在於暴露於uPA後產生裂解產物，其中該裂解產物具有與野生型干擾素α-2b大約相同之干擾素活性，其中干擾素活性係在淋巴瘤細胞之抗增殖分析中測量或在干擾素反應性HEK293細胞之誘導分泌型胚胎鹼性磷酸酶產生的分析中測量。

【請求項140】一種治療有此需要之個體之方法，其包含對該個體投予可經活化之細胞介素構築體(ACC)和PD-1/PD-L1路徑抑制劑之組合，其中該ACC包含第一單體構築體和第二單體構築體，其中：

(a)該第一單體構築體包含第一肽掩蔽物(PM1)、第一成熟細胞介素蛋白(CP1)、第一和第三可裂解部分(CM1和CM3)及第一二聚化結構域(DD1)；

(b)該第二單體構築體為多肽，該多肽包含第二肽掩蔽物(PM2)、第二成熟細胞介素蛋白(CP2)、第二和第四可裂解部分(CM2和CM4)及第二二聚化結構域(DD2)；

(c)該第一單體構築體為多肽，該多肽於N端至C端之方向包含該PM1、該CM3、該CP1、該CM1及該DD1，進

一步其中：

(i) 該PM1包含與SEQ ID NO：292具有至少85%同一性之序列；

(ii) 該CM1與該DD1彼此直接相鄰；

(iii) 該CM1包含與SEQ ID NO：41具有至少85%同一性之序列；且

(iv) 該CP1包含與SEQ ID NO：1具有至少85%同一性之序列；

(d) 進一步其中：

(i) 該第二單體構築體與該第一單體構築體係相同；

(ii) 該DD1和該DD2為一對人IgG4 Fc結構域；

(e)該DD1與該DD2係經由至少一個二硫鍵彼此共價結合，從而形成該第一單體構築體與該第二單體構築體之同源二聚體；且

(f)該ACC之特徵在於與聚乙二醇化干擾素α-2b的干擾素α活性相比較，具有降低之干擾素α活性水準。

【請求項141】如請求項140之方法，其中該第一和第二單體構築體各自包含與SEQ ID NO：290具有至少95%同一性之序列，或者其中該第一和第二單體構築體各自包含SEQ ID NO：290之序列，其中與野生型干擾素α-2b或聚乙二醇化干擾素α-2b相比較，該ACC顯示活體內較低之毒性。

【請求項142】如請求項1至141中任一項之方法，其

中該CM1和該CM3各自作為經腫瘤組織過度表現之蛋白酶的受質。

【請求項143】如請求項1至142中任一項之方法，其中該PD1/PD-L1路徑抑制劑係選自PD-1抗體、可經活化之PD-1抗體、PD-L1抗體或該可經活化之PD-L1抗體。

【請求項144】如請求項143之方法，其中該可經活化之PD-1抗體或該可經活化之PD-L1抗體包含：(i)與PD-1或PD-L1特異地結合之抗體或其抗原結合片段(AB)；(ii) 掩蔽部分(MM)，其當該可經活化之抗體處於未裂解狀態時抑制該AB與PD-1或PD-L1結合；及(iii)與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶的受質之多肽；及可選擇地第一連接肽和/或第二連接肽。

【請求項145】如請求項1至142中任一項之方法，其中該PD1/PD-L1路徑抑制劑包含尼維魯單抗(nivolumab)、派姆單抗(pembrolizumab)、提利珠單抗(tislelizumab)、巴泰利珠單抗(spartalizumab)、卡利珠單抗(camrelizumab)、賽特利單抗(cetrelimab)、巴西利單抗(Balstilimab)、多塔利單抗(Dostarlimab)、普戈利單抗(Prolgolimab)、沙山利單抗(Sasanlimab)、辛布利單抗(zimberelimab)、阿舒利珠單抗(Atezolizumab)、阿維魯單抗(Avelumab)、德維魯單抗(Durvalumab)、德布利單抗(adebrelimab)、洛普利單抗(Lodapolimab)、英佛利單抗(Envafolimab)、科貝利單抗(Cosibelimab)、布嘉利單抗(budigalimab)、薩本利單抗(ezabenlimab)、芬托利單抗(finotonlimab)、杰諾利單抗

(geptanolimab)、洛普利單抗(lodapolimab)、潘普利單抗(penpulimab)、皮瓦利單抗(pimivalimab)、樸可利單抗(pucotenlimab)、思普利單抗(serplulimab)、西提利單抗(Sintilimab)、托巴利單抗(toripalimab)、哲瓦利單抗(zeluvalimab)、巴洛利單抗(iparomlimab)、諾辛利單抗(nofazinlimab)、魯洛利單抗(rulonilimab)、嘉維利單抗(garivulimab)、曼利單抗(manelimab)、歐普利單抗(opucolimab)、舒多利單抗(sudubrilimab)、舒馬利單抗(sugemalimab)、索卡利單抗(socazolimab)或吉坦利單抗(tagitanlimab)。

【請求項146】如請求項1至142及145中任一項之方法，其中該PD1/PD-L1路徑抑制劑包含帕米單抗(pacmilimab)(CX-072)、CX-075、CX-171或CX-188。

【請求項147】如請求項1至146中任一項之方法，其中該個體需要減少、抑制和/或延遲該個體中PD-1或PD-L1之發生或進展。

【請求項148】如請求項1至146中任一項之方法，其中該個體需要減輕與該個體中PD-1或PD-L1之異常表現和/或異常活性相關的症狀。

【請求項149】如請求項1至148中任一項之方法，其中該個體已被鑑定或診斷為患有癌症。

【請求項150】如請求項149之方法，其中該癌症為淋巴瘤。

【請求項151】如請求項150之方法，其中該淋巴瘤為

伯基特(Burkitt's)氏淋巴瘤。

【請求項152】如請求項1至151中任一項之方法，其中該方法包含增進或加強相對於該個體之常規細胞介素療法之治療功效和/或治療指數。

【請求項153】如請求項1至151中任一項之方法，其中該方法包含增進或加強相對於該個體之常規PD1/PDL1抑制劑療法之治療功效和/或治療指數。

【請求項154】如請求項1至151中任一項之方法，其中該方法包含增進或加強相對於該個體之常規細胞介素和PD1/PDL1抑制劑組合療法之治療功效和/或治療指數。

【請求項155】如請求項1至149中任一項之方法，其中該方法包含增進或加強相對於投予單獨ACC之治療功效和/或治療指數。

【請求項156】一種組合或組成物，其包含如請求項1至148中任一項所述之該ACC及該PD-1/PD-L1路徑抑制劑。

【請求項157】如請求項156之組合或組成物，其中該組合或組成物為醫藥組成物。

【請求項158】如請求項156之組合或組成物，其中該組合或組成物係用於治療。

【請求項159】如請求項156之組合或組成物，其中該組合或組成物係用於治療癌症。

【請求項160】如請求項156之組合或組成物，其中該組合或組成物係用於治療感染。

【請求項161】一種容器、小瓶、注射器、注射筆或套組，其包含至少一個劑量之如請求項156至160之組合或組成物。

【請求項162】一種治療有此需要之個體之方法，其包含對該個體投予可經活化之細胞介素構築體(ACC)和PD-1/PD-L1路徑抑制劑之組合，其中該ACC包含第一單體構築體和第二單體構築體，其中：

(a)該第一單體構築體包含第一成熟細胞介素蛋白(CP1)、第一可裂解部分(CM1)及第一二聚化結構域(DD1)，

其中該CM1位於該CP1與該DD1之間；且

(b)該第二單體構築體包含第二成熟細胞介素蛋白(CP2)、第二可裂解部分(CM2)及第二二聚化結構域(DD2)，

其中該CM2位於該CP2與該DD2之間；或

(a)該第一單體構築體包含第一成熟細胞介素蛋白(CP1)和第一二聚化結構域(DD1)；且

(b)該第二單體構築體包含第二成熟細胞介素蛋白(CP2)、可裂解部分(CM)及第二二聚化結構域(DD2)，其中該CM位於該CP2與該DD2之間，其中該CM係作為蛋白酶之受質；或

(a)該第一單體構築體包含第一成熟細胞介素蛋白(CP1)、可裂解部分(CM)及第一二聚化結構域(DD1)，其中該CM位於該CP1與該DD1之間；且

(b)該第二單體構築體包含第二成熟細胞介素蛋白(CP2)和第二二聚化結構域(DD2)，

其中該CM係作為蛋白酶之受質；或

(a)該第一單體構築體包含第一成熟細胞介素蛋白(CP1)和第一二聚化結構域(DD1)；且

(b)該第二單體構築體包含第二成熟細胞介素蛋白(CP2)和第二二聚化結構域(DD2)，其中該CP1、該CP2或該CP1和該CP2二者包括作為蛋白酶之受質之胺基酸序列；

進一步其中(c)該DD1與該DD2彼此結合從而形成該第一單體構築體與該第二單體構築體之二聚體；且

進一步其中(d)該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，該至少一種CP1和/或CP2活性水準降低。

【請求項163】如請求項162之方法，其中該第一單體構築體包含第一多肽，該第一多肽包含該CP1、該CM1和該DD1。

【請求項164】如請求項162或163之方法，其中該第二單體構築體包含第二多肽，該第二多肽包含該CP2、該CM2和該DD2。

【請求項165】如請求項162至164中任一項之方法，其中該DD1和該DD2為選自由下列所組成之群組的一對：一對Fc結構域；源自人IL-15受體之α鏈(IL15Rα)之sushi結構域和可溶性IL-15；barnase和barnstar；PKA和AKAP；

基於突變之RNase I片段之適配體構件/對接標籤構件；表位和sdAb；表位和scFv；基於蛋白突觸融合蛋白、突觸結合蛋白、突觸小蛋白和SNAP25之交互作用的SNARE構件；及抗原結合結構域和表位。

【請求項166】如請求項162至165中任一項之方法，其中該DD1和該DD2為一對Fc結構域。

【請求項167】如請求項166之方法，其中該對Fc結構域為一對人Fc結構域。

【請求項168】如請求項167之方法，其中該人Fc結構域為人IgG1 Fc結構域、人IgG2 Fc結構域、人IgG3 Fc結構域或人IgG4 Fc結構域。

【請求項169】如請求項168之方法，其中該人Fc結構域為人IgG4 Fc結構域。

【請求項170】如請求項167之方法，其中該人Fc結構域包含與SEQ ID NO：3具有至少80%同一性之序列。

【請求項171】如請求項167之方法，其中該人Fc結構域包含與SEQ ID NO：3具有至少90%同一性之序列。

【請求項172】如請求項167之方法，其中該人Fc結構域包含SEQ ID NO：3。

【請求項173】如請求項162之方法，其中該DD1和該DD2分別包含SEQ ID NO：287和288。

【請求項174】如請求項162至173中任一項之方法，其中該DD1和該DD2係相同。

【請求項175】如請求項165之方法，其中該DD1包含

抗原結合結構域且該DD2包含對應之表位。

【請求項176】如請求項175之方法，其中該抗原結合結構域為抗His標籤抗原結合結構域且其中該DD2包含His標籤。

【請求項177】如請求項175之方法，其中該抗原結合結構域為單鏈可變片段(scFv)。

【請求項178】如請求項175之方法，其中該抗原結合結構域為單結構域抗體(sdAb)。

【請求項179】如請求項165之方法，其中該DD1和該DD2中至少一者包含選自由非多肽聚合物和小分子所組成之群組的二聚化結構域取代基。

【請求項180】如請求項179之方法，其中該DD1和該DD2包含彼此共價結合之非多肽聚合物。

【請求項181】如請求項180之方法，其中該非多肽聚合物為含硫聚乙二醇，且其中該DD1與該DD2係經由一或多個二硫鍵彼此共價結合。

【請求項182】如請求項179之方法，其中該DD1和該DD2中至少一者包含小分子。

【請求項183】如請求項182之方法，其中該小分子為生物素。

【請求項184】如請求項183之方法，其中該DD1包含生物素且該DD2包含抗生物素蛋白。

【請求項185】如請求項162至184中任一項之方法，其中該CP1和該CP2為成熟細胞介素。

【請求項186】如請求項162至184中任一項之方法，其中該CP1和該CP2包含信號肽。

【請求項187】如請求項162至186中任一項之方法，其中該CP1和該CP2係相同。

【請求項188】如請求項162至186中任一項之方法，其中該CP1和該CP2係不同。

【請求項189】如請求項162至186中任一項之方法，其中該CP1和/或該CP2為干擾素。

【請求項190】如請求項189之方法，其中該CP1和該CP2為干擾素。

【請求項191】如請求項189之方法，其中該CP1和該CP2為不同干擾素。

【請求項192】如請求項189之方法，其中該CP1和該CP2為相同干擾素。

【請求項193】如請求項189至192中任一項之方法，其中該干擾素為人野生型成熟干擾素。

【請求項194】如請求項189至193中任一項之方法，其中該干擾素係選自由下列所組成之群組：干擾素α、干擾素β、干擾素ω和干擾素τ。

【請求項195】如請求項194之方法，其中該干擾素為干擾素α。

【請求項196】如請求項195之方法，其中該干擾素係選自由下列所組成之群組：干擾素α-2a、干擾素α-2b和干擾素α-n3。

【請求項197】如請求項196之方法，其中該干擾素為干擾素α-2b。

【請求項198】如請求項197之方法，其中該CP1和/或該CP2包含與SEQ ID NO：1具有至少80%同一性之序列。

【請求項199】如請求項198之方法，其中該CP1和/或該CP2包含與SEQ ID NO：1具有至少90%同一性之序列。

【請求項200】如請求項199之方法，其中該CP1和/或該CP2包含SEQ ID NO：1之序列。

【請求項201】如請求項194之方法，其中該干擾素為干擾素β。

【請求項202】如請求項201之方法，其中該干擾素β係選自由干擾素β-1a和干擾素β-1b所組成之群組。

【請求項203】如請求項162至202中任一項之方法，其中該CP1和/或該CP2包含IFab結構域。

【請求項204】如請求項162至189中任一項之方法，其中該CP1和/或該CP2包含介白素。

【請求項205】如請求項204之方法，其中該介白素係選自由下列所組成之群組：IL-1α、IL-1β、IL-1RA、IL-18、IL-2、IL-4、IL-7、IL-9、IL-13、IL-15、IL-3、IL-5、IL-6、IL-11、IL-12、IL-10、IL-20、IL-21、IL-14、IL-16和IL-17。

【請求項206】如請求項162至205中任一項之方法，其中該CM1和該CM2各自包含總共約3個胺基酸至約15個胺基酸。

【請求項207】如請求項162至206中任一項之方法，其中該CM1、該CM2、該CM3和該CM4中一或多者包含不同蛋白酶之受質。

【請求項208】如請求項162至207中任一項之方法，其中該CM1、該CM2和該CM3包含相同蛋白酶之受質。

【請求項209】如請求項162至208中任一項之方法，其中該蛋白酶係選自由下列所組成之群組：ADAM8、ADAM9、ADAM10、ADAM12、ADAM15、ADAM17/TACE、ADAMDEC1、ADAMTS1、ADAMTS4、ADAMTS5、BACE、腎素、組織蛋白酶D、組織蛋白酶E、凋亡蛋白酶1、凋亡蛋白酶2、凋亡蛋白酶3、凋亡蛋白酶4、凋亡蛋白酶5、凋亡蛋白酶6、凋亡蛋白酶7、凋亡蛋白酶8、凋亡蛋白酶9、凋亡蛋白酶10、凋亡蛋白酶14、組織蛋白酶B、組織蛋白酶C、組織蛋白酶K、組織蛋白酶L、組織蛋白酶S、組織蛋白酶V/L2、組織蛋白酶X/Z/P、Cruzipain、天冬醯胺內肽酶、Otubain-2、KLK4、KLK5、KLK6、KLK7、KLK8、KLK10、KLK11、KLK13、KLK14、Meprin、腦啡肽酶(Neprilysin)、PSMA、BMP-1、MMP-1、MMP-2、MMP-3、MMP-7、MMP-9、MMP-10、MMP-11、MMP-12、MMP-13、MMP-14、MMP-15、MMP -16、MMP-17、MMP-19、MMP-20、MMP-23、MMP-24、MMP-26、MMP-27、活化蛋白C、組織蛋白酶A、組織蛋白酶G、凝乳酶、FVIIa、FIXa、FXa、FXIa、FXIIa、彈性蛋白酶、顆粒酶B、胍基苯甲酸酶、HtrA1、

人嗜中性粒細胞裂解酶、乳鐵蛋白、marapsin、NS3/4A、PACE4、纖溶酶、PSA、tPA、凝血酶、類胰蛋白酶、uPA、DESC1、DPP-4、FAP、Hepsin、膜型絲胺酸蛋白酶(Matriptase)-2、MT-SP1/Matripase、TMPRSS2、TMPRSS3和TMPRSS4。

【請求項210】如請求項209之方法，其中該蛋白酶係選自由下列所組成之群組：uPA、天冬醯胺內肽酶、MT-SP1、ADAM17、BMP-1、TMPRSS3、TMPRSS4、MMP-2、MMP-9、MMP- 12、MMP-13和MMP-14。

【請求項211】如請求項162至208中任一項或其組合之方法，其中該CM1、該CM2、該CM3和/或該CM4包含選自由下列所組成之群組的序列：LSGRSDNH(SEQ ID NO：5)、TGRGPSWV(SEQ ID NO：6)、PLTGRSGG(SEQ ID NO：7)、TARGPSFK(SEQ ID NO：8)、NTLSGRSENHSG(SEQ ID NO：9)、NTLSGRSGNHGS(SEQ ID NO：10)、TSTSGRSANPRG(SEQ ID NO：11)、TSGRSANP(SEQ ID NO：12)、VHMPLGFLGP(SEQ ID NO：13)、AVGLLAPP(SEQ ID NO：14)、AQNLLGMV(SEQ ID NO：15)、QNQALRMA(SEQ ID NO：16)、LAAPLGLL(SEQ ID NO：17)、STFPFGMF(SEQ ID NO：18)、ISSGLLSS(SEQ ID NO：19)、PAGLWLDP(SEQ ID NO：20)、VAGRSMRP(SEQ ID NO：21)、VVPEGRRS(SEQ ID NO：22)、ILPRSPAF(SEQ ID NO：23)、MVLGRSLL(SEQ ID NO：24)、QGRAITFI(SEQ ID NO：25)、SPRSIMLA(SEQ ID

NO：26)、SMLRSMPL(SEQ ID NO：27)、ISSGLLSGRSDNH(SEQ ID NO：28)、AVGLLAPPGGLSGRSDNH(SEQ ID NO：29)、ISSGLLSSGGSGGSLSGRSDNH(SEQ ID NO：30)、LSGRSGNH(SEQ ID NO：31)、SGRSANPRG(SEQ ID NO：32)、LSGRSDDH(SEQ ID NO：33)、LSGRSDIH(SEQ ID NO：34)、LSGRSDQH(SEQ ID NO：35)、LSGRSDTH(SEQ ID NO：36)、LSGRSDYH(SEQ ID NO：37)、LSGRSDNP(SEQ ID NO：38)、LSGRSANP(SEQ ID NO：39)、LSGRSANI(SEQ ID NO：40)、LSGRSDNI(SEQ ID NO：41)、MIAPVAYR(SEQ ID NO：42)、RPSPMWAY(SEQ ID NO：43)、WATPRPMR(SEQ ID NO：44)、FRLLDWQW(SEQ ID NO：45)、ISSGL(SEQ ID NO：46)、ISSGLLS(SEQ ID NO：47)、ISSGLL(SEQ ID NO：48)、ISSGLLSGRSANPRG(SEQ ID NO：49)、AVGLLAPPTSGRSANPRG(SEQ ID NO：50)、AVGLLAPPSGRSANPRG(SEQ ID NO：51)、ISSGLLSGRSDDH(SEQ ID NO：52)、ISSGLLSGRSDIH(SEQ ID NO：53)、ISSGLLSGRSDQH(SEQ ID NO：54)、ISSGLLSGRSDTH(SEQ ID NO：55)、ISSGLLSGRSDYH(SEQ ID NO：56)、ISSGLLSGRSDNP(SEQ ID NO：57)、ISSGLLSGRSANP(SEQ ID NO：58)、

ISSGLLSGRSANI(SEQ ID NO：59)、
AVGLLAPPGGLSGRSDDH(SEQ ID NO：60)、
AVGLLAPPGGLSGRSDIH(SEQ ID NO：61)、
AVGLLAPPGGLSGRSDQH(SEQ ID NO：62)、
AVGLLAPPGGLSGRSDTH(SEQ ID NO：63)、
AVGLLAPPGGLSGRSDYH(SEQ ID NO：64)、
AVGLLAPPGGLSGRSDNP(SEQ ID NO：65)、
AVGLLAPPGGLSGRSANP(SEQ ID NO：66)、
AVGLLAPPGGLSGRSANI(SEQ ID NO：67)、
ISSGLLSGRSDNI(SEQ ID NO：68)、
AVGLLAPPGGLSGRSDNI(SEQ ID NO：69)、
GLSGRSDNHGGAVGLLAPP(SEQ ID NO：70)、
GLSGRSDNHGGVHMPLGFLGP(SEQ ID NO：71)、
LSGRSDNHGGVHMPLGFLGP(SEQ ID NO：72)、
ISSGLSS(SEQ ID NO：73)、PVGYTSSL(SEQ ID NO：74)、DWLYWPGI(SEQ ID NO：75)、LKAAPRWA(SEQ ID NO：76)、GPSHLVLT(SEQ ID NO：77)、LPGGLSPW(SEQ ID NO：78)、MGLFSEAG(SEQ ID NO：79)、SPLPLRVP(SEQ ID NO：80)、RMHLRSLG(SEQ ID NO：81)、LLAPSHRA(SEQ ID NO：82)、GPRSFGL(SEQ ID NO：83)、GPRSFG(SEQ ID NO：84)、SARGPSRW(SEQ ID NO：85)、GGWHTGRN(SEQ ID NO：86)、HTGRSGAL(SEQ ID NO：87)、AARGPAIH(SEQ ID NO：88)、RGPAFNPM(SEQ ID NO：89)、SSRGPAYL(SEQ ID NO：

90)、RGPATPIM(SEQ ID NO：91)、RGPA(SEQ ID NO：92)、GGQPSGMWGW(SEQ ID NO：93)、FPRPLGITGL(SEQ ID NO：94)、SPLTGRSG(SEQ ID NO：95)、SAGFSLPA(SEQ ID NO：96)、LAPLGLQRR(SEQ ID NO：97)、SGGPLGVR(SEQ ID NO：98)、PLGL(SEQ ID NO：99)和SGRSDNI(SEQ ID NO：100)。

【請求項212】如請求項211之方法，其中該CM1、該CM2、該CM3和/或該CM4包含選自由下列所組成之群組的序列：ISSGLLSGRSDNH(SEQ ID NO：28)、LSGRSDDH(SEQ ID NO：33)、ISSGLLSGRSDQH(SEQ ID NO：54)、SGRSDNI(SEQ ID NO：100)和ISSGLLSGRSDNI(SEQ ID NO：68)。

【請求項213】如請求項162至211中任一項之方法，其中該蛋白酶係由個體之腫瘤產生。

【請求項214】如請求項213之方法，其中該個體已被診斷或鑑定為患有癌症。

【請求項215】如請求項162至214中任一項之方法，其中該CP1與該CM1在該第一單體構築體中彼此直接鄰接。

【請求項216】如請求項162至215中任一項之方法，其中該CM1與該DD1在該第一單體構築體中彼此直接鄰接。

【請求項217】如請求項162至217中任一項之方法，其中該CP2與該CM2在該第二單體構築體中彼此直接鄰

接。

【請求項218】如請求項162至217中任一項之方法，其中該CM2與該DD2在該第二單體構築體中彼此直接鄰接。

【請求項219】如請求項162至214中任一項之方法，其中該第一單體構築體包含至少一個連接子。

【請求項220】如請求項219之方法，其中該至少一個連接子為位於該PM1與該CM3之間的連接子L1和/或位於該CM3與該CP1之間的連接子L2。

【請求項221】如請求項219之方法，其中該第二單體構築體包含至少一個連接子。

【請求項222】如請求項221之方法，其中該至少一個連接子為位位於該PM2與該CM4之間的連接子L3和/或位於該CM4與該CP2之間的連接子L4。

【請求項223】如請求項222之方法，其中該第一單體構築體包含連接子L1且該第二單體構築體包含連接子L3。

【請求項224】如請求項223之方法，其中L1和L3係相同。

【請求項225】如請求項222之方法，其中該第一單體構築體包含連接子L2且該第二單體構築體包含連接子L4。

【請求項226】如請求項225之方法，其中L2和L4係相同。

【請求項227】如請求項219至226中任一項之方法，其中各連接子之總長度為1個胺基酸至約15個胺基酸。

【請求項228】如請求項227之方法，其中各連接子之總長度為至少5個胺基酸。

【請求項229】如請求項219至225中任一項之方法，其中各連接子係獨立選自由下列所組成之群組：GSSGGSGGSGG(SEQ ID NO：210)；GGGS(SEQ ID NO：2)；GGGSGGGS(SEQ ID NO：211)；GGGSGGGSGGGS(SEQ ID NO：212)；GGGGSGGGGSGGGGS(SEQ ID NO：213)；GGGGSGGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)；GGGGSGGGGS(SEQ ID NO：215)；GGGGS(SEQ ID NO：216)；GS；GGGGSGS(SEQ ID NO：217)；GGGGSGGGGSGGGGSGS(SEQ ID NO：218)；GGSLDPKGGGGS(SEQ ID NO：219)；PKSCDKTHTCPPCPAPELLG(SEQ ID NO：220)；SKYGPPCPPCPAPEFLG(SEQ ID NO：221)；GKSSGSGSESKS(SEQ ID NO：222)；GSTSGSGKSSEGKG(SEQ ID NO：223)；GSTSGSGKSSEGSGSTKG(SEQ ID NO：224)；GSTSGSGKPGSGEGSTKG(SEQ ID NO：225)；GSTSGSGKPGSSEGST(SEQ ID NO：226)；(GS)n、(GGS)n、(GSGGS)n(SEQ ID NO：227)、(GGGS)n(SEQ ID NO：228)、(GGGGS)n(SEQ ID NO：216)，其中各個n為至少1之整數；GGSG(SEQ ID NO：229)；GGSGG(SEQ ID NO：230)；GSGSG(SEQ ID NO：231)；GSGGG(SEQ ID NO：232)；GGGSG(SEQ ID NO：233)；GSSSG(SEQ ID NO：

234)；GGGGSGGGGSGGGGS(SEQ ID NO：213)；GGGGSGGGGSGGGGSGGGGS(SEQ ID NO：214)；GSTSGSGKPGSSEGST(SEQ ID NO：226)；SGGG(SEQ ID NO：296)；和SGGGG(SEQ ID NO：459)。

【請求項230】如請求項229之方法，其中該連接子包含GGGS(SEQ ID NO：2)之序列。

【請求項231】如請求項162至230中任一項之方法，其中該第一單體構築體於N端至C端之方向包含該PM1、該CM3、該CP1、該CM1和該DD1。

【請求項232】如請求項162至230中任一項之方法，其中該第一多肽於C端至N端之方向包含該PM1、該CM3、該CP1、該CM1和該DD1。

【請求項233】如請求項162至232中任一項之方法，其中該第二多肽於N端至C端之方向包含該CP2、該CM2和該DD2。

【請求項234】如請求項162至233中任一項之方法，其中該第二多肽於C端至N端之方向包含該CP2、該CM2和該DD2。

【請求項235】如請求項162至187、189、190及192至234中任一項之方法，其中該第一單體構築體和該第二單體構築體係相同。

【請求項236】如請求項162至230中任一項之方法，其中該第一單體構築體於N端至C端之方向包含該PM1、可選擇之連接子、該CM3、可選擇之連接子、該CP1、該

CM1和該DD1，其中該CP1與該CM1彼此直接鄰接，其中該CM1與該DD1彼此直接鄰接，其中該CM1為不超過10個胺基酸之肽，其中該第二單體構築體與該第一單體構築體係相同，且其中該第一和第二單體構築體係經由至少二個二硫鍵彼此共價結合。

【請求項237】如請求項236之方法，其中該DD1和該DD2各自為在根據EU編號的半胱胺酸216處具有N端之人Fc結構域。

【請求項238】如請求項236或237之方法，其中該CM1為不超過7個胺基酸之肽。

【請求項239】如請求項236至238中任一項或其組合之方法，其中該CP1和該CP2包含與SEQ ID NO：1具有至少90%同一性之胺基酸序列。

【請求項240】如請求項162至239中任一項之方法，其中該ACC之特徵在於與至少一種CP1和/或CP2活性之對照水準相比較，該至少一種CP1和/或CP2活性之水準降低。

【請求項241】如請求項240之方法，其中該CP1和該CP2活性中至少一者為淋巴瘤細胞之增殖水準。

【請求項242】如請求項240之方法，其中該CP1和該CP2活性中至少一者為淋巴瘤細胞中JAK/STAT/ISGF3路徑活化之水準。

【請求項243】如請求項240之方法，其中該至少一種活性為淋巴瘤細胞中SEAP產生之水準。

【請求項244】如請求項240之方法，其中該ACC之特徵在於與該對照水準相比較，該CP1和該CP2活性中至少一者降低至少2倍。

【請求項245】如請求項244之方法，其中該ACC之特徵在於與該對照水準相比較，該CP1和該CP2活性中至少一者降低至少5倍。

【請求項246】如請求項245之方法，其中該ACC之特徵在於與該對照水準相比較，該CP1和該CP2活性中至少一者降低至少10倍。

【請求項247】如請求項246之方法，其中該ACC之特徵在於與該對照水準相比較，該CP1和該CP2活性中至少一者降低至少500倍。

【請求項248】如請求項240至247中任一項之方法，其中該CP1和該CP2活性中至少一者之該對照水準為該ACC暴露於該蛋白酶後該ACC之該CP1和/或該CP2的活性。

【請求項249】如請求項240至248中任一項之方法，其中該CP1和該CP2中至少一者之該對照水準為對應之野生型成熟細胞介素的對應CP1和/或CP2活性。

【請求項250】如請求項240至249中任一項之方法，其中該ACC之特徵在於暴露於該蛋白酶後產生裂解產物，其中該裂解產物包含該至少一種CP1和/或CP2活性。

【請求項251】如請求項250之方法，其中該至少一種CP1和/或CP2活性為抗增殖活性。

【請求項252】如請求項251之方法，其中該對照水準為EC50值，且其中EC50(裂解產物)對EC50(對照水準)之比率小於約10、或小於約9、或小於約8、或小於約7、或小於約6、或小於約5、或小於約4、或小於約3、或小於約2、或小於約1.5、或小於約1.0。

【請求項253】如請求項240至252中任一項之方法，其中該CP1和該CP2活性中至少一者為如使用表面等離子共振所測定之該CP1和/或該CP2對其同源受體之結合親和力。

【請求項254】如請求項162之方法，其中該第一和第二單體構築體各自包含與SEQ ID NO：290具有至少95%同一性之序列，或者其中該第一和第二單體構築體各自包含SEQ ID NO：290之序列，其中與野生型干擾素α-2b或聚乙二醇化干擾素α-2b相比較，該ACC顯示活體內較低之毒性。

【請求項255】如請求項162至254中任一項之方法，其中該CM1和該CM2各自作為經腫瘤組織過度表現之蛋白酶的受質。

【請求項256】如請求項162至255中任一項之方法，其中該PD1/PD-L1路徑抑制劑係選自PD-1抗體、可經活化之PD-1抗體、PD-L1抗體或該可經活化之PD-L1抗體。

【請求項257】如請求項256之方法，其中該可經活化之PD-1抗體或該可經活化之PD-L1抗體包含：(i)特異地結合PD-1或PD-L1之抗體或其抗原結合片段(AB)；(ii)掩蔽部

分(MM)，其當該可經活化之抗體為未經裂解之狀態時抑制該AB與PD-1或PD-L1結合；及(iii)與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶之受質的多肽；及可選擇地第一連接肽和/或第二連接肽。

【請求項258】如前述請求項中任一項之方法，其中該PD1/PD-L1路徑抑制劑包括尼維魯單抗、派姆單抗、提利珠單抗、巴泰利珠單抗、卡利珠單抗、賽特利單抗、巴西利單抗、多塔利單抗、普戈利單抗、沙山利單抗、辛布利單抗、阿舒利珠單抗、阿維魯單抗、德維魯單抗、德布利單抗、洛普利單抗、英佛利單抗、科貝利單抗、布嘉利單抗、薩本利單抗、芬托利單抗、杰諾利單抗、洛普利單抗、潘普利單抗、皮瓦利單抗、樸可利單抗、思普利單抗、西提利單抗、托巴利單抗、哲瓦利單抗、巴洛利單抗、諾辛利單抗、魯洛利單抗、嘉維利單抗、曼利單抗、歐普利單抗、舒多利單抗、舒馬利單抗、索卡利單抗或吉坦利單抗。

【請求項259】如前述請求項中任一項之方法，其中該PD1/PD-L1路徑抑制劑包含帕米單抗(CX-072)、CX-075、CX-171或CX-188。

【請求項260】如前述請求項中任一項之方法，其中該PD1/PD-L1路徑抑制劑為PD-1路徑抑制劑，可選擇地PD-1抗體或可經活化之PD-1抗體，可選擇地其中該PD-1路徑抑制劑為包含WO2017011580A2之表7至9之一或多個序列的抗體。

【請求項261】如前述請求項中任一項之方法，其中該PD1/PD-L1路徑抑制劑為PD-L1路徑抑制劑，可選擇地PD-L1抗體或可經活化之PD-L1抗體，可選擇地其中該PD-L1路徑抑制劑為包含WO2016149201A2之表15至17之一或多個序列的抗體。

【請求項262】如請求項256之方法，其中該可經活化之PD-1抗體或該可經活化之PD-L1抗體包含：(i)特異地結合PD-1或PD-L1之抗體或其抗原結合片段(AB)；(ii)掩蔽部分(MM)，其當該可經活化之抗體處於未經裂解之狀態時抑制該AB與PD-1或PD-L1結合；及(iii)與該AB偶聯之可裂解部分(CM)，其中該CM為作為蛋白酶之受質的多肽；及可選擇地第一連接肽和/或第二連接肽。

【請求項263】如請求項262之方法，其中該可經活化之抗PD-1抗體包含MM，該MM包含選自由下列所組成之群組的胺基酸序列：AMSGCSWSAFCPYLA(SEQ ID NO：550)、DVNCAIWYSVCITVP(SEQ ID NO：551)、LVCPLYALSSGVCMG(SEQ ID NO：552)、SVNCRIWSAVCAGYE(SEQ ID NO：553)、MLVCSLQPTAMCERV(SEQ ID NO：554)、APRCYMFASYCKSQY(SEQ ID NO：555)、VGPCELTPKPVCNTY(SEQ ID NO：556)、ETCNQYERSSGLCFA(SEQ ID NO：557)、APRTCYTYQCSSFYT(SEQ ID NO：558)、GLCSWYLSSSGLCVD(SEQ ID NO：559)、

VPWCQLTPRVMCMWA(SEQ ID NO：560)、

NWLDCQFYSECSVYG(SEQ ID NO：561)、

SCPLYVMSSFGGCWD(SEQ ID NO：562)、

MSHCWMFSSSCDGVK(SEQ ID NO：563)、

VSYCTWLIEVICLRG(SEQ ID NO：564)、

VLCAAYALSSGICGG(SEQ ID NO：565)、

TTCNLYQQSSMFCNA(SEQ ID NO：566)、

APRCYMFASYCKSQY(SEQ ID NO：567)、

PCDQNPYFYPYVCHA(SEQ ID NO：568)、

SVCPMYALSSMLCGA(SEQ ID NO：569)、

LSVECYVFSRCSSLP(SEQ ID NO：570)、

FYCTYLVSLTCHPQ(SEQ ID NO：571)、

SMAGCQWSSFCVQRD(SEQ ID NO：572)、

IYSCYMFASRCTSDK(SEQ ID NO：573)、

SRCSVYEVSSGLCDW(SEQ ID NO：574)、

GMCSAYAYSSKLCTI(SEQ ID NO：575)、

MTTNTCNLLCQQFLT(SEQ ID NO：576)、

FQPCLMFASSCFTSK(SEQ ID NO：577)、

WNCHPAGVGPVFCEV(SEQ ID NO：578)、

ALCSMYLASSGLCNK(SEQ ID NO：579)、

NYLSCQFFQNCYETY(SEQ ID NO：580)、

GWCLFSDMWLGLCSA(SEQ ID NO：581)、

EFCARDWLPYQCSSF(SEQ ID NO：582)和

TSYCSIEHYPCNTHH(SEQ ID NO：583)。

【請求項264】如請求項262之方法，其中該可經活化之抗PD-L1抗體包含掩蔽部分(MM)，該掩蔽部分(MM)包含選自由下列所組成之群組的胺基酸序列：

YCEVSELFVLPWCMG(SEQ ID NO：584)、

SCLMHPHYAHDYCYV(SEQ ID NO：585)、

LCEVLMLLQHPWCMG(SEQ ID NO：586)、

IACRHFMEQLPFCHH(SEQ ID NO：587)、

FGPRCGEASTCVPYE(SEQ ID NO: 588)、

LYCDSWGAGCLTRP(SEQ ID NO：589)、

GIALCPSHFCQLPQT(SEQ ID NO：590)、

DGPRCFVSGECSPIG(SEQ ID NO：591)、

LCYKLDYDDRSYCHI(SEQ ID NO：592)、

PCHPHPYDARPYCNV(SEQ ID NO：593)、

PCYWHPFFAYRYCNT(SEQ ID NO：594)、

VCYYMDWLGRNWCSS(SEQ ID NO：595)、

LCDLFKLREFPYCMG(SEQ ID NO：596)、

YLPCHFVPIGACNNK(SEQ ID NO：597)、

FCHMGVVVPQCANY(SEQ ID NO：598)、

ACHPHPYDARPYCNV(SEQ ID NO：599)、

PCHPAPYDARPYCNV(SEQ ID NO：600)、

PCHPHAYDARPYCNV(SEQ ID NO：601)、

PCHPHPADARPYCNV(SEQ ID NO：602)、

PCHPHPYAARPYCNV(SEQ ID NO：603)、

PCHPHPYDAAPYCNV(SEQ ID NO：604)、

PCHPHPYDARPACNV(SEQ ID NO：605)、
PCHPHPYDARPYCAV(SEQ ID NO：606)、
PCHAHPYDARPYCNV(SEQ ID NO：607)和
PCHPHPYDARAYCNV(SEQ ID NO：608)。

【請求項265】如請求項162至264中任一項之方法，其中該個體需要減少、抑制和/或延遲該個體中PD-1或PD-L1之發生或進展。

【請求項266】如請求項162至264中任一項之方法，其中該個體需要減輕與該個體中PD-1或PD-L1之異常表現和/或異常活性相關的症狀。

【請求項267】如請求項162至266中任一項之方法，其中該個體已被鑑定或診斷為患有癌症。

【請求項268】如請求項267之方法，其中該癌症為淋巴瘤。

【請求項269】如請求項268之方法，其中該淋巴瘤為伯基特氏淋巴瘤。

【請求項270】如請求項162至269中任一項之方法，其中該方法包含增進或加強相對於該個體之常規細胞介素療法相關之治療功效和/或治療指數。

【請求項271】如請求項162至269中任一項之方法，其中該方法包含增進或加強相對於該個體之常規PD1/PDL1抑制劑療法之治療功效和/或治療指數。

【請求項272】如請求項162至269中任一項之方法，其中該方法包含增進或加強相對於該個體之常規細胞介素

和PD1/PDL1抑制劑組合療法之治療功效和/或治療指數。

【請求項273】如請求項162至269中任一項之方法，其中該方法包含增進或加強相對於投予單獨ACC之治療功效和/或治療指數。

【請求項274】一種組合或組成物，其包含如請求項162至262中任一項所述之該PD-1/PD-L1路徑抑制劑。

【請求項275】如請求項274之組合或組成物，其中該組合或組成物為醫藥組成物。

【請求項276】一種容器、小瓶、注射器、注射筆或套組，其包含至少一個劑量之如請求項274或275之組合或組成物。

【請求項277】如前述請求項中任一項之方法，其中該ACC和該PD-1/PD-L1路徑抑制劑係同時或依序投予。

【請求項278】如前述請求項中任一項之方法，其中該ACC和該PD-1/PD-L1路徑抑制劑係分開投予。

【請求項279】一種治療有此需要之個體之方法，其包含對該個體投予可經活化之細胞介素構築體(ACC)和PD-1/PD-L1路徑抑制劑之組合，其中該ACC包含第一單體構築體和第二單體構築體，其中：

(a)該第一單體構築體包含第一肽掩蔽物(PM1)、第一成熟細胞介素蛋白(CP1)、第一和第三可裂解部分(CM1和CM3)及第一二聚化結構域(DD1)，其中該CM1係位於該CP1與該DD1之間且該CM3係位於該PM1與該CP1之間；且

(b)該第二單體構築體包含第二成熟細胞介素蛋白

(CP2)、第二可裂解部分(CM2)及第二二聚化結構域(DD2)，其中該CM2係位於該CP2與該DD2之間；

其中該DD1與該DD2彼此結合從而形成該第一單體構築體與該第二單體構築體之二聚體，

該ACC之特徵在於其具有至少一種下列特徵：

(i) 於N端至C端方向之結構排列包含：PM1-CM3-CP1-CM1-DD1和CP2-CM2-DD2，其中DD1和DD2係經二聚化；

(ii) 其中該第一單體構築體之特徵在於該CP1和該DD1係藉由不超過18個胺基酸之連接區連接，使得該不超過18個胺基酸之連接區包括該CM3；

(iii) 其中該第二單體構築體之特徵在於該CP2和該DD2係藉由不超過18個胺基酸之連接區連接，使得該不超過18個胺基酸之連接區包括該CM2；

(iv) 其中該PM1和該PM2各少於40個胺基酸；

(v) 其中該PM1和該PM2各為13至49個胺基酸；和/或

(vi) 其中該PM1和該PM2各自不為該CP1和該CP2之受體且其中該PM1和該PM2各自不為該CP1和該CP2之受體片段。

【請求項280】如請求項279之方法，其中該第一單體構築體之特徵在於該CP1和該DD1係藉由不超過12個胺基酸之連接區連接，使得該不超過12個胺基酸之連接區包括該CM3。

【請求項281】如請求項279至280之方法，其中該第

二單體構築體之特徵在於該CP2和該DD2係藉由不超過12個胺基酸之連接區連接，使得該不超過12個胺基酸之連接區包括該CM2。

【請求項282】如前述請求項中任一項之方法，其在該PM1與該CP1之間包含掩蔽物連接區，該掩蔽物連接區包含15、16、17、18、19、20、21或22個胺基酸。

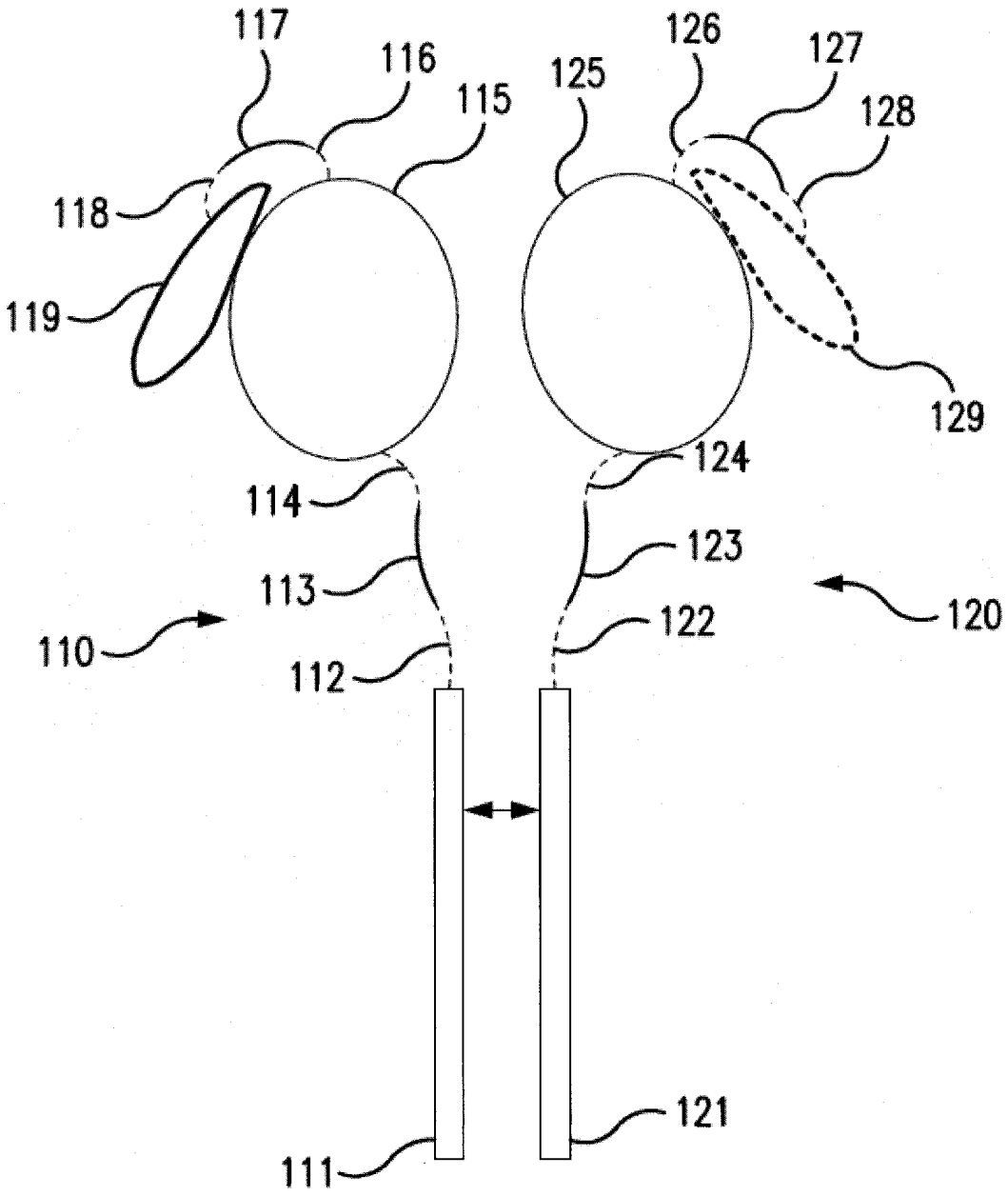
【請求項283】如前述請求項中任一項之方法，其在該PM2與該CP2之間包含掩蔽物連接區，該掩蔽物連接區包含15、16、17、18、19、20、21或22個胺基酸。

【請求項284】如前述請求項中任一項之方法，其中該第一單體構築體僅具有一個肽掩蔽物。

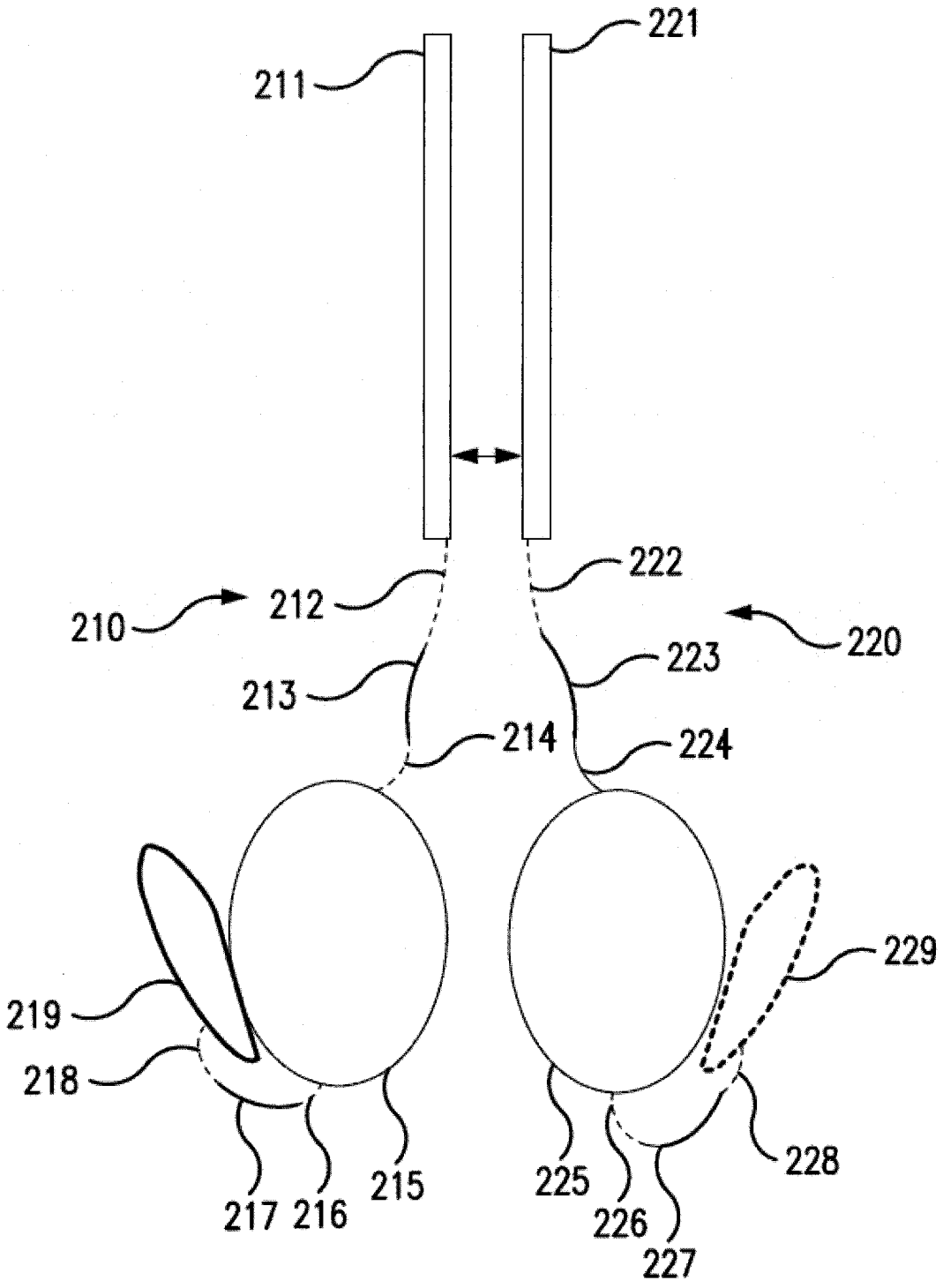
【請求項285】如前述請求項中任一項之方法，其中該第二單體構築體僅具有一個肽掩蔽物。

【請求項286】如前述請求項中任一項之方法，其中該第一單體構築體僅具有一個肽掩蔽物且該第二單體構築體僅具有一個肽掩蔽物。

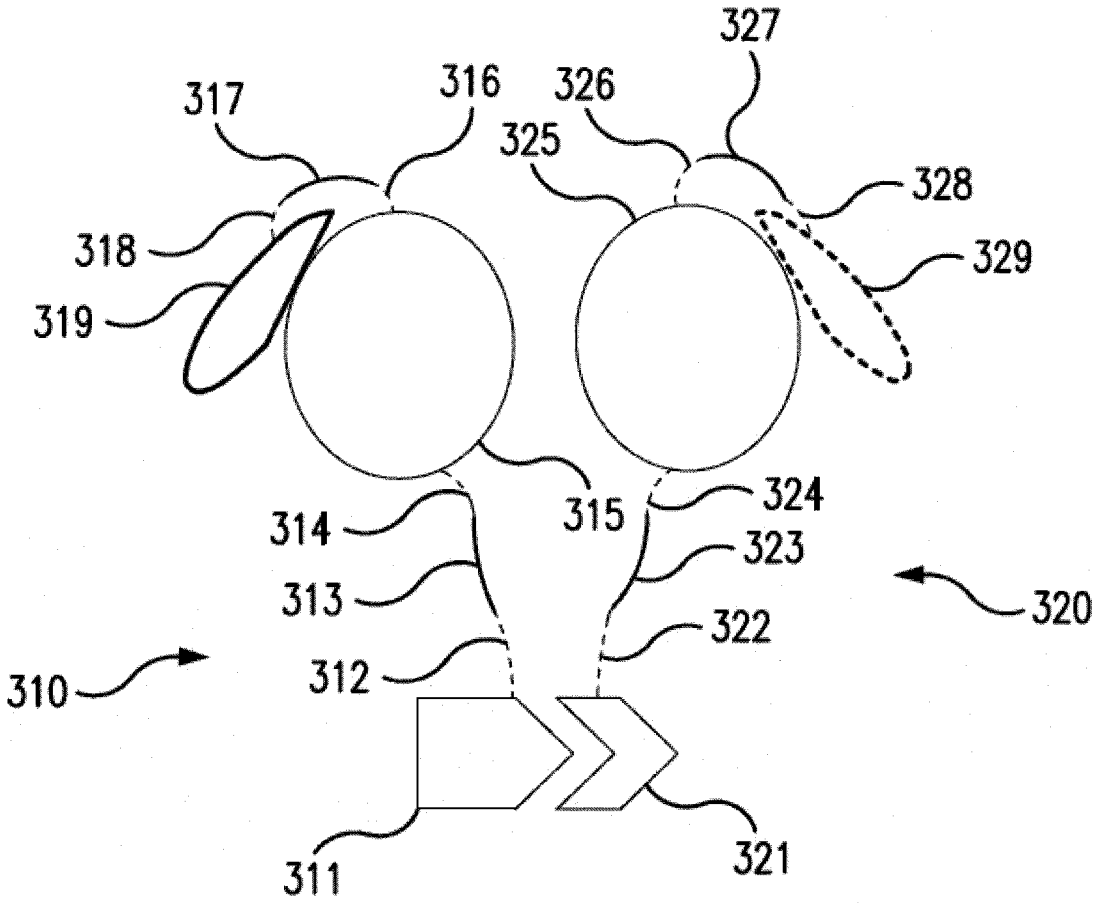
【發明圖式】


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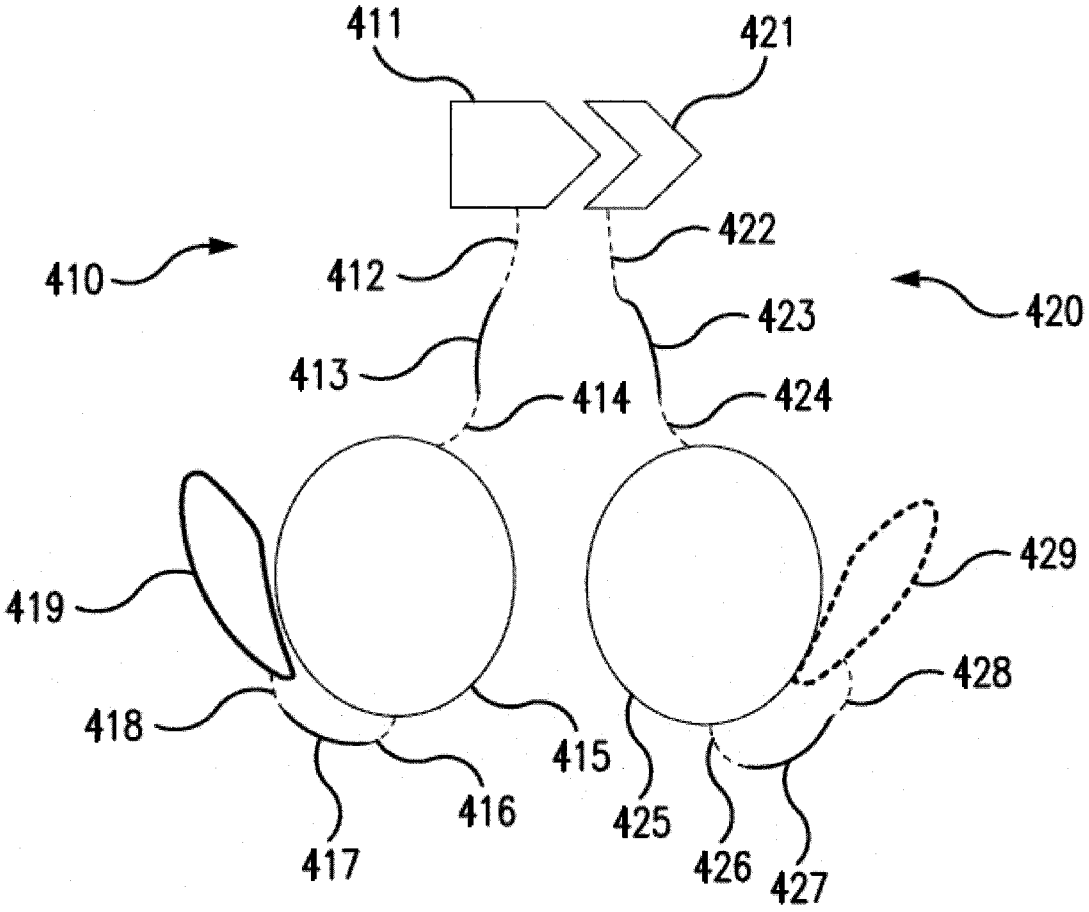
【圖 1】


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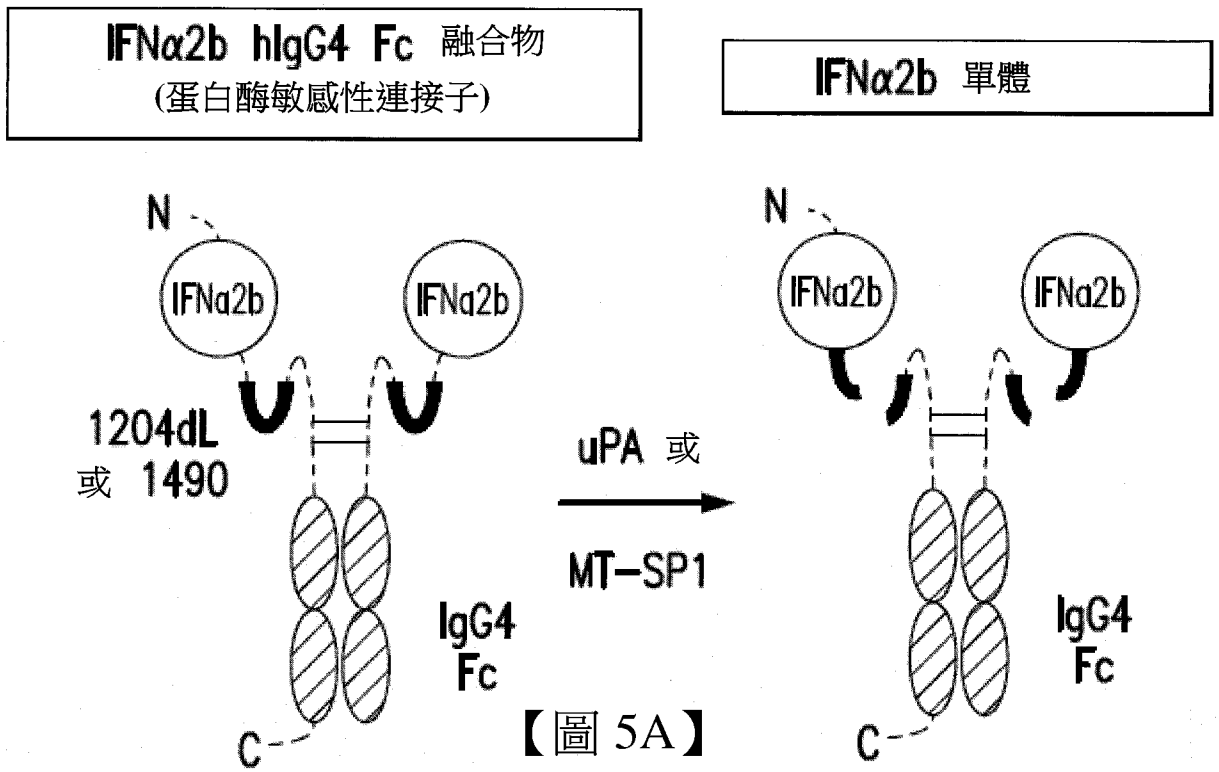
【圖 2】


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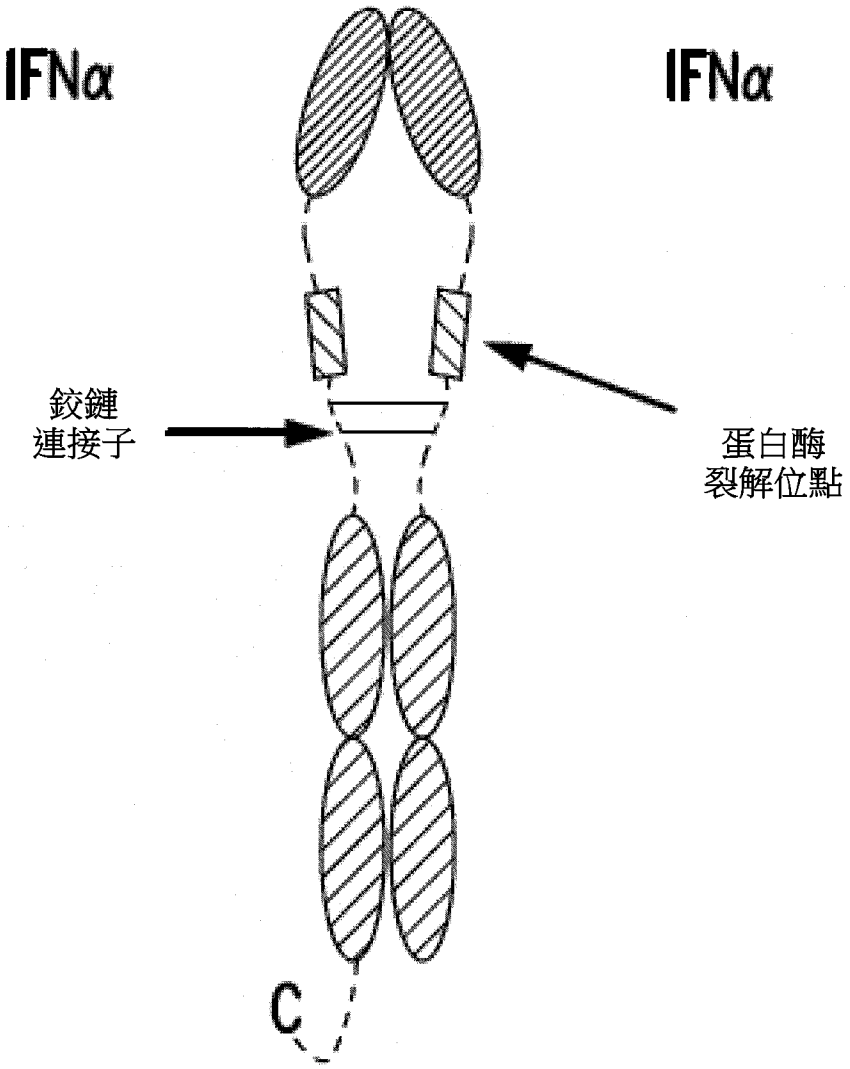
【圖 3】


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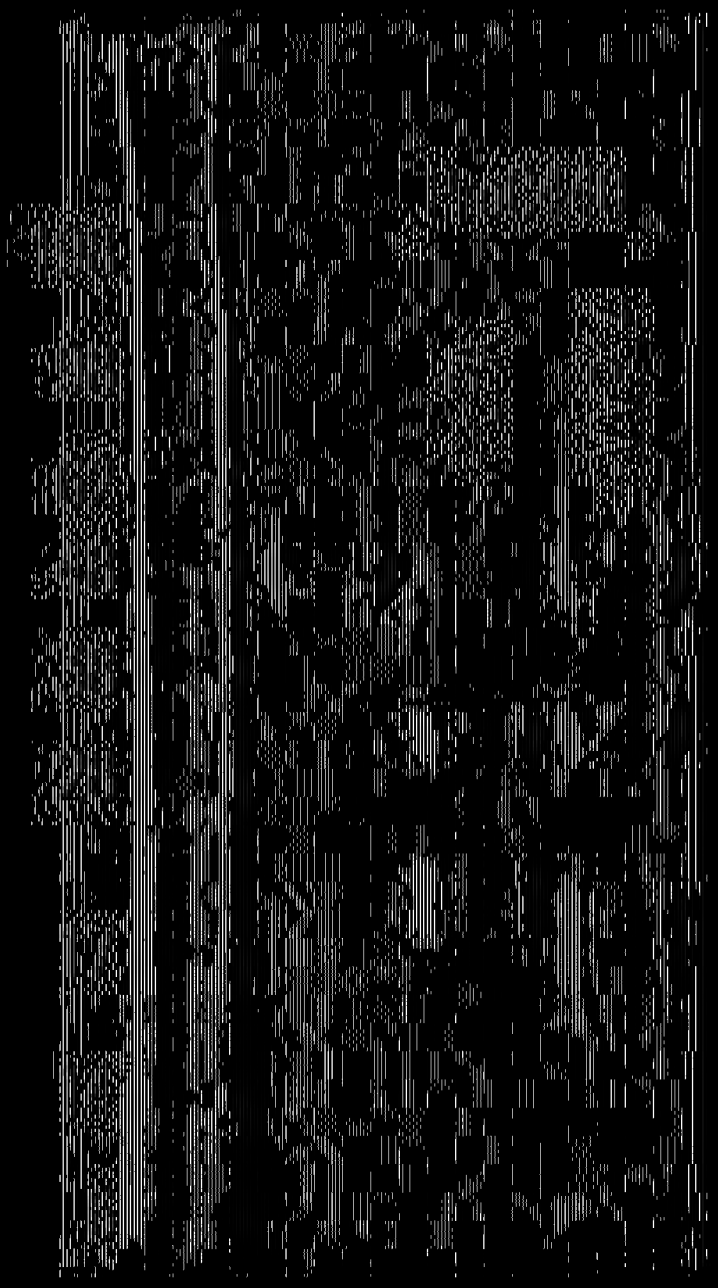
【圖 4】


IFNα2b hIgG4 Fc 融合物
(蛋白酶敏感性連接子)
IFNα2b 單體
N
IFNa2b
IFNa2b
1204dL
或 1490
IgG4
Fc
C
uPA 或
MT-SP1
N
IFNa2b
IFNa2b
IgG4
Fc
C

【圖 5A】

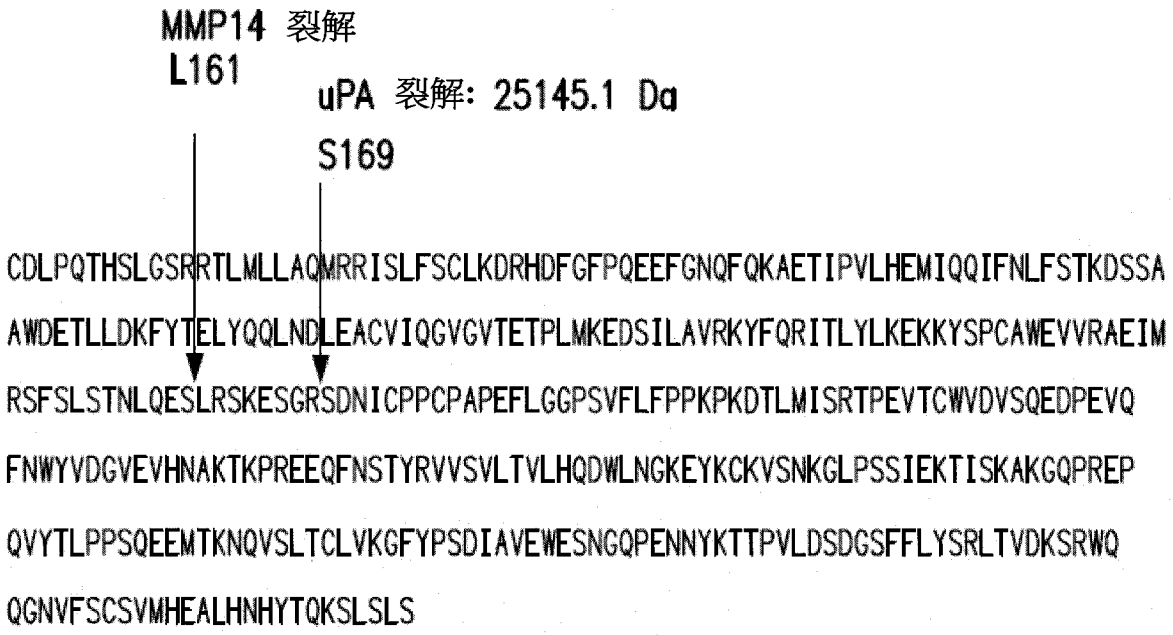


【圖 5B】

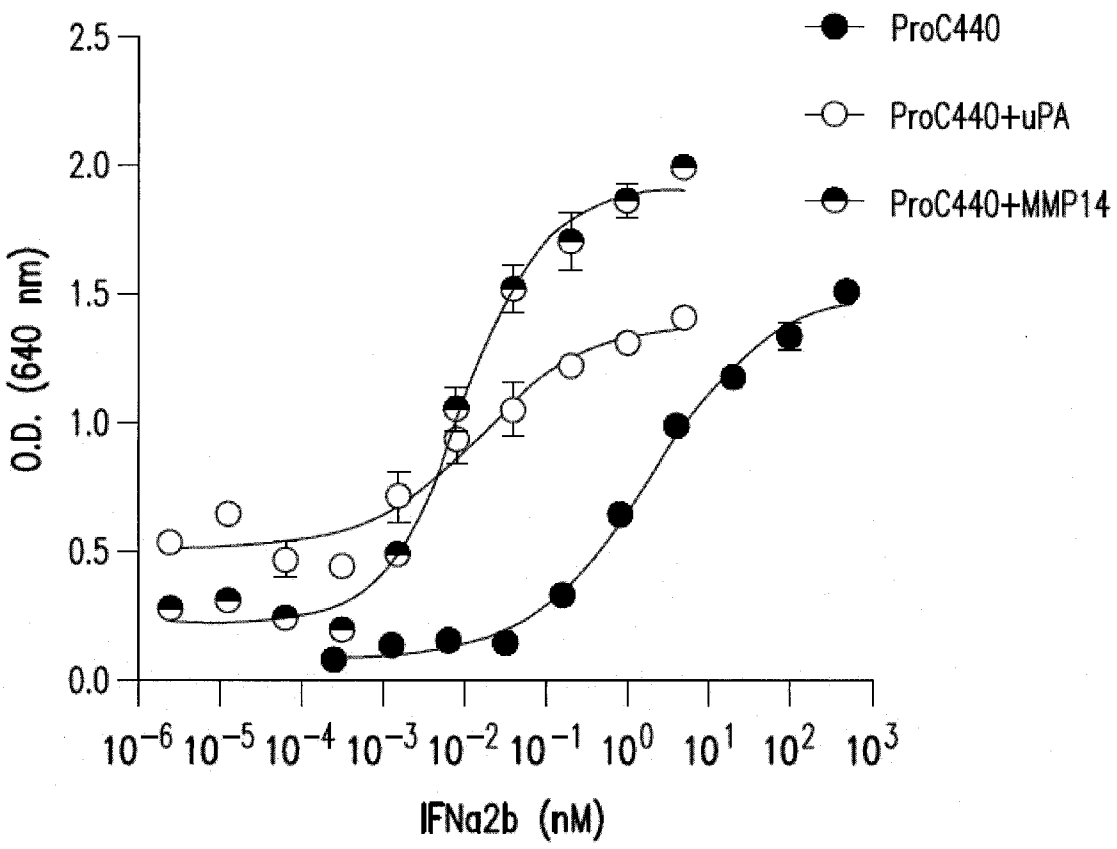


[圖 6A]

ProC440 LC-MS 數據:

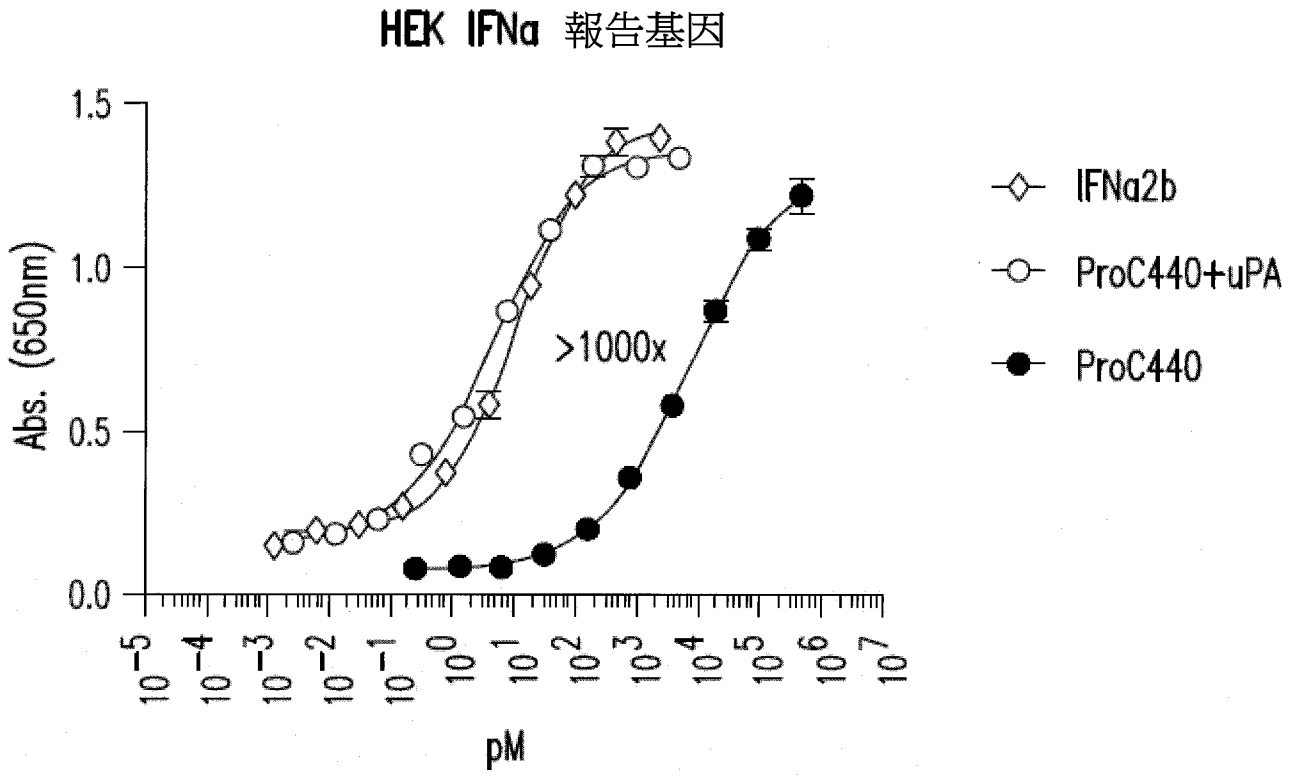


【圖 6B】

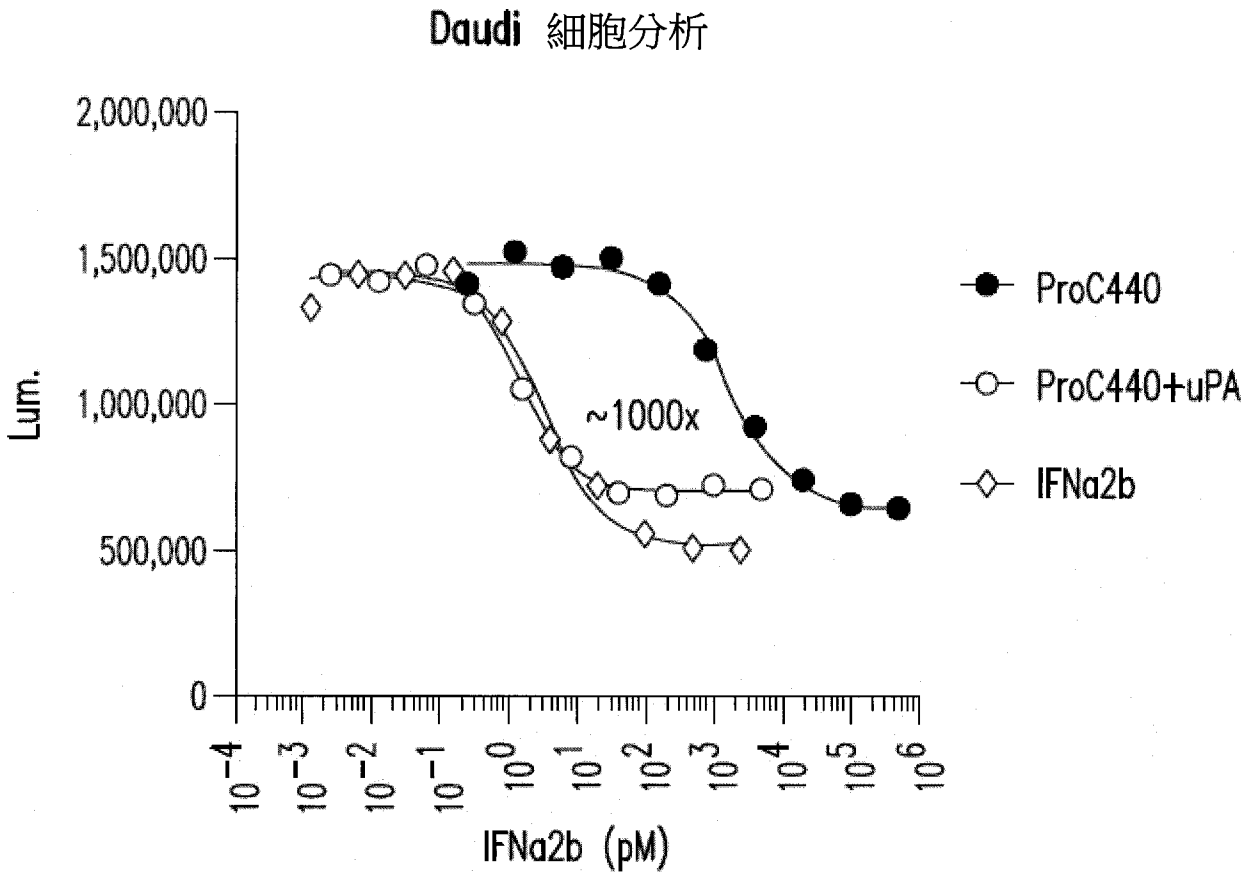


	ProC440	ProC440+uPA	ProC440+MMP14
EC50	1.861	0.01503	0.009833

【圖 6C】


HEK IFNa 報告基因
1.5
1.0
0.5
0.0
Abs. (650nm)
>1000x
pM
IFNa2b
ProC440+uPA
ProC440

【圖 7A】


Daudi 細胞分析
2,000,000
1,500,000
1,000,000
500,000
0
Lum.
~1000x
ProC440
ProC440+uPA
IFNa2b
IFNa2b (pM)

【圖 7B】

METDTLLLWVLLLWVPGSTG

QSGQTDVDYYREWSWTQVSGSSGGS**LSGRSDNI**GSGGSCDLPQTHSLGSRRTLMLLAQM
RRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETL
LDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCA
WEVVRAEIMRSFSLSTNLQESLRSKE**LSGRSDNI**CPPCPAPEFLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL
VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLS

(ProC732)

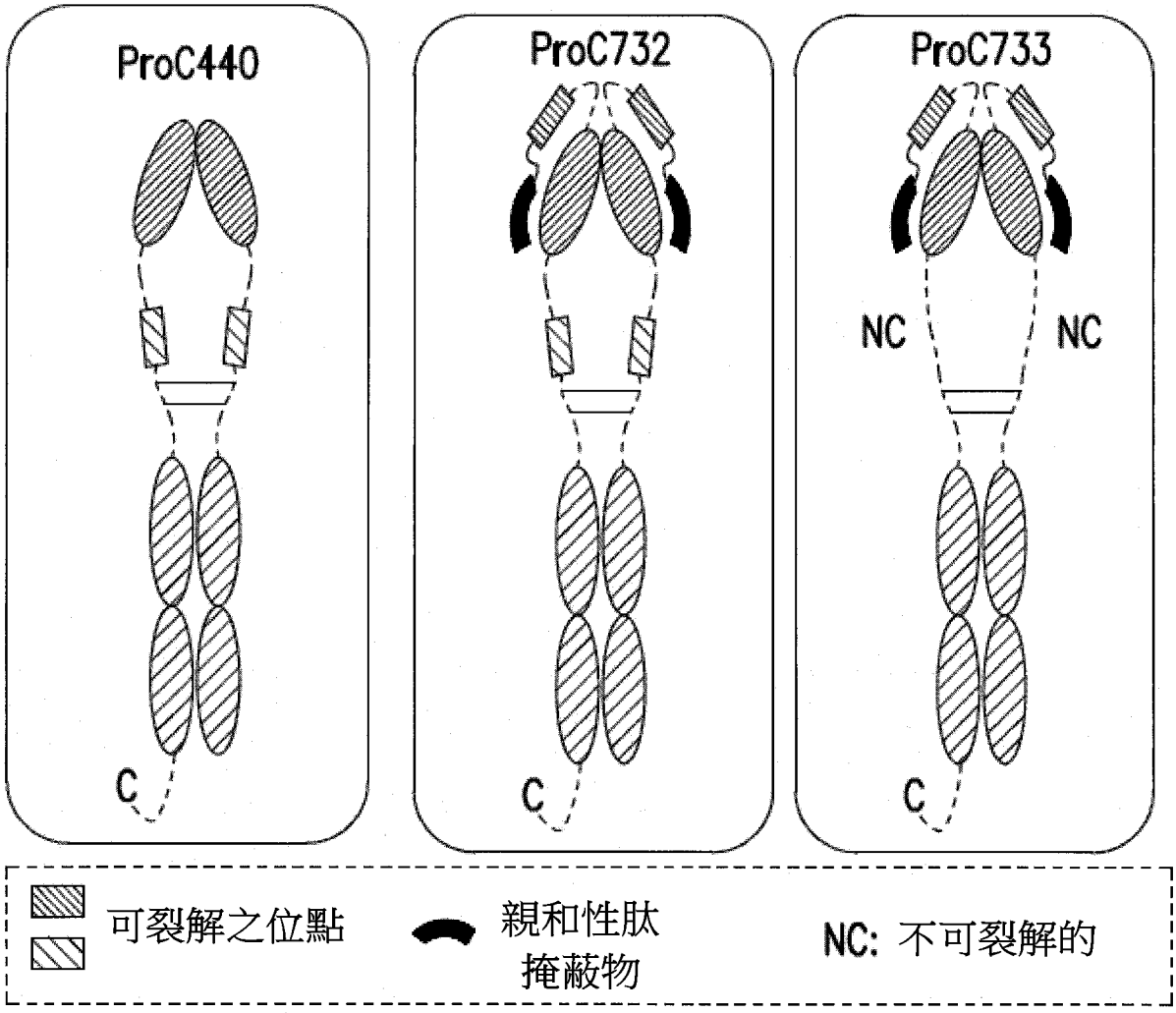
【圖 8】

METDTLLLWVLLLWVPGSTG

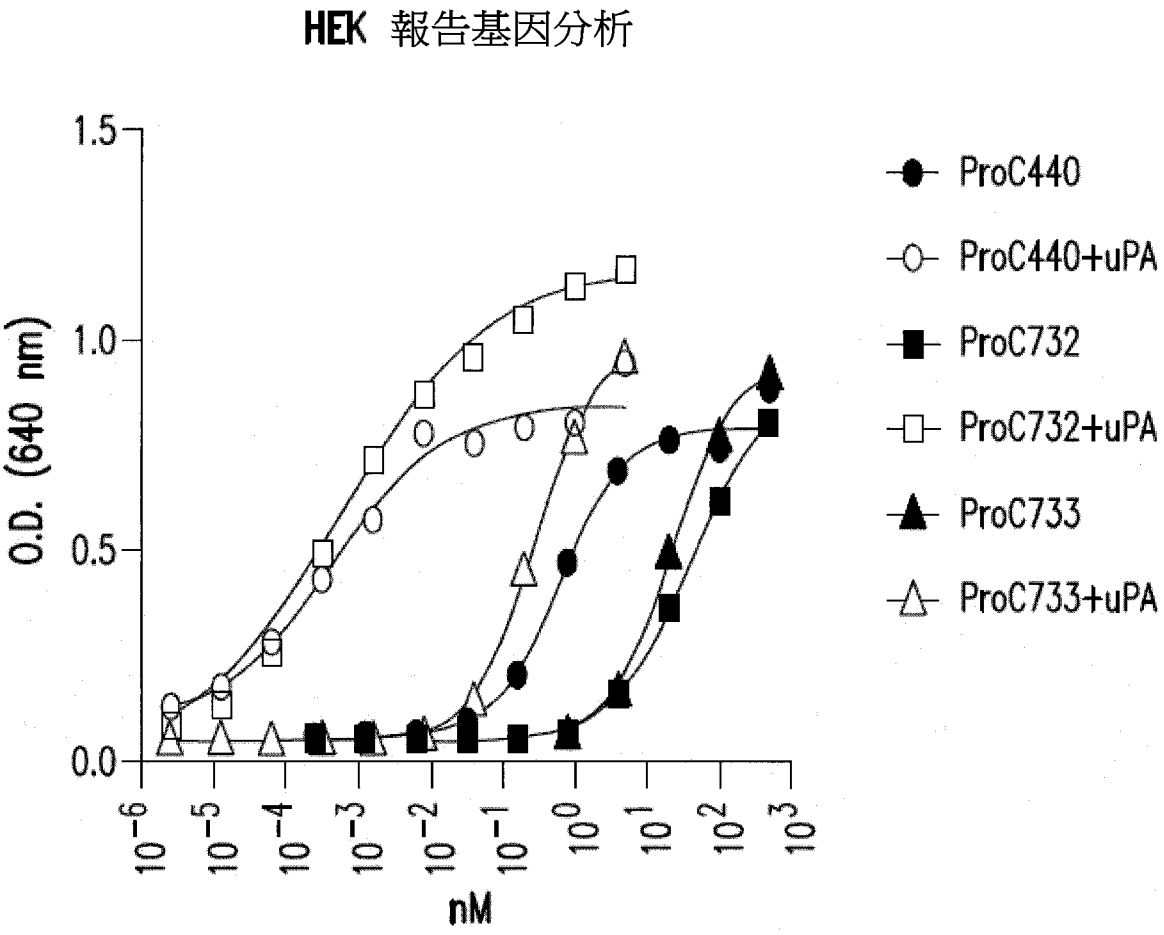
QSGQTDVDYYREWSWTQVSGSSGGS**LSGRSDNI**GSGGSCDLPQTHSLGSRRTLMLLAQM
RRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETL
LDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCA
WEVVRAEIMRSFSLSTNLQESLRSKEESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLS

(ProC733)

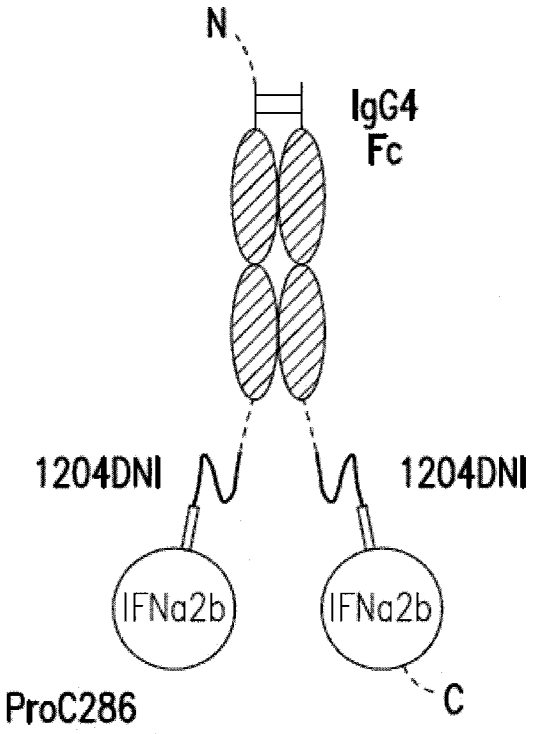
【圖 9】

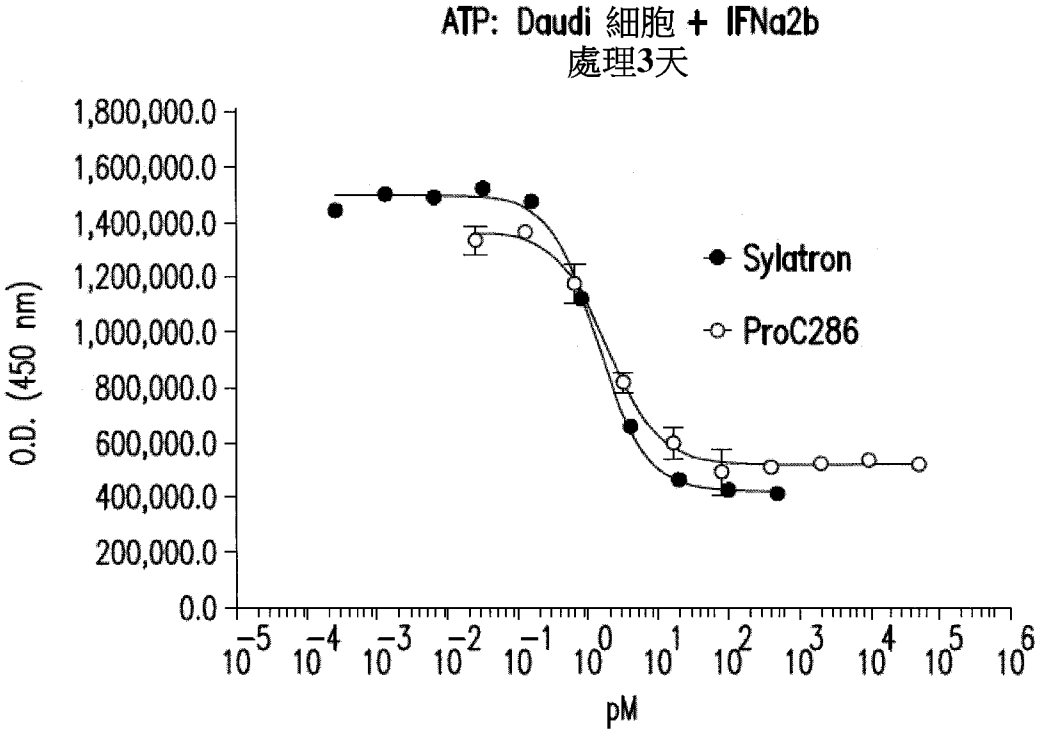


【圖 10A】

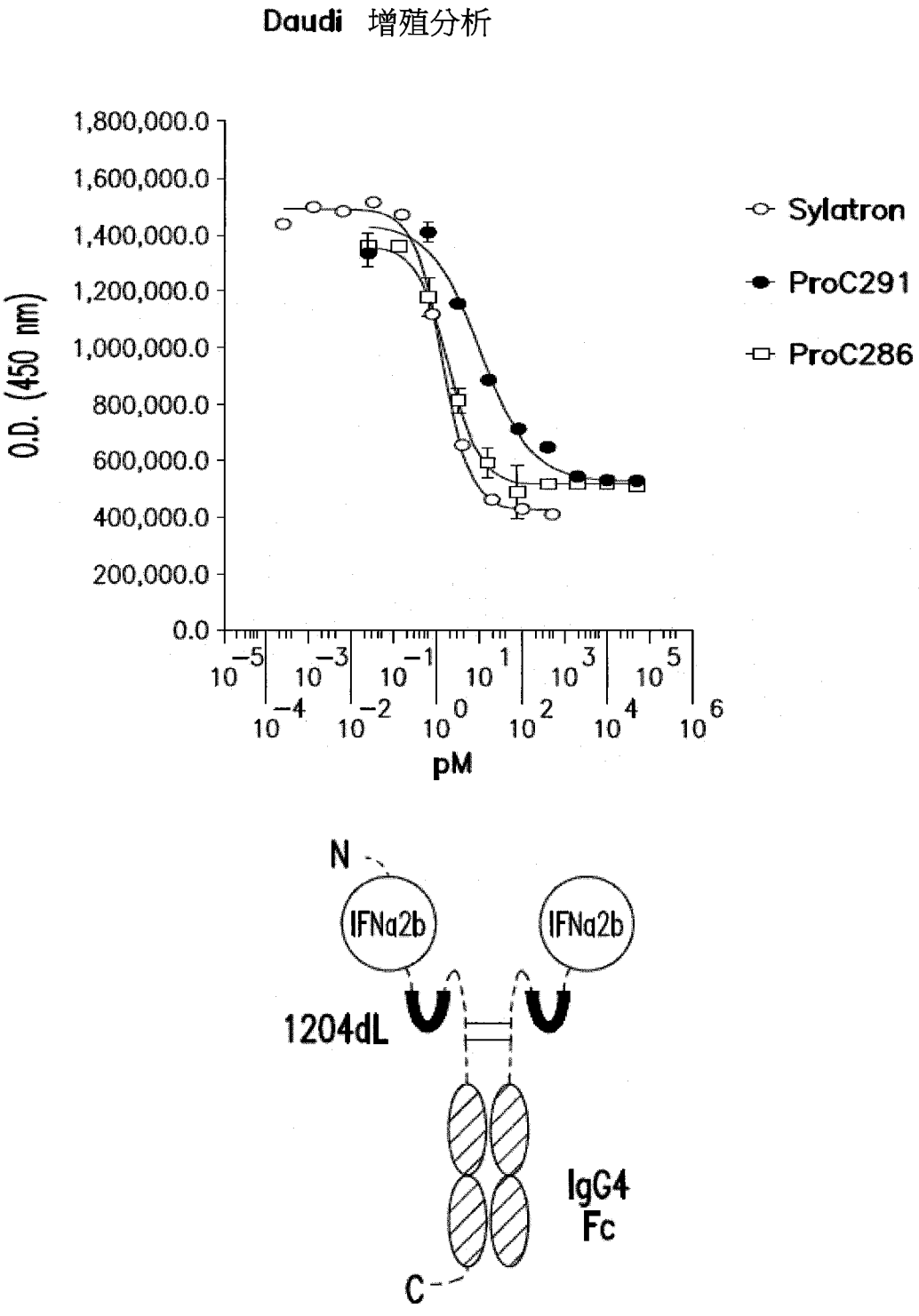

HEK 報告基因分析
O.D. (640 nm)
1.5
1.0
0.5
0.0
10⁻⁶
10⁻⁵
10⁻⁴
10⁻³
10⁻²
10⁻¹
10⁰
10¹
10²
10³
nM
ProC440
ProC440+uPA
ProC732
ProC732+uPA
ProC733
ProC733+uPA

【圖 10B】


N
IgG4
Fc
1204DNI
1204DNI
IFNa2b
IFNa2b
ProC286
C


ATP: Daudi 細胞 + IFNa2b
處理3天
O.D. (450 nm)
1,800,000.0
1,600,000.0
1,400,000.0
1,200,000.0
1,000,000.0
800,000.0
600,000.0
400,000.0
200,000.0
0.0
Sylatron
ProC286
10^-5 10^-4 10^-3 10^-2 10^-1 10^0 10^1 10^2 10^3 10^4 10^5 10^6
pM

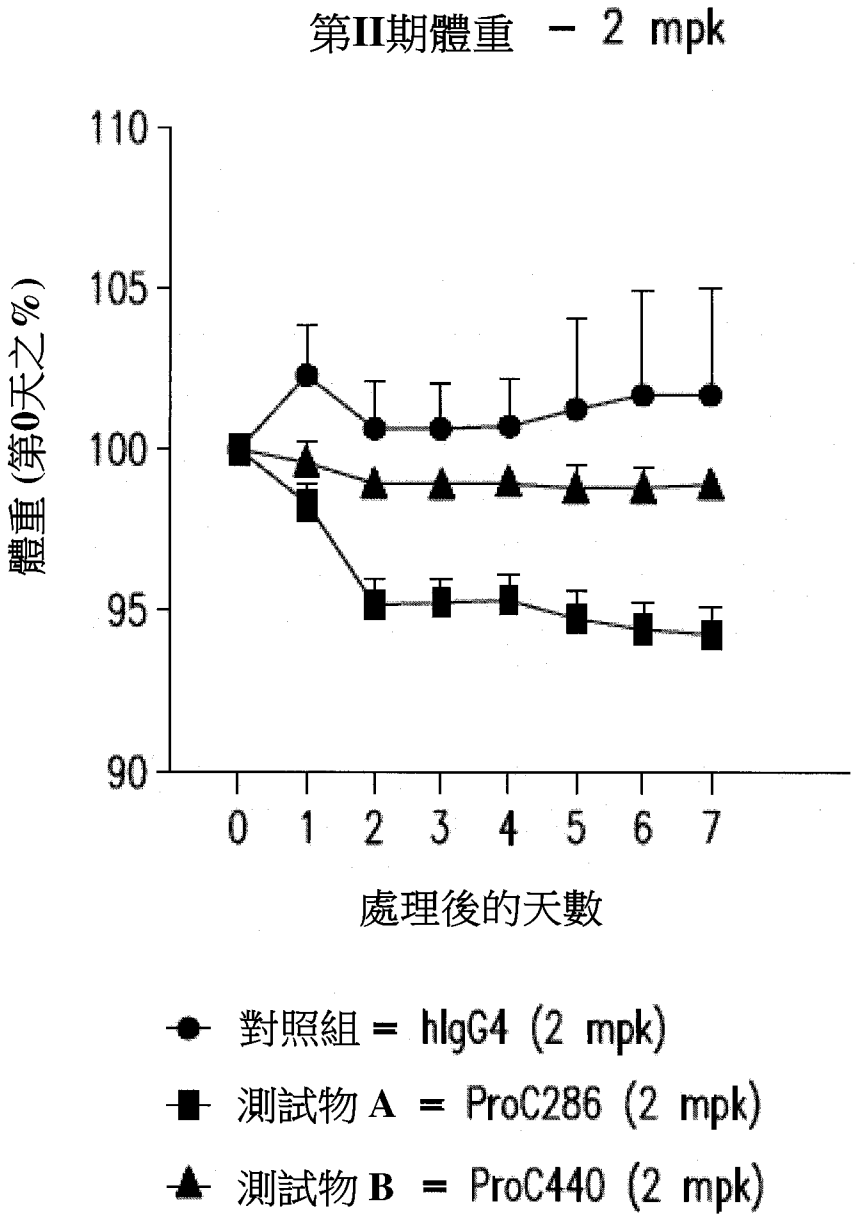
【圖 11A】


Daudi 增殖分析
1,800,000.0
1,600,000.0
1,400,000.0
1,200,000.0
1,000,000.0
800,000.0
600,000.0
400,000.0
200,000.0
0.0
O.D. (450 nm)
Sylatron
ProC291
ProC286
10 -5
10 -4
10 -3
10 -2
10 -1
10 0
10 1
10 2
10 3
10 4
10 5
10 6
pM
N
IFNα2b
IFNα2b
1204dL
IgG4
Fc
C

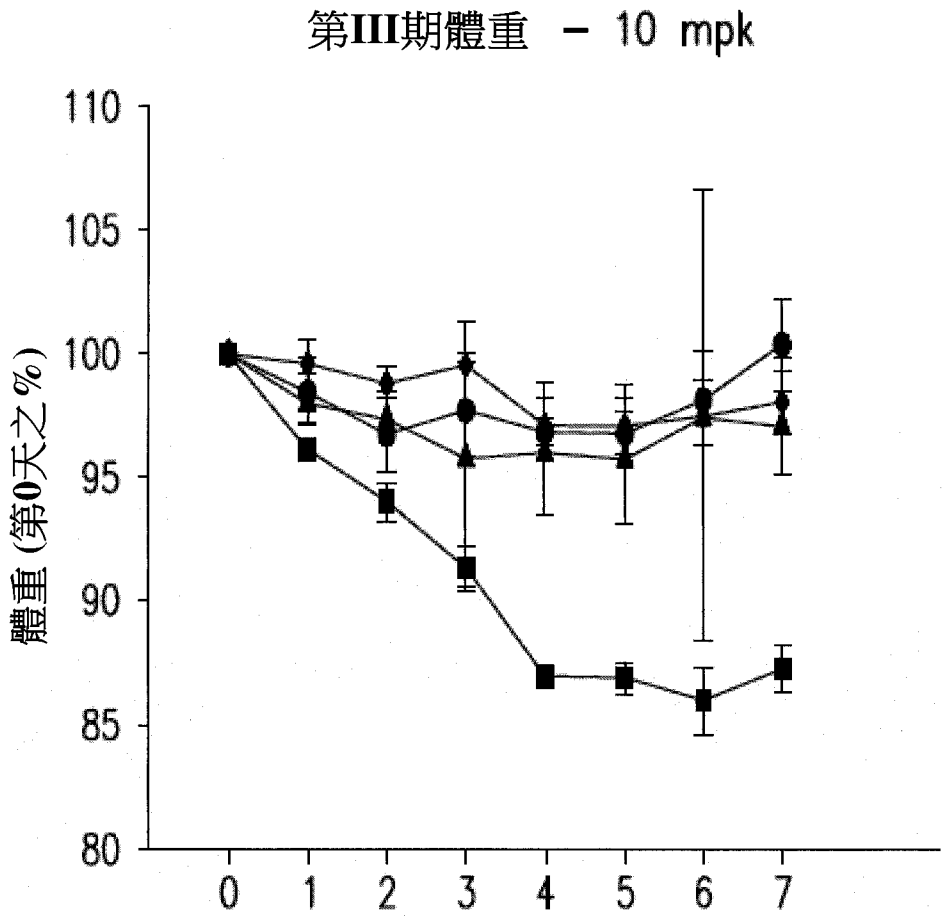
【圖 11B】

	IFNa-con	ProC440+uPA	PEG-IFNa2b (Sylatron)	ProC440
比活性	$1-2 \times 10^{9}$ U/mg	3.5×10^{8} U/mg	0.7×10^{8} U/mg	1.3×10^{7} U/mg
預期之毒性劑量	0.1 mpk *	0.288 mpk	1.43 mpk	7.68 mpk

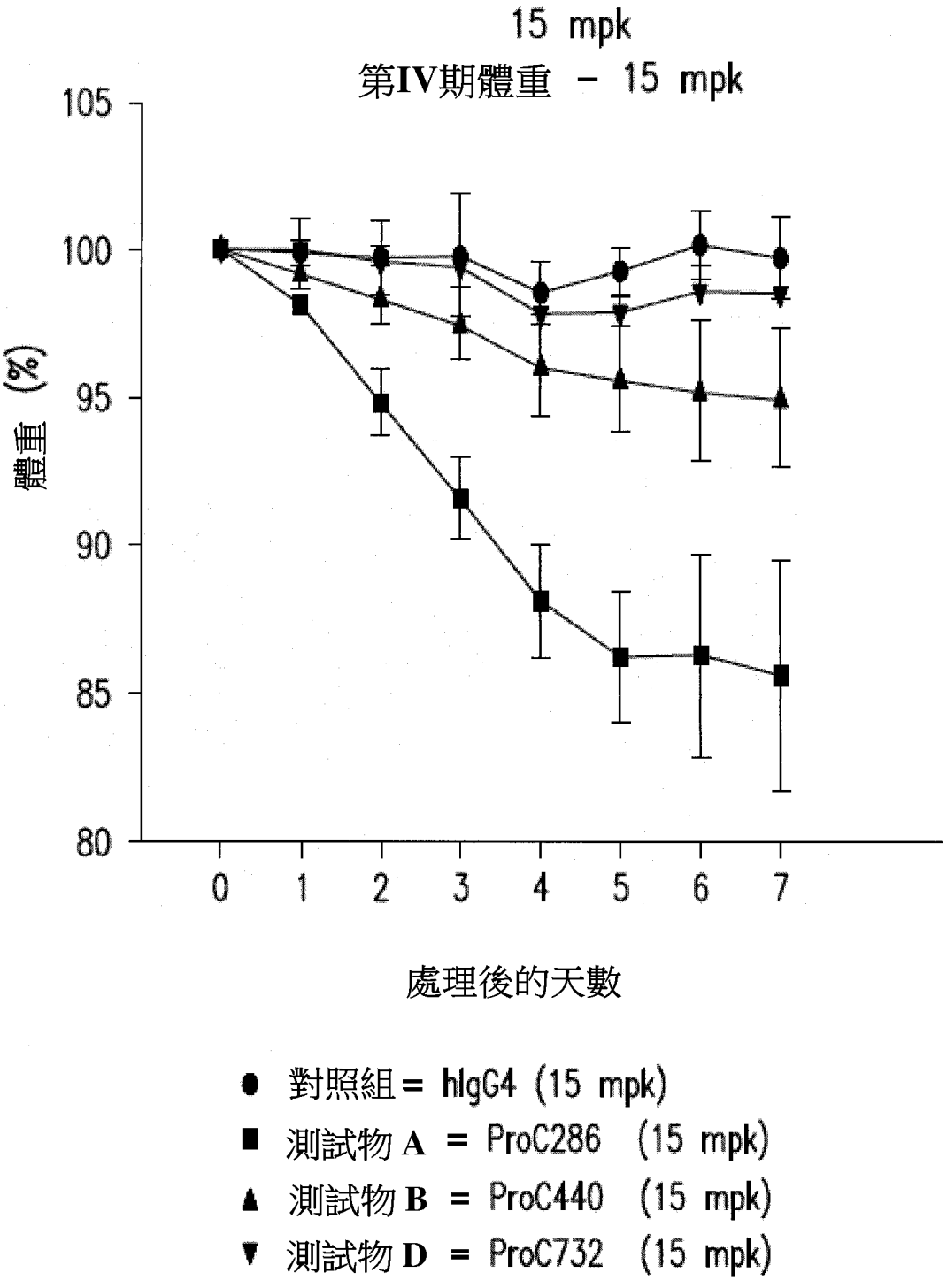
【圖 12】


第II期體重 – 2 mpk
體重 (第0天之%)
110
105
100
95
90
0
1
2
3
4
5
6
7
處理後的天數
對照組 = hIgG4 (2 mpk)
測試物 A = ProC286 (2 mpk)
測試物 B = ProC440 (2 mpk)

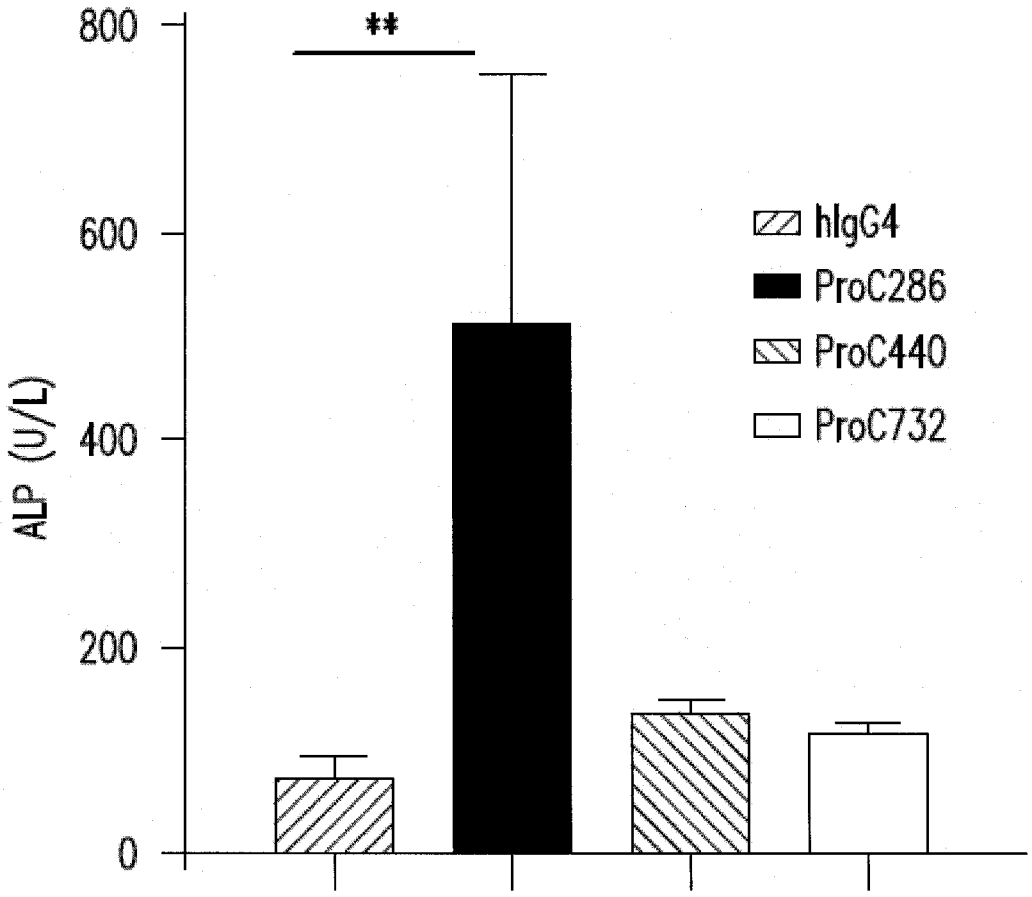
【圖 13A】


第III期體重 – 10 mpk
體重 (第0天之%)
110
105
100
95
90
85
80
0
1
2
3
4
5
6
7
處理後的天數
對照組 = hIgG4 (10 mpk)
測試物 A = ProC286 (10 mpk)
測試物 B = ProC440 (10 mpk)
測試物 D = ProC732 (10 mpk)

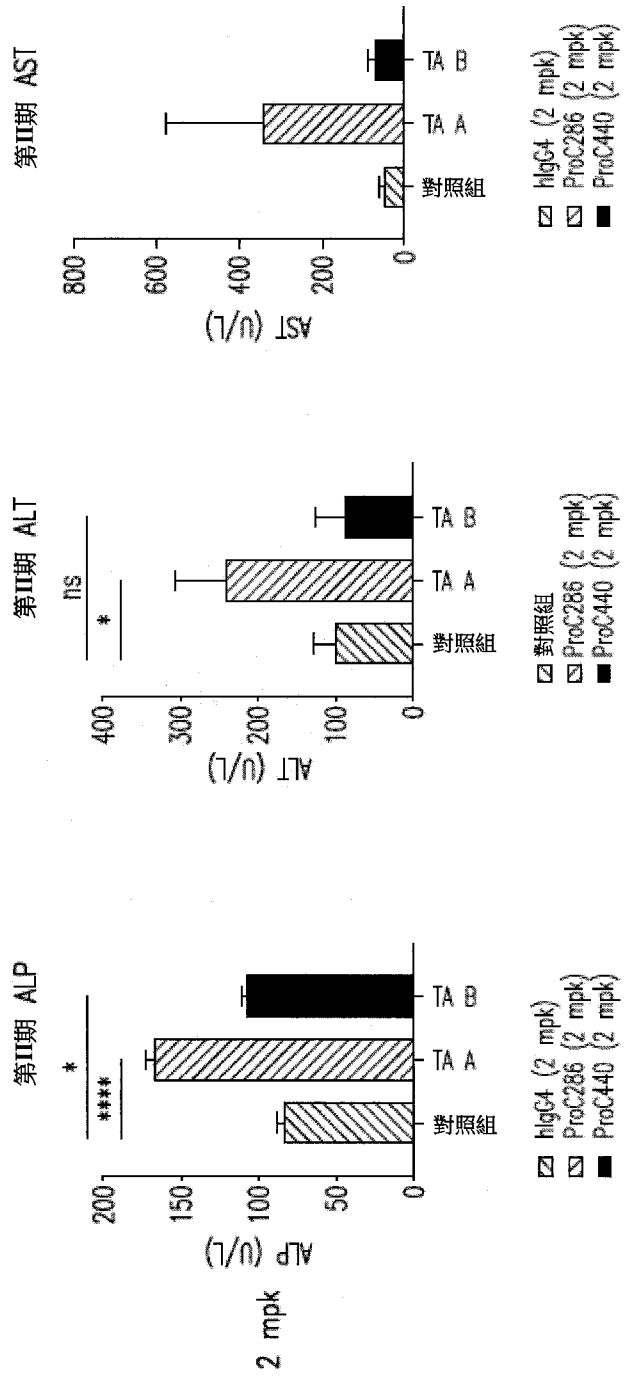
【圖 13B】


15 mpk
第IV期體重 - 15 mpk
105
100
95
90
85
80
體重 (%)
0
1
2
3
4
5
6
7
處理後的天數
對照組= hIgG4 (15 mpk)
測試物 A = ProC286 (15 mpk)
測試物 B = ProC440 (15 mpk)
測試物 D = ProC732 (15 mpk)

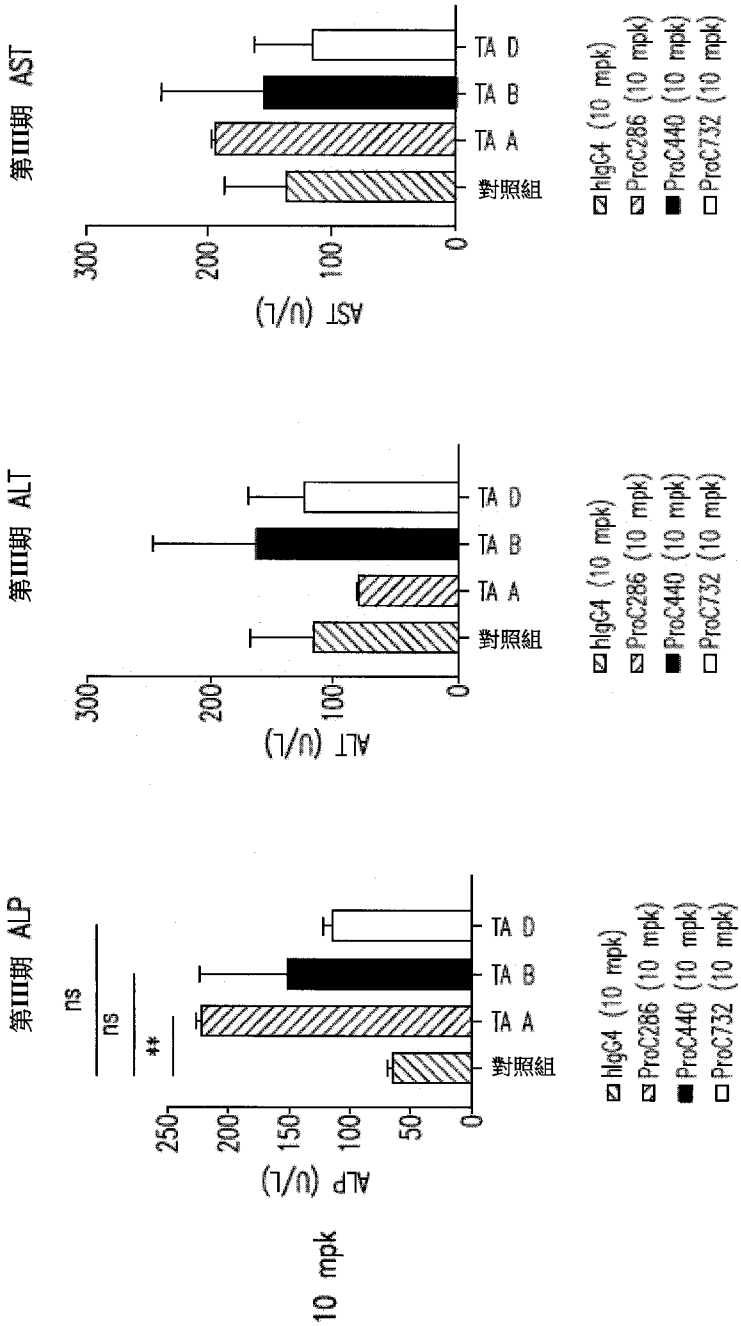
【圖 13C】



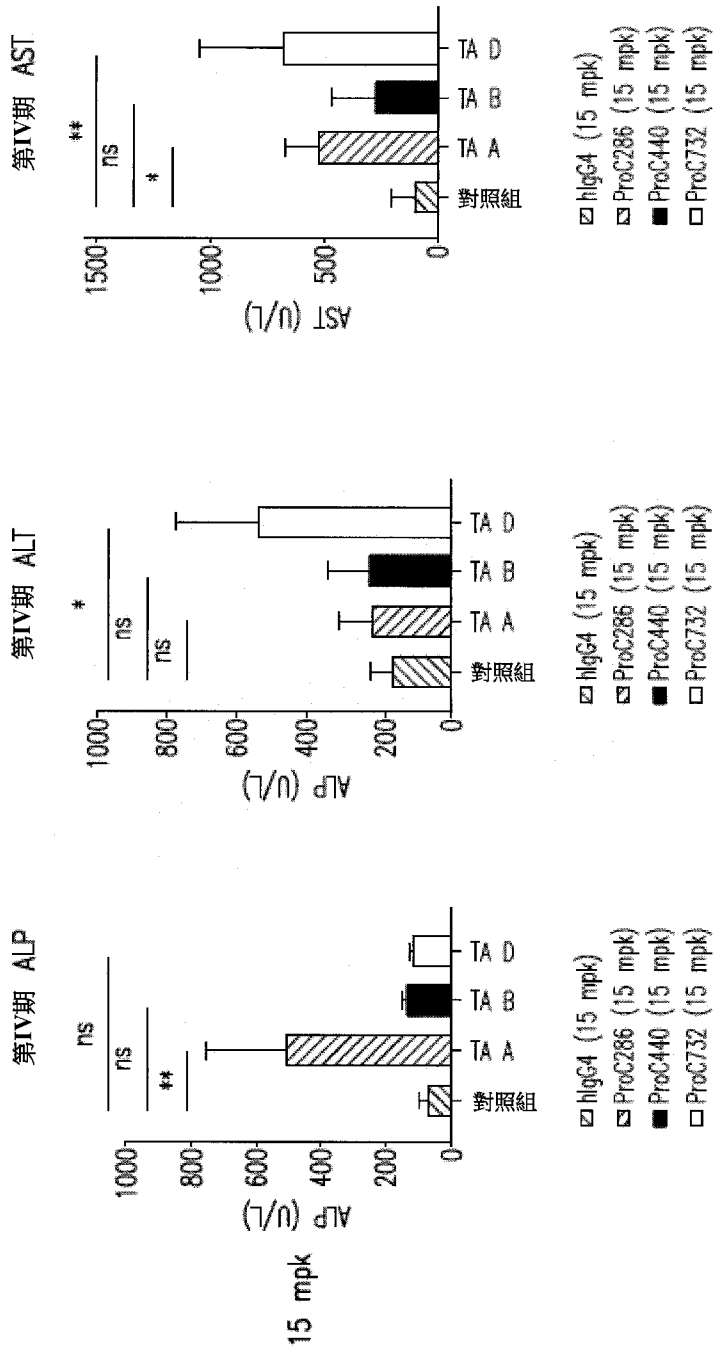
【圖 13D】


第II期 ALP
ALP (U/L)
200
150
100
50
0
*
****
TA B
TA A
對照組
2 mpk
第II期 ALT
ALT (U/L)
400
300
200
100
0
ns
*
TA B
TA A
對照組
hIgG4 (2 mpk)
ProC286 (2 mpk)
ProC440 (2 mpk)
第II期 AST
AST (U/L)
800
600
400
200
0
TA B
TA A
對照組
hIgG4 (2 mpk)
ProC286 (2 mpk)
ProC440 (2 mpk)

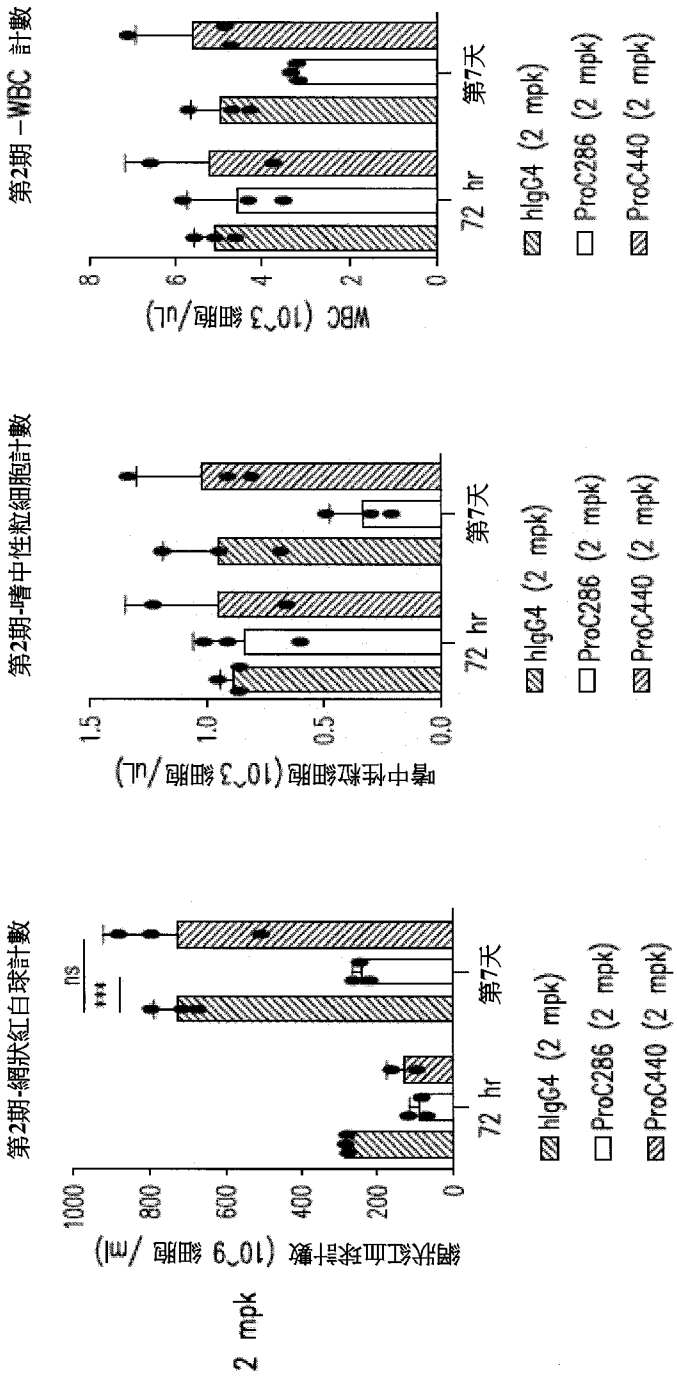
【圖 14】


第III期 ALP
ns
ns
**
ALP (U/L)
250
200
150
100
50
0
TA D
TA B
TA A
對照組
10 mpk
hIgG4 (10 mpk)
ProC286 (10 mpk)
ProC440 (10 mpk)
ProC732 (10 mpk)
第III期 ALT
ALT (U/L)
300
200
100
0
TA D
TA B
TA A
對照組
hIgG4 (10 mpk)
ProC286 (10 mpk)
ProC440 (10 mpk)
ProC732 (10 mpk)
第III期 AST
AST (U/L)
300
200
100
0
TA D
TA B
TA A
對照組
hIgG4 (10 mpk)
ProC286 (10 mpk)
ProC440 (10 mpk)
ProC732 (10 mpk)

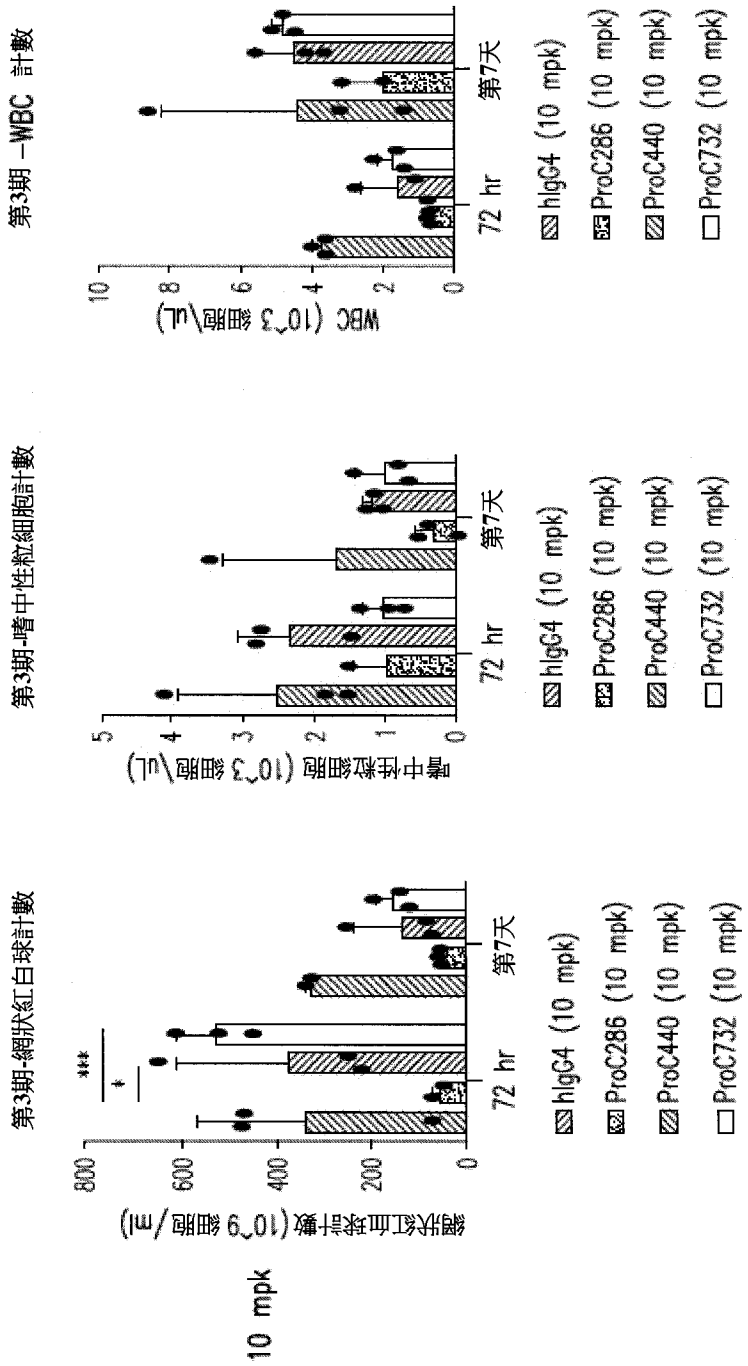
【圖 14】(續)


第IV期 ALP
第IV期 ALT
第IV期 AST
15 mpk
ALP (U/L)
ALT (U/L)
AST (U/L)
對照組
TA A
TA B
TA D
ns
*
**
hIgG4 (15 mpk)
ProC286 (15 mpk)
ProC440 (15 mpk)
ProC732 (15 mpk)

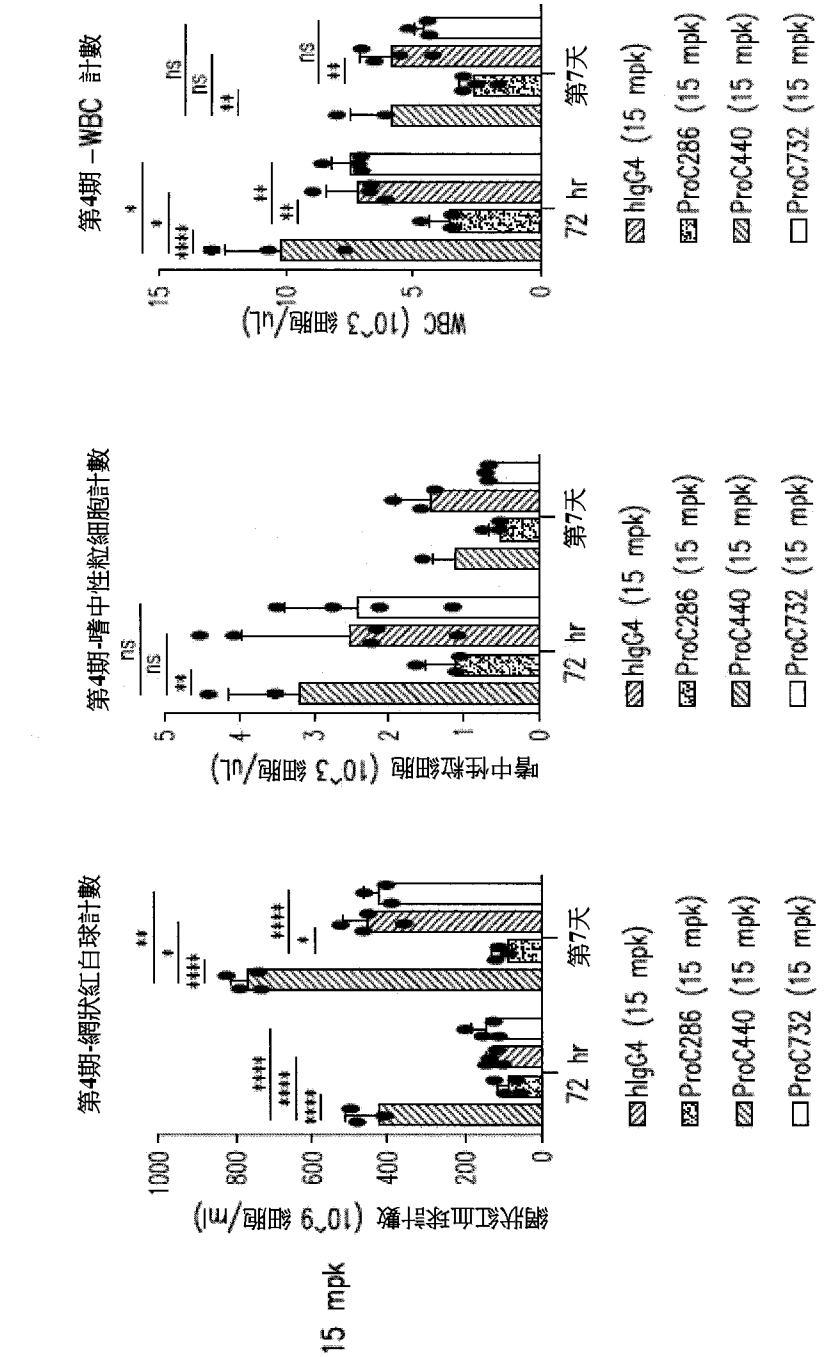
【圖 14】(續)


第2期-網狀紅白球計數
第2期-嗜中性粒細胞計數
第2期 -WBC 計數
2 mpk
網狀紅血球計數 (10^9 細胞 /ml)
嗜中性粒細胞 (10^3 細胞/uL)
WBC (10^3 細胞/uL)
ns
***
72 hr
第7天
hIgG4 (2 mpk)
ProC286 (2 mpk)
ProC440 (2 mpk)

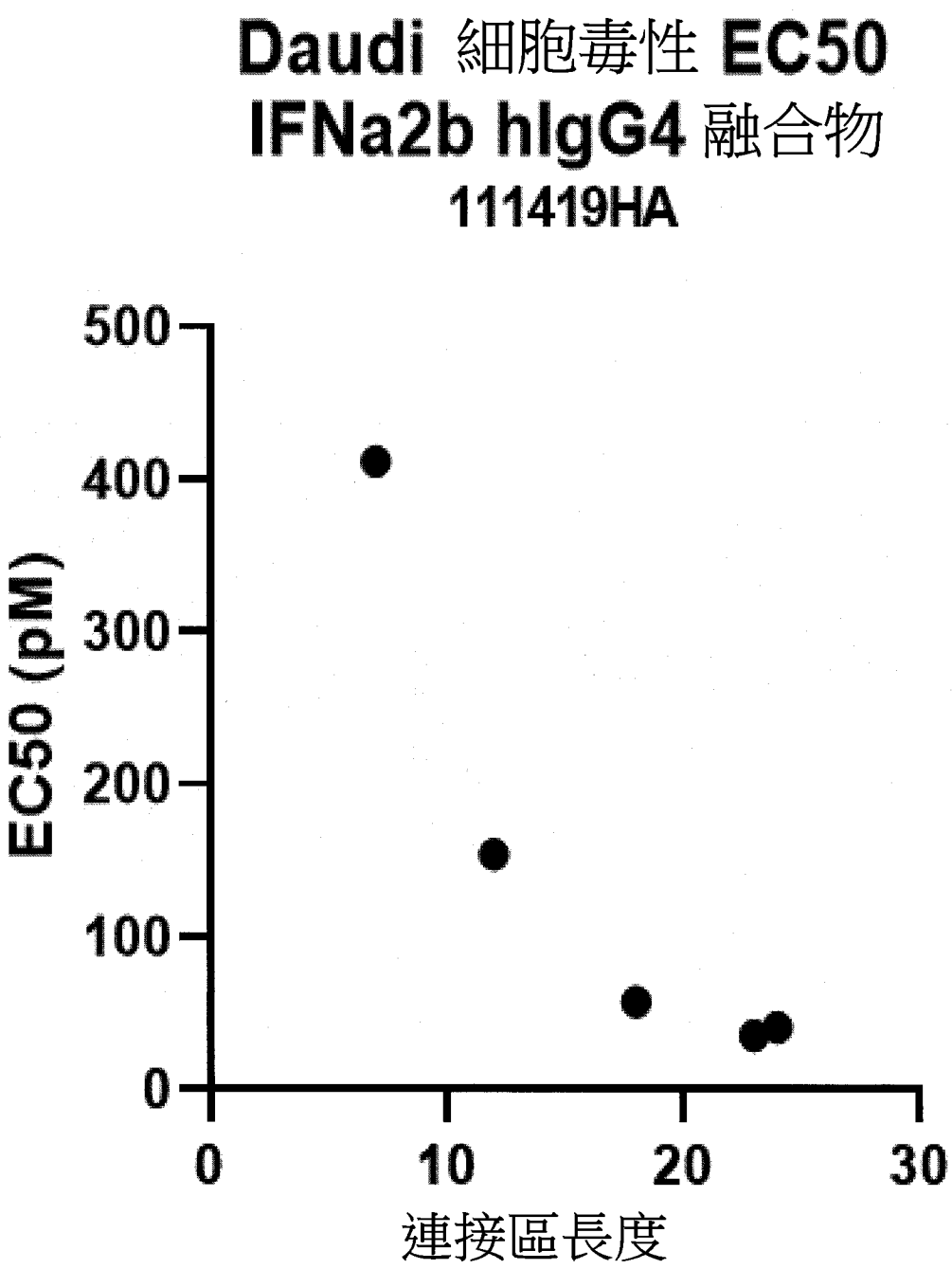
【圖 15】


第3期-網狀紅白球計數
網狀紅血球計數 (10^9 細胞/ml)
800
600
400
200
0
***
*
72 hr
第7天
10 mpk
hIgG4 (10 mpk)
ProC286 (10 mpk)
ProC440 (10 mpk)
ProC732 (10 mpk)
第3期-嗜中性粒細胞計數
嗜中性粒細胞 (10^3 細胞/uL)
5
4
3
2
1
0
72 hr
第7天
hIgG4 (10 mpk)
ProC286 (10 mpk)
ProC440 (10 mpk)
ProC732 (10 mpk)
第3期 –WBC 計數
WBC (10^3 細胞/uL)
10
8
6
4
2
0
72 hr
第7天
hIgG4 (10 mpk)
ProC286 (10 mpk)
ProC440 (10 mpk)
ProC732 (10 mpk)

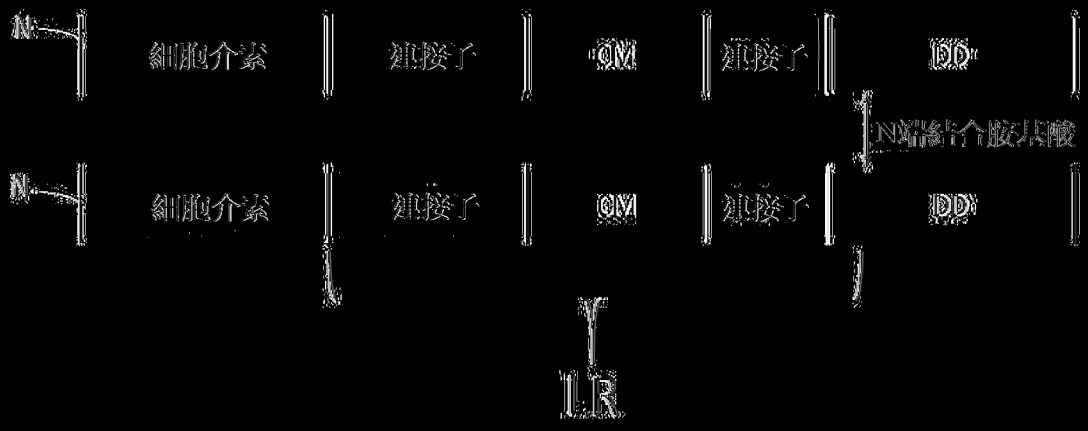
【圖 15】(續)


第4期-網狀紅白球計數
網狀紅血球計數 (10^9 細胞/ml)
15 mpk
72 hr
第7天
第4期-嗜中性粒細胞計數
嗜中性粒細胞 (10^3 細胞/uL)
第4期 –WBC 計數
WBC (10^3 細胞/uL)
hIgG4 (15 mpk)
ProC286 (15 mpk)
ProC440 (15 mpk)
ProC732 (15 mpk)

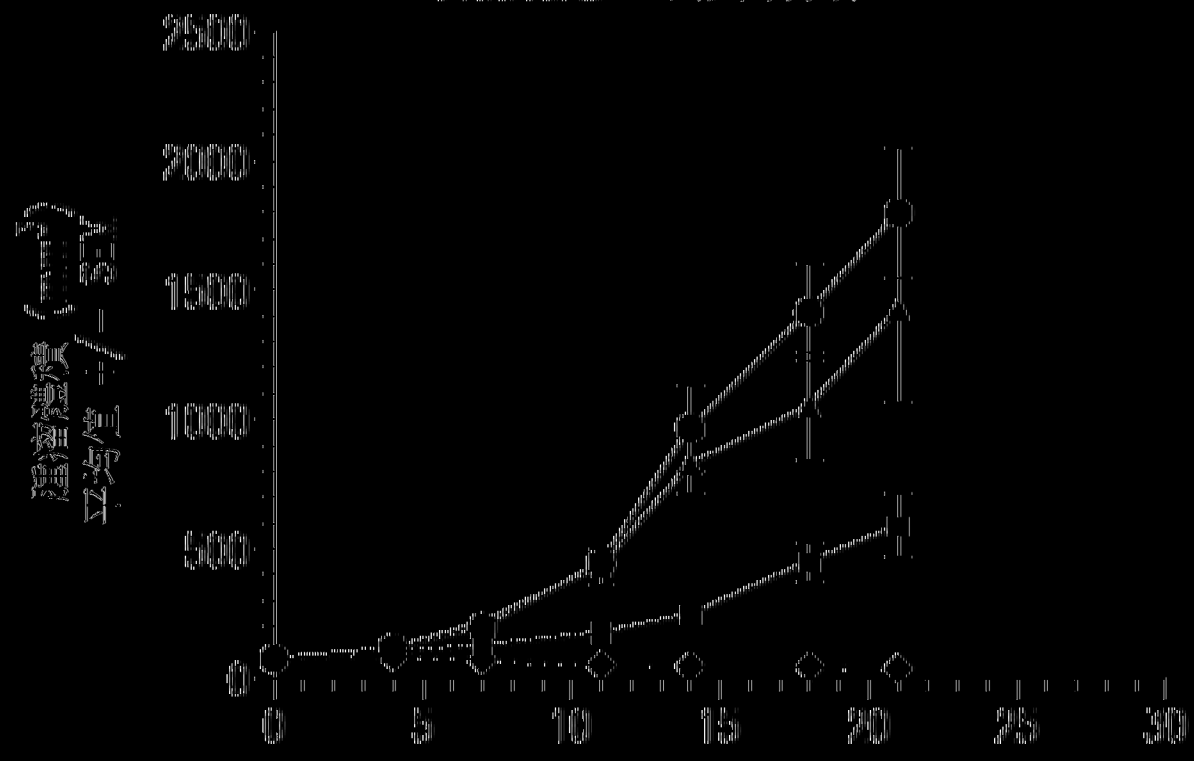
【圖 15】(續)


Daudi 細胞毒性 EC50
IFNa2b hIgG4 融合物
111419HA
EC50 (pM)
500
400
300
200
100
0
0
10
20
30
連接區長度

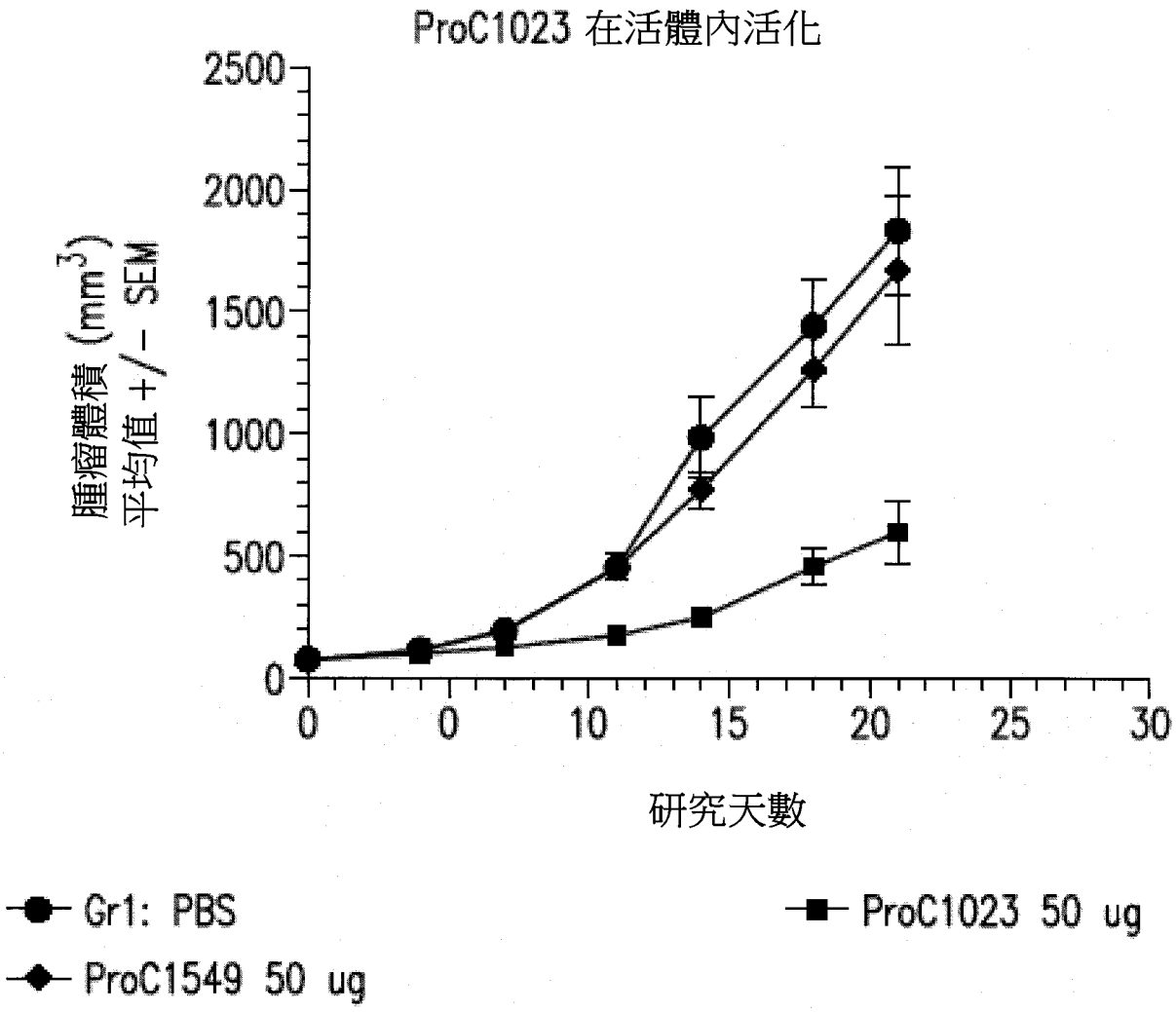
【圖 16】


N
細胞介素
連接子
VH
連接子
DD
N端結合胺基酸
N
細胞介素
連接子
VH
連接子
DD
VL
R

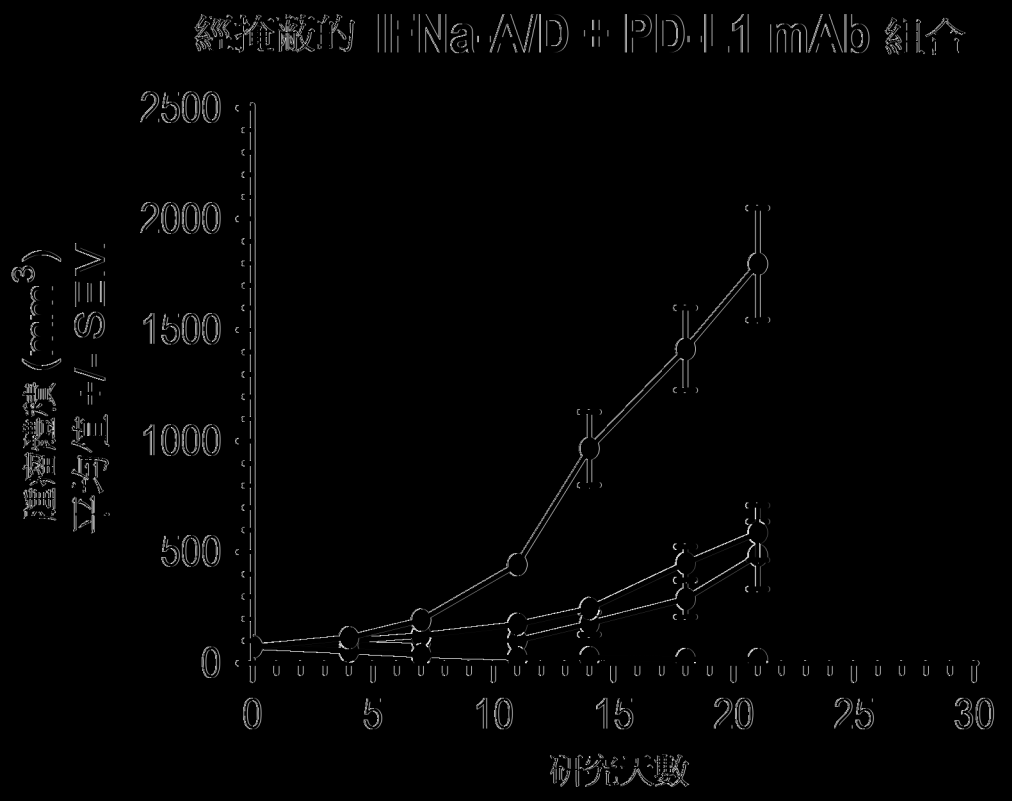
圖(圖 1’)


ProC1025 之活體內功效
腫瘤體積 立方公分
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
研究天數
Gr1: PBS
ProC1025 50 ug
ProC1025 200 ug
ProC1025 10 ug

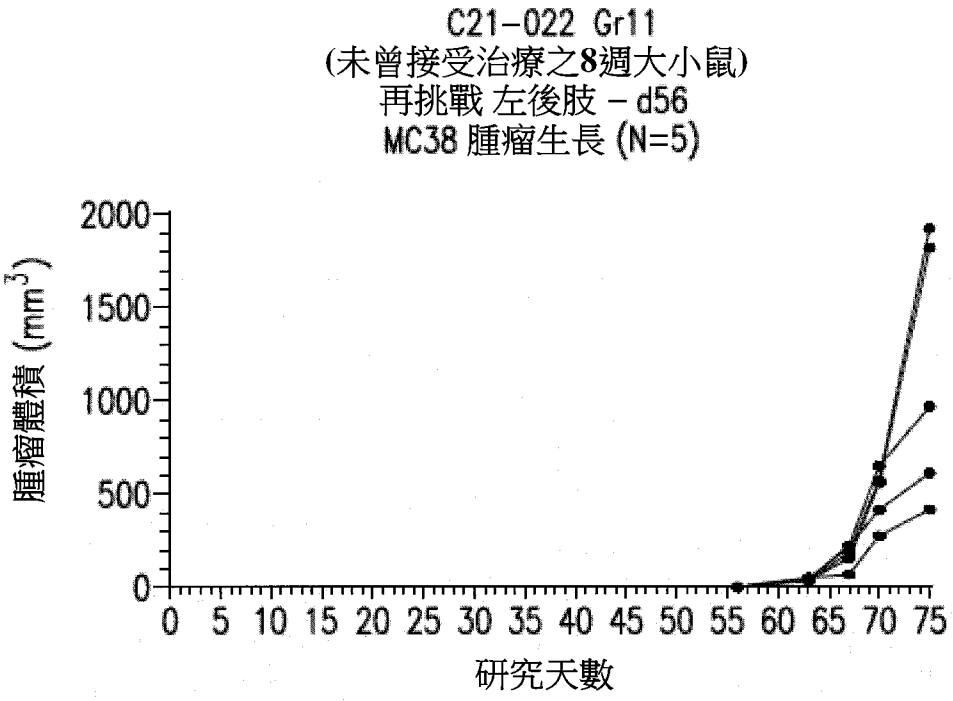
圖(圖 18A)


ProC1023 在活體內活化
腫瘤體積 (mm^3)
平均值 +/- SEM
2500
2000
1500
1000
500
0
0
0
10
15
20
25
30
研究天數
Gr1: PBS
ProC1023 50 ug
ProC1549 50 ug

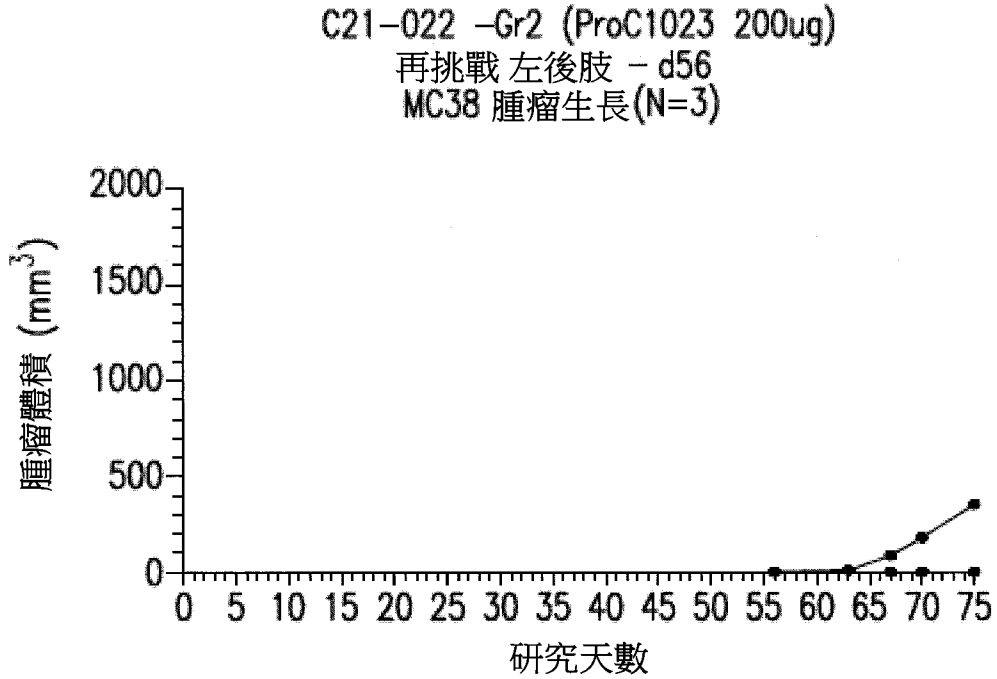
【圖 18B】


經捨棄的 II Na A/D + PD-L1 mAb 組合
腫瘤體積 (mm3) 平均值 +/- SEM
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
研究天數
PBS
經捨棄的 II Na A/D 50 ug
PD-L1 mAb 200 ug
經捨棄的 II Na A/D + PD-L1 mAb

|(圖 18C)|

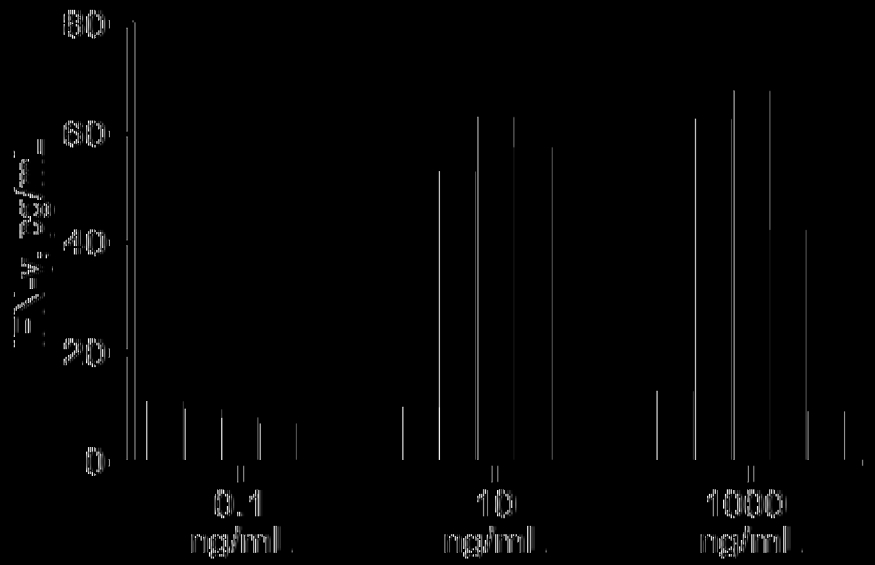

C21-022 Gr11
(未曾接受治療之8週大小鼠)
再挑戰 左後肢 – d56
MC38 腫瘤生長 (N=5)
腫瘤體積 (mm3)
2000
1500
1000
500
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
研究天數

【圖 19A】

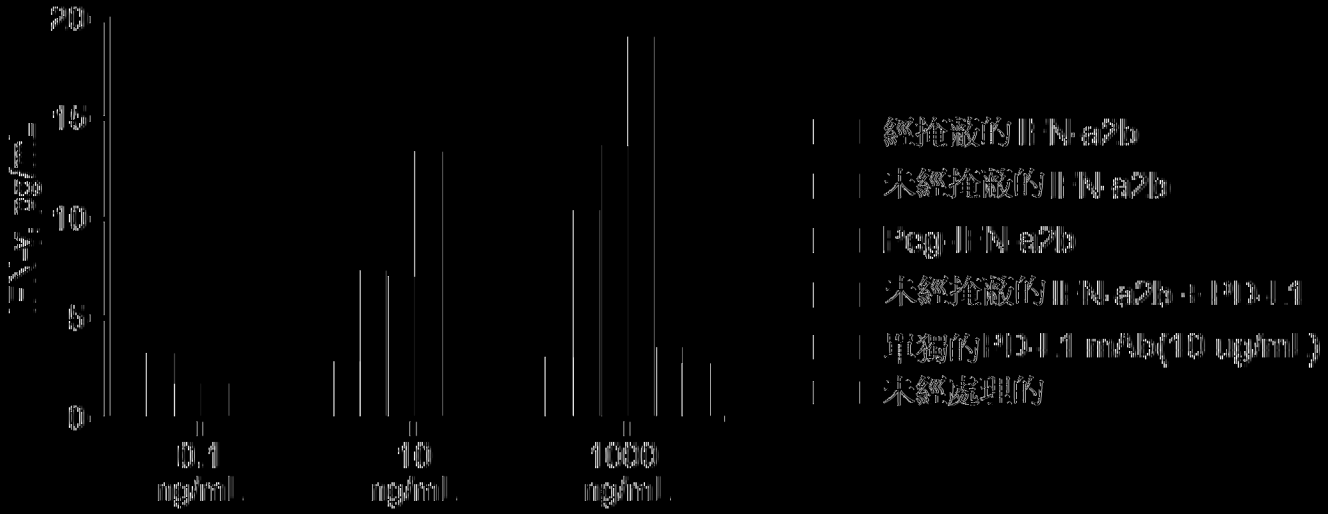

C21-022 –Gr2 (ProC1023 200ug)
再挑戰 左後肢 – d56
MC38 腫瘤生長(N=3)
腫瘤體積 (mm3)
2000
1500
1000
500
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
研究天數

【圖 19B】

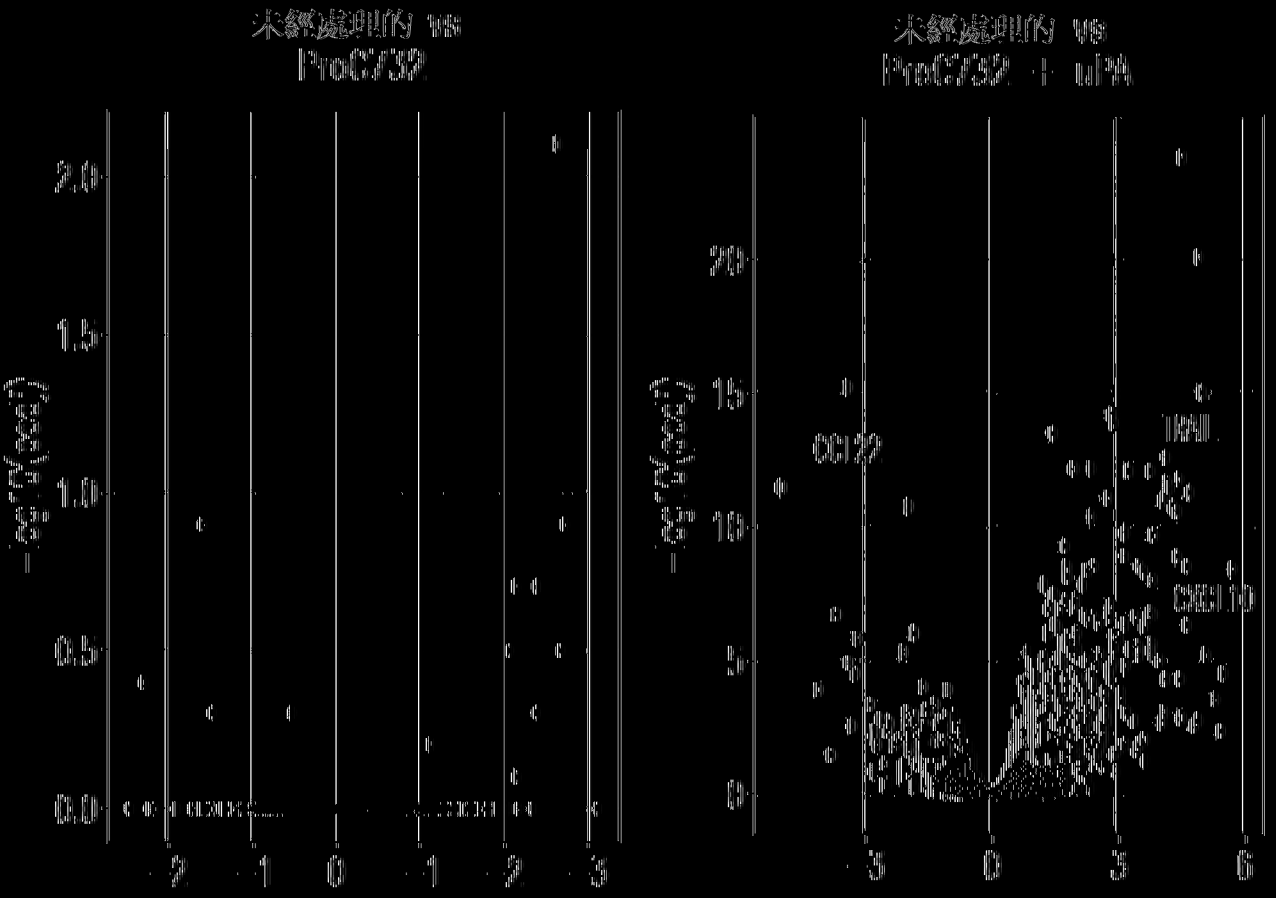
患者之 PBMC



經分離的腫瘤



|(圖 20)|



log2 (倍數變化)
同 24.2 火山圖

↑ 其內：1
↓ 其內：0

↑ 其內：418
↓ 其內：77

|(圖 21)|

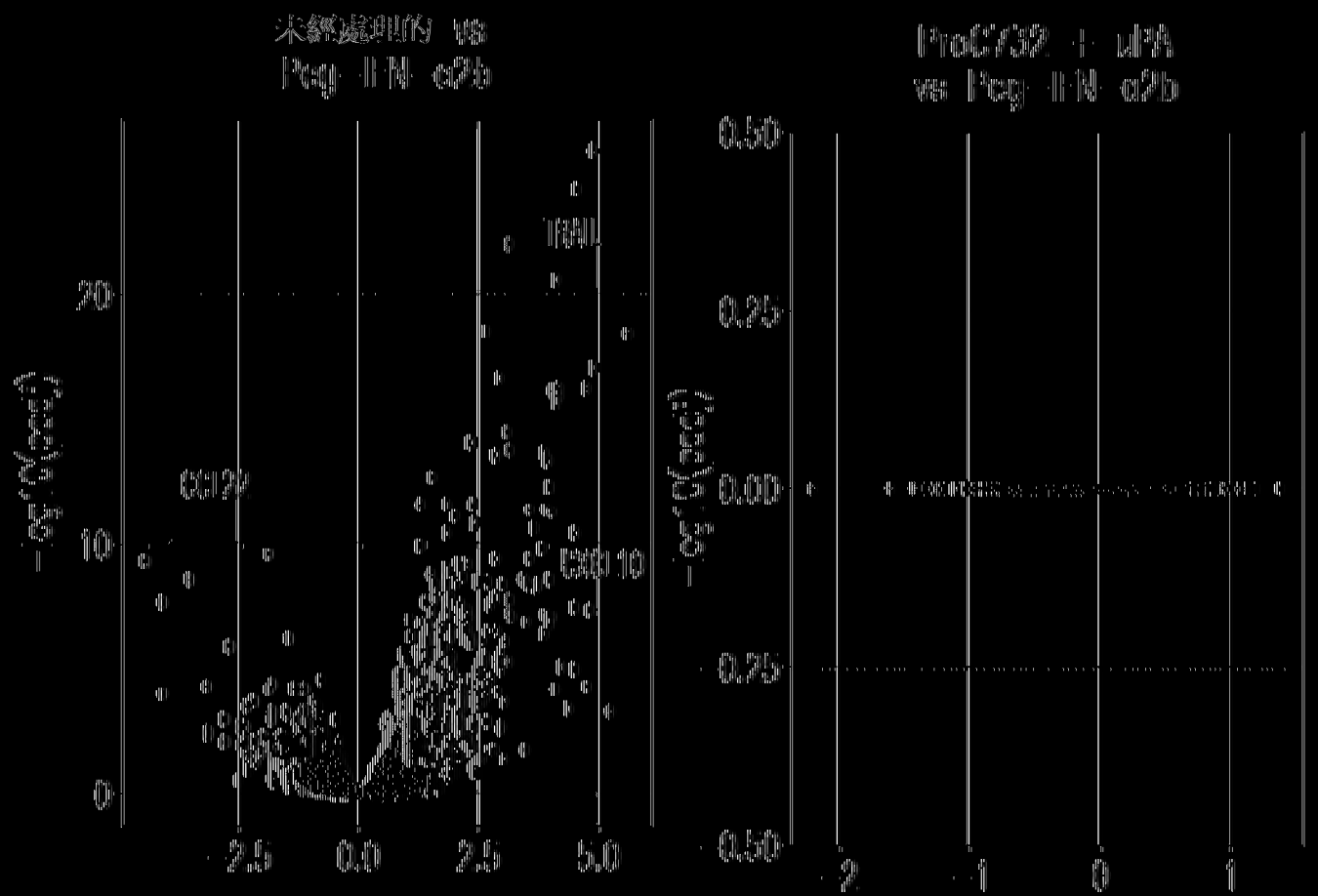
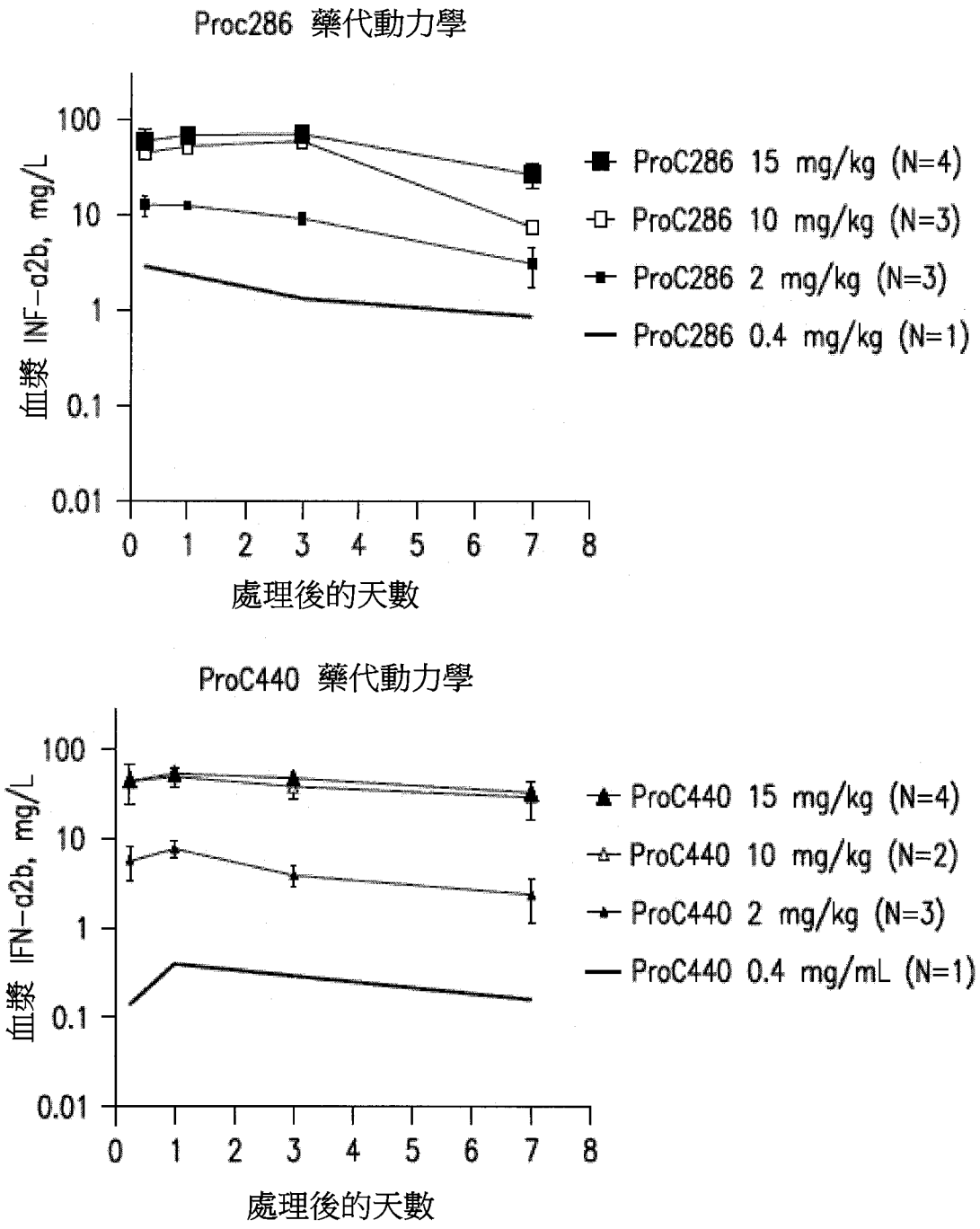
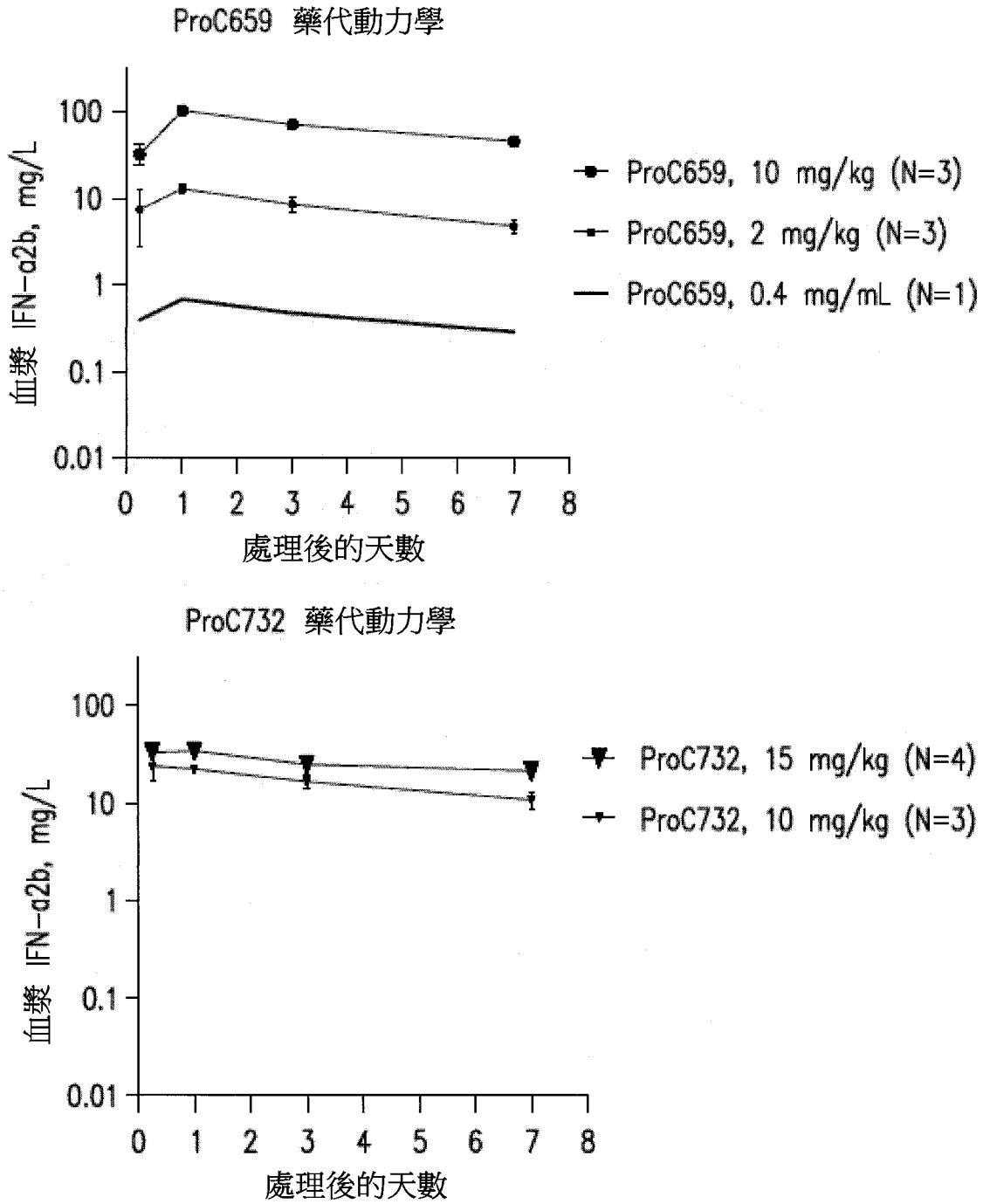

未經處理的 vs
Pcg-1N-cp5
ProC332 + uPA
vs Pcg-1N-cp5
-log10(p-value)
20
10
0
0.50
0.25
0.00
0.25
0.50
-25
0.0
2.5
5.0
2
1
0
1
log2 (倍數變化)
同 2.42 火山圖
log2 (倍數變化)
↑ 其內：480
↓ 其內：66
↑ 其內：0
↓ 其內：0

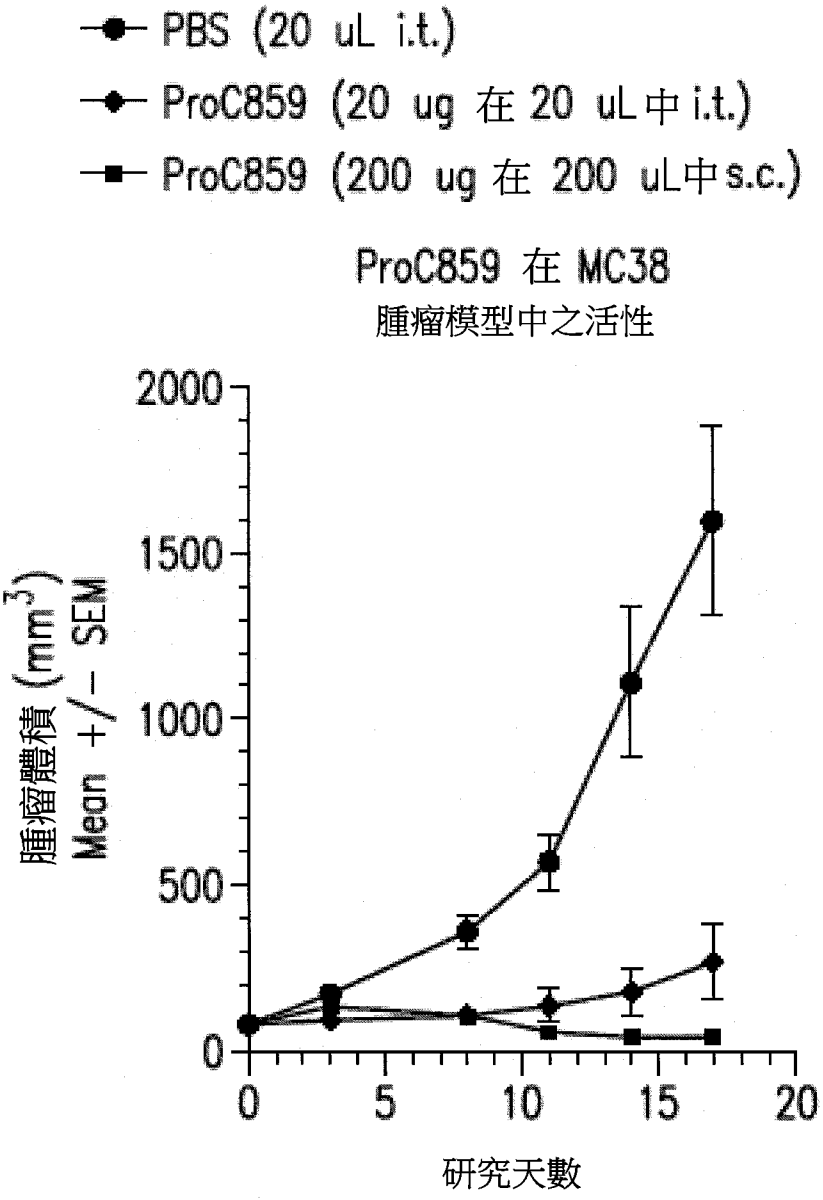
圖 21 (續)


Proc286 藥代動力學
血漿 INF-α2b, mg/L
100
10
1
0.1
0.01
0 1 2 3 4 5 6 7 8
處理後的天數
ProC286 15 mg/kg (N=4)
ProC286 10 mg/kg (N=3)
ProC286 2 mg/kg (N=3)
ProC286 0.4 mg/kg (N=1)
ProC440 藥代動力學
血漿 IFN-α2b, mg/L
100
10
1
0.1
0.01
0 1 2 3 4 5 6 7 8
處理後的天數
ProC440 15 mg/kg (N=4)
ProC440 10 mg/kg (N=2)
ProC440 2 mg/kg (N=3)
ProC440 0.4 mg/mL (N=1)

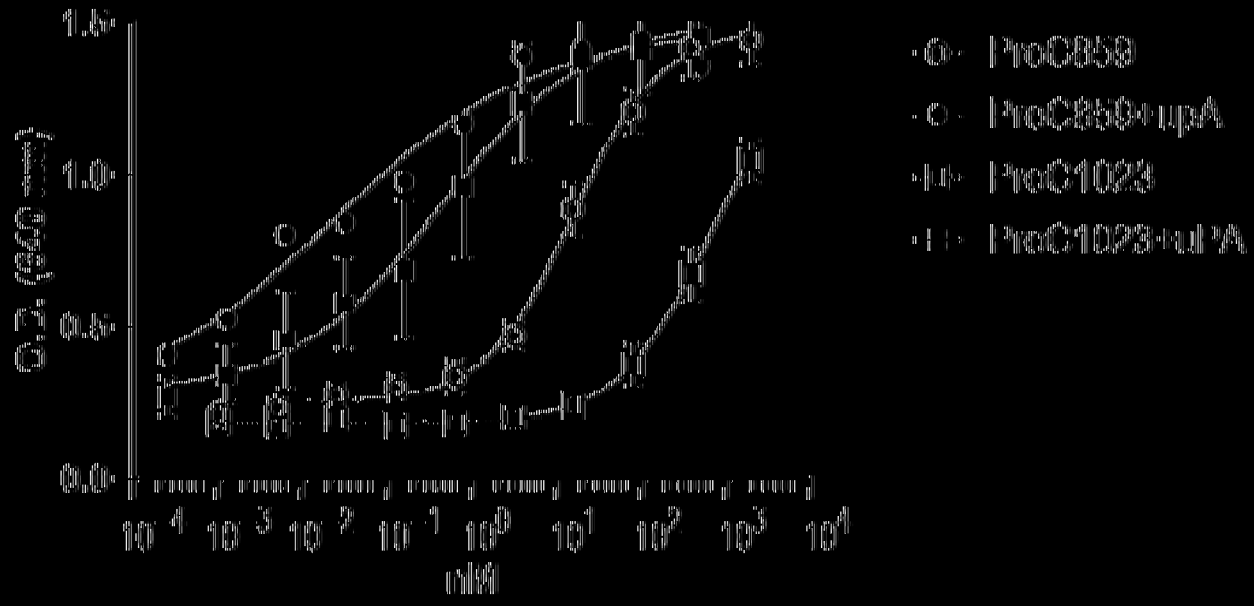
【圖 22】


ProC659 藥代動力學
血漿 IFN-α2b, mg/L
100
10
1
0.1
0.01
0 1 2 3 4 5 6 7 8
處理後的天數
ProC659, 10 mg/kg (N=3)
ProC659, 2 mg/kg (N=3)
ProC659, 0.4 mg/mL (N=1)
ProC732 藥代動力學
血漿 IFN-α2b, mg/L
100
10
1
0.1
0.01
0 1 2 3 4 5 6 7 8
處理後的天數
ProC732, 15 mg/kg (N=4)
ProC732, 10 mg/kg (N=3)

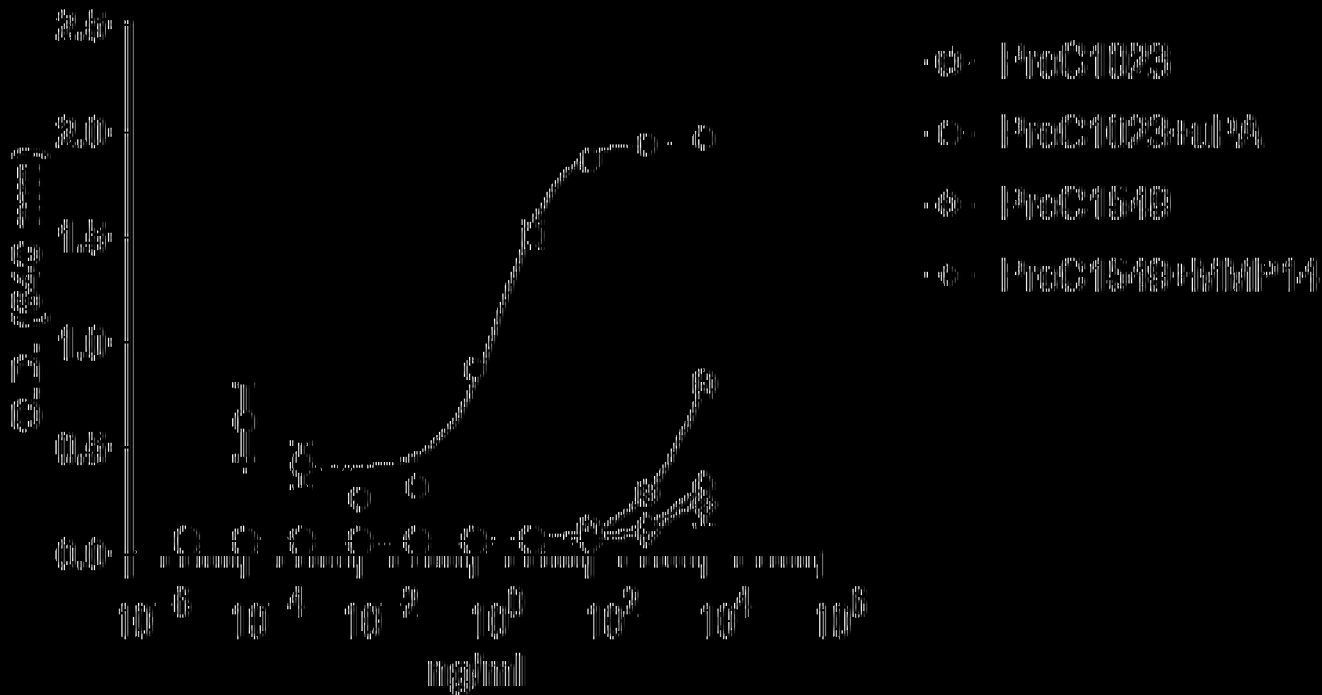
【圖 22】(續)


PBS (20 uL i.t.)
ProC859 (20 ug 在 20 uL中 i.t.)
ProC859 (200 ug 在 200 uL中 s.c.)
ProC859 在 MC38
腫瘤模型中之活性
腫瘤體積 (mm3)
Mean +/- SEM
2000
1500
1000
500
0
0
5
10
15
20
研究天數

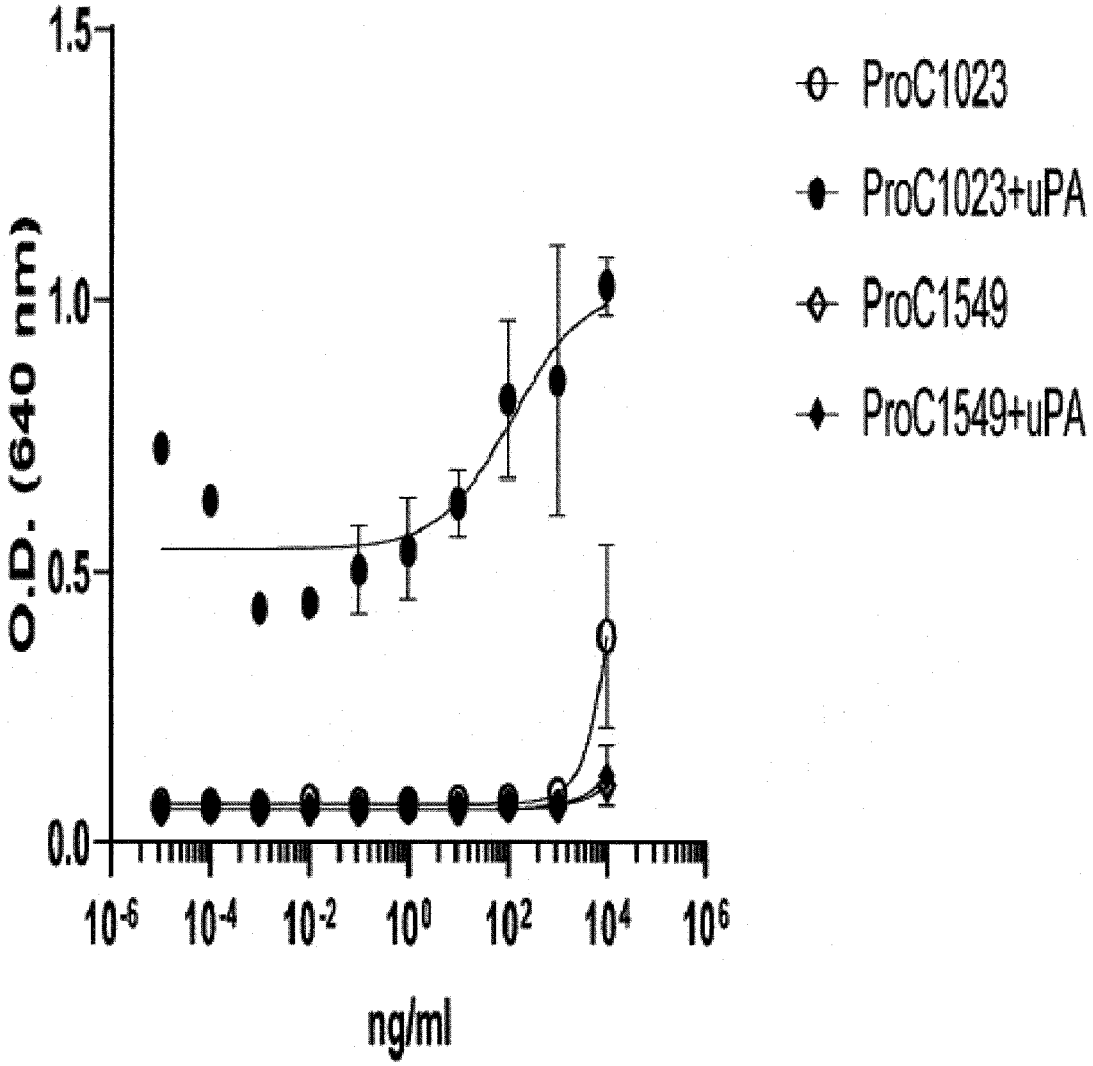
【圖 23】


1.6
1.0
0.6
0.0
nM
PreC858
PreC858+μrA
PreC1023
PreC1023+ulA

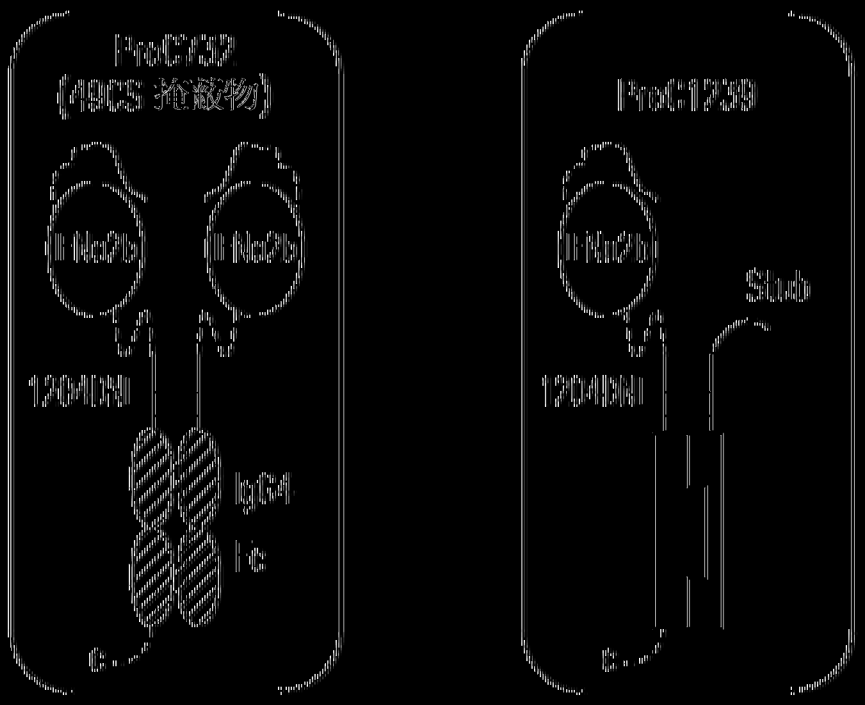
圖(圖 24A)

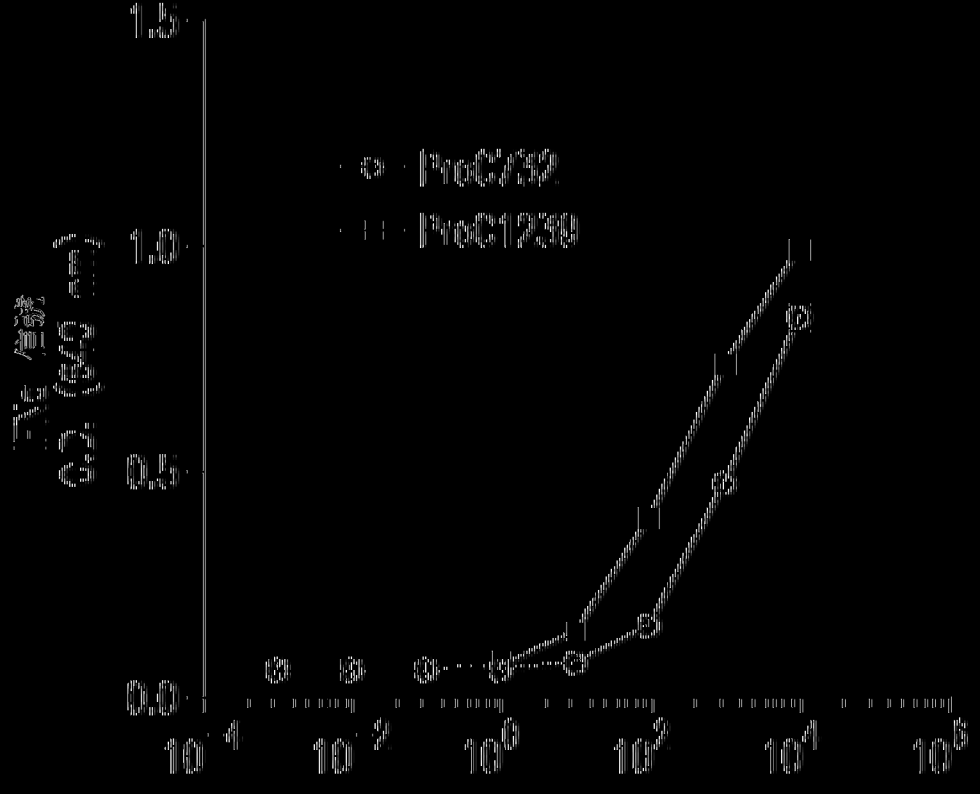

2.6
2.0
1.5
1.0
0.5
0.0
ng/ml
PreC1023
PreC1023+ulA
PreC1548
PreC1548+MMP14

圖(圖 24B)


1.5
1.0
0.5
0.0
O.D. (640 nm)
10-6
10-4
10-2
100
102
104
106
ng/ml
ProC1023
ProC1023+uPA
ProC1549
ProC1549+uPA

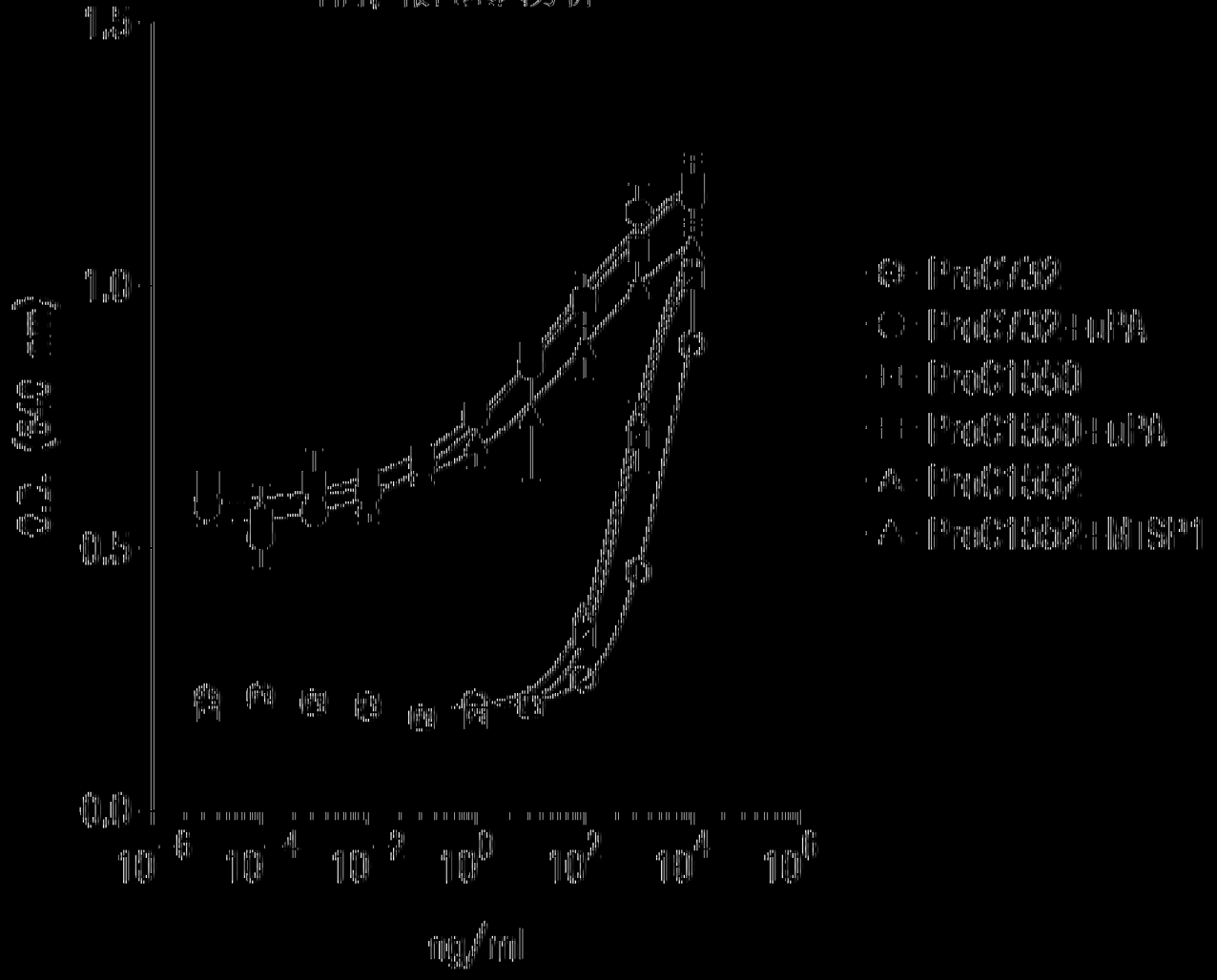
【圖 24C】


PrC232
(1905 抗體物)
VH2b
VL2b
120kDa
b/c1
k
PrC1239
VH2b
Sub
120kDa

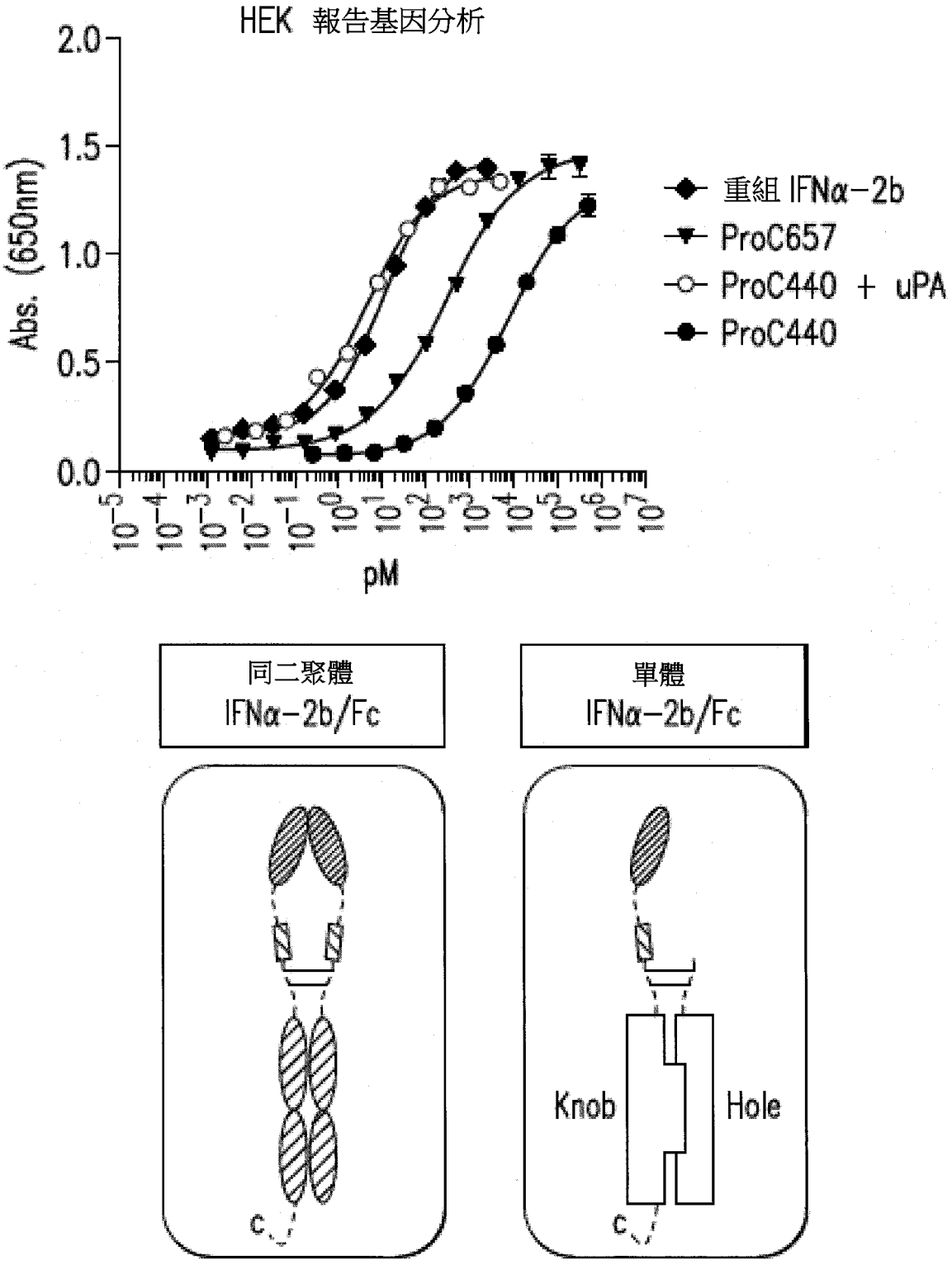

1.5
1.0
0.5
0.0
PrC232
PrC1239
結合訊號 (OD450)
10-1
10-2
10-3
10-4
10-5
10-6
ng/ml

(圖 25)

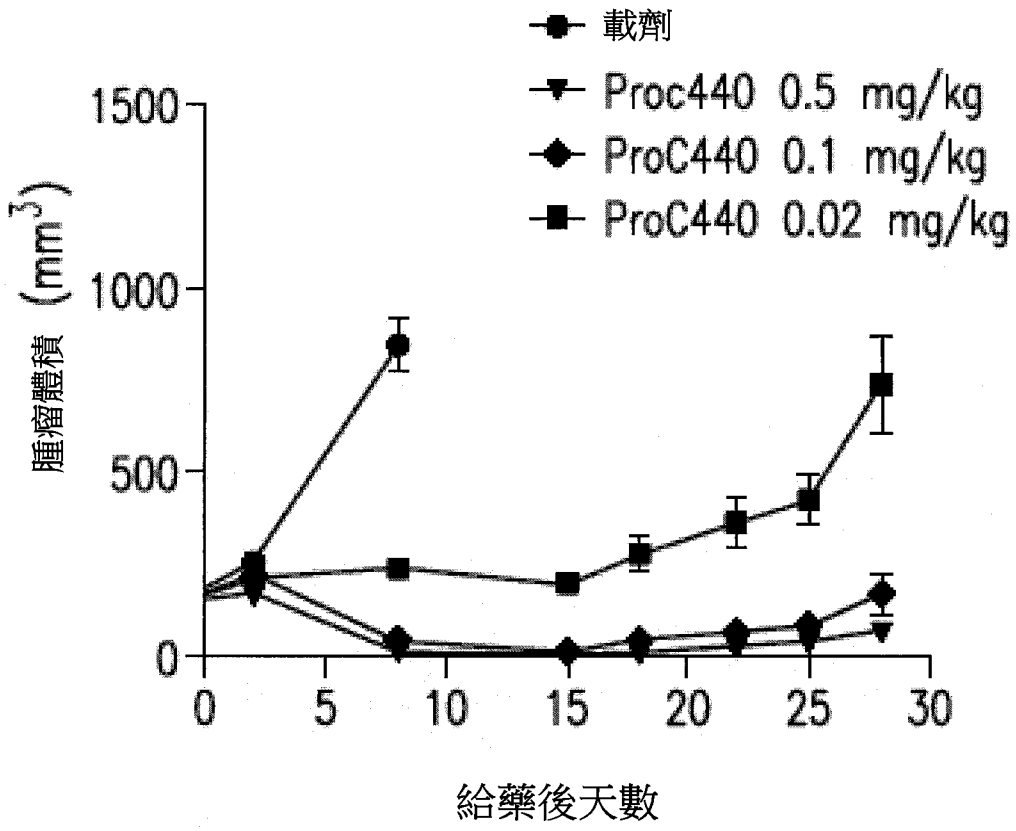
IHC 報告訊內分析

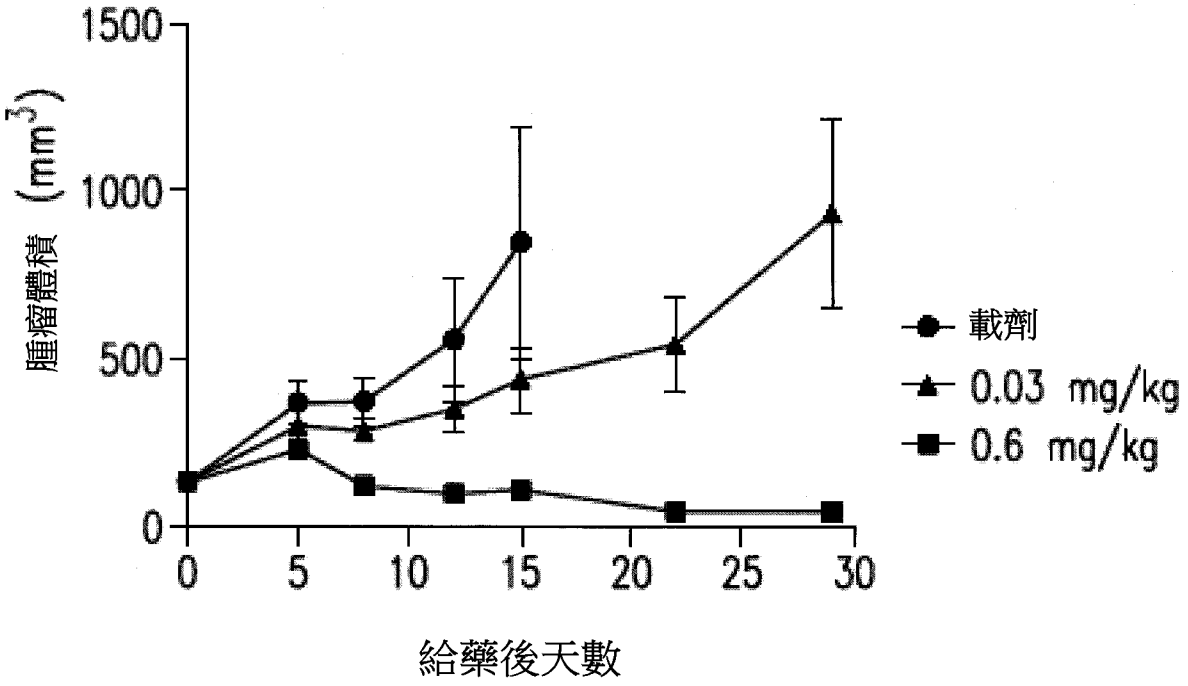


圖(Fig 26)

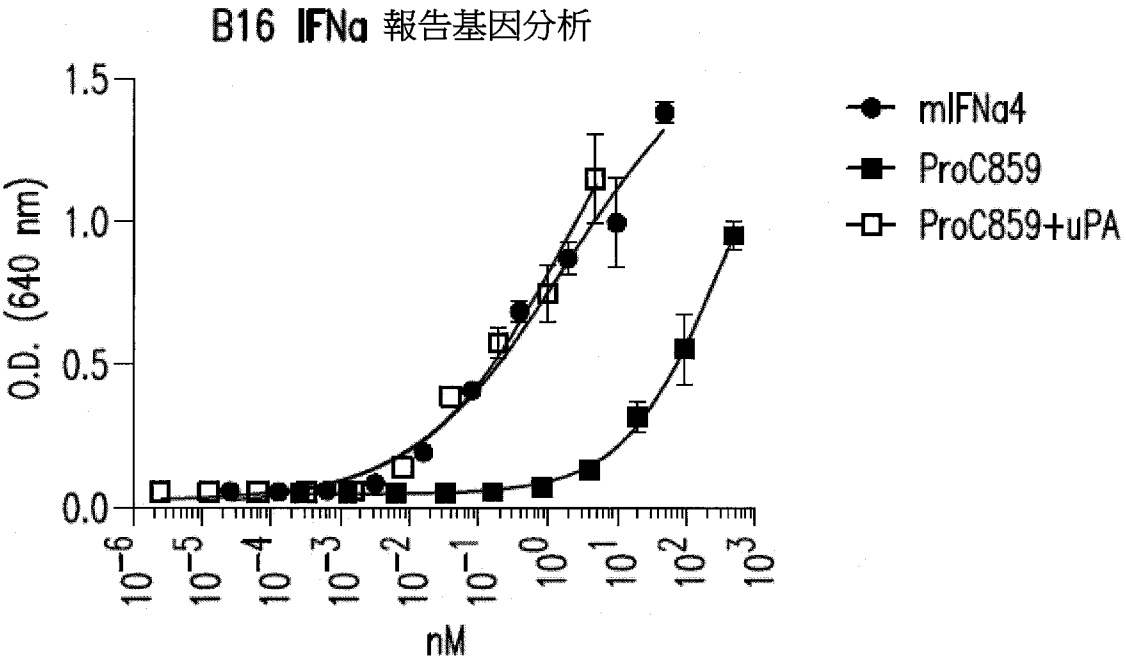

HEK 報告基因分析
Abs. (650nm)
2.0
1.5
1.0
0.5
0.0
pM
重組 IFNα-2b
ProC657
ProC440 + uPA
ProC440
同二聚體
IFNα-2b/Fc
單體
IFNα-2b/Fc
Knob
Hole
C
C

【圖 27】

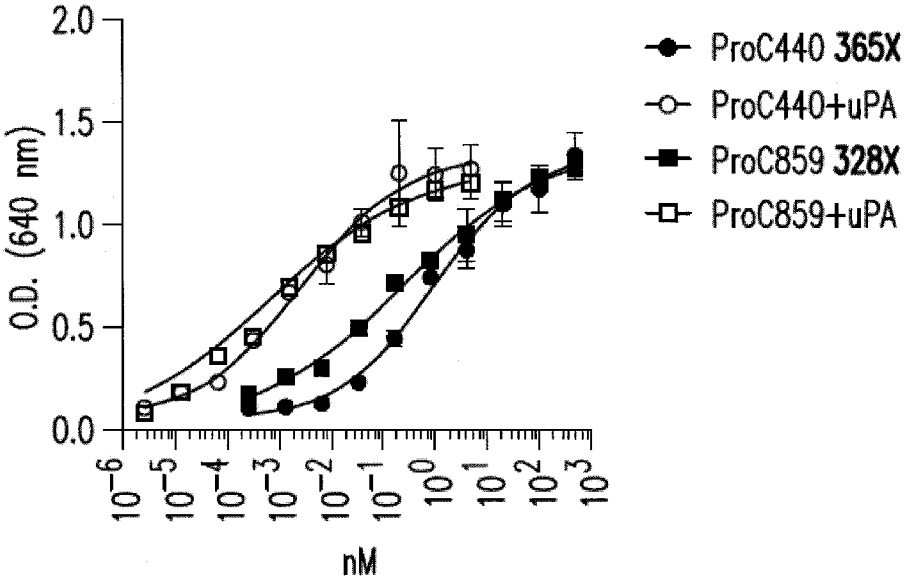

載劑
Proc440 0.5 mg/kg
ProC440 0.1 mg/kg
ProC440 0.02 mg/kg
腫瘤體積 (mm3)
1500
1000
500
0
0
5
10
15
20
25
30
給藥後天數


腫瘤體積 (mm3)
1500
1000
500
0
0
5
10
15
20
25
30
給藥後天數
載劑
0.03 mg/kg
0.6 mg/kg

【圖 28】



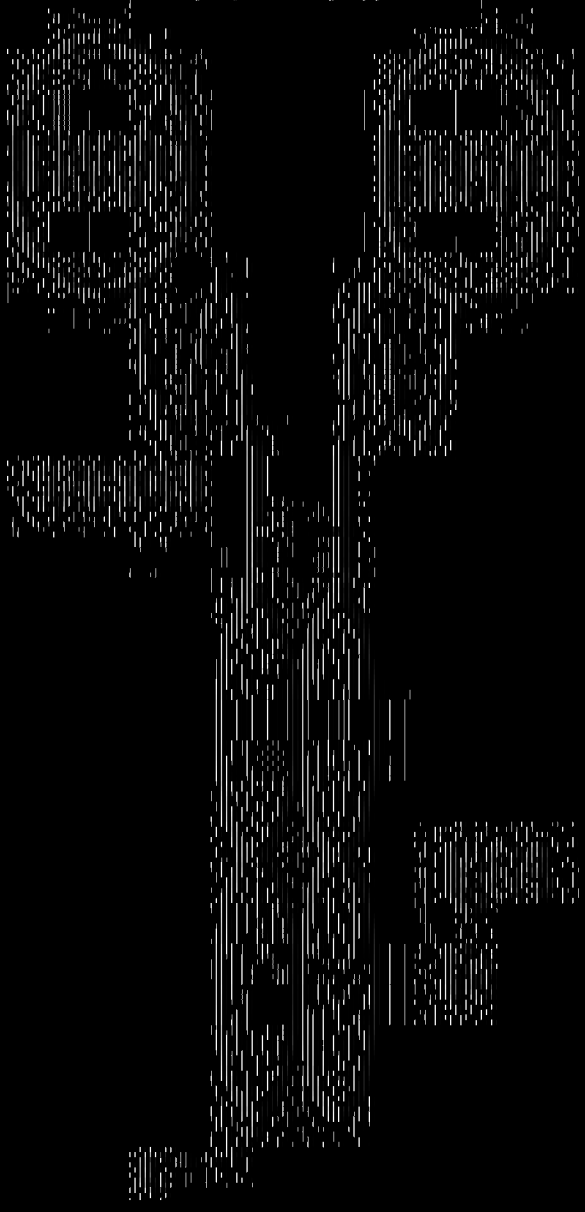
	mIFNα4	ProC859	ProC859+uPA
EC50	1.966	293.7	1.951



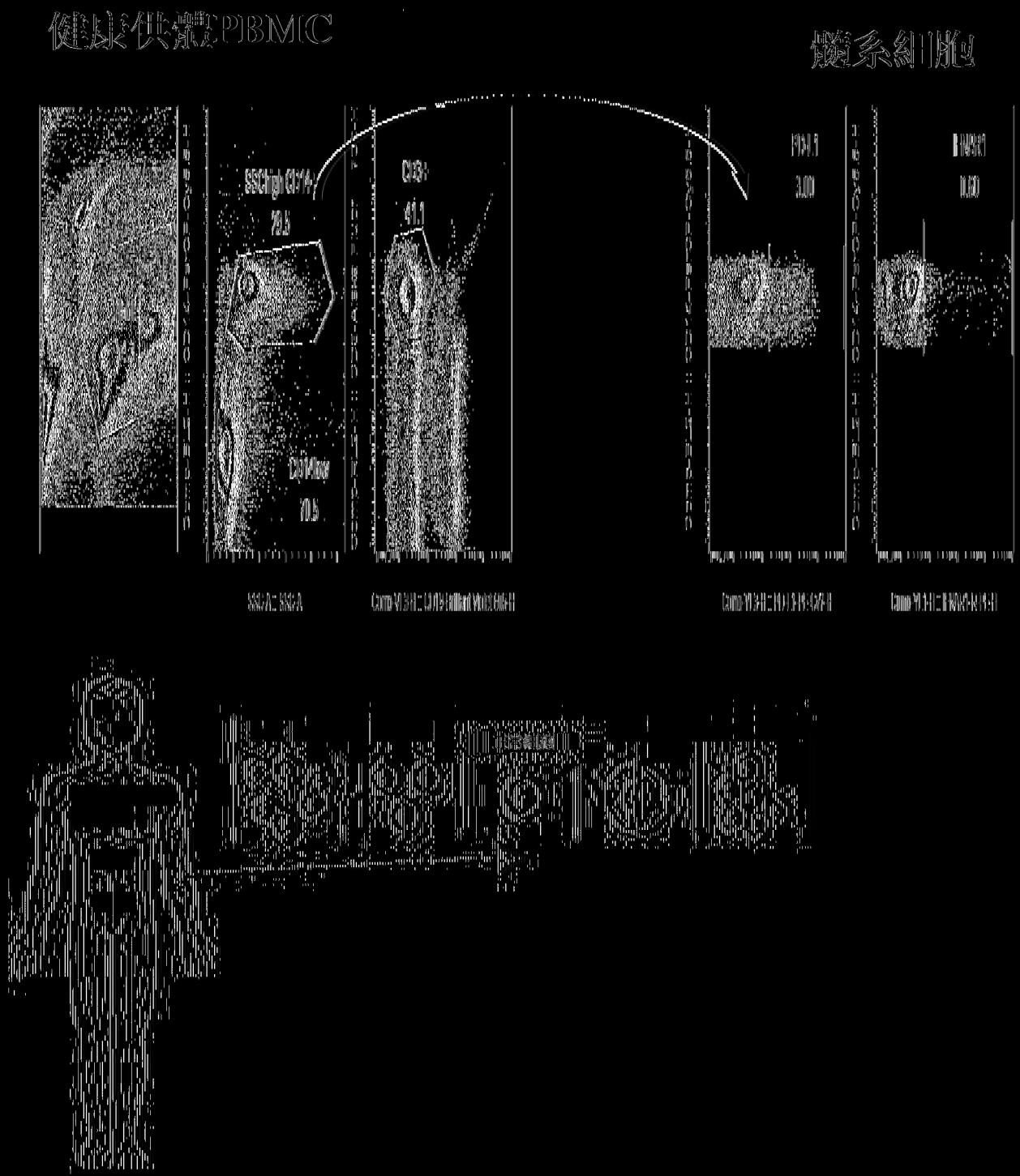
	ProC440	ProC440+uPA	ProC859	ProC859+uPA
EC50	0.9502	0.002580	0.2321	0.0006991

【圖 29】

同步裝置

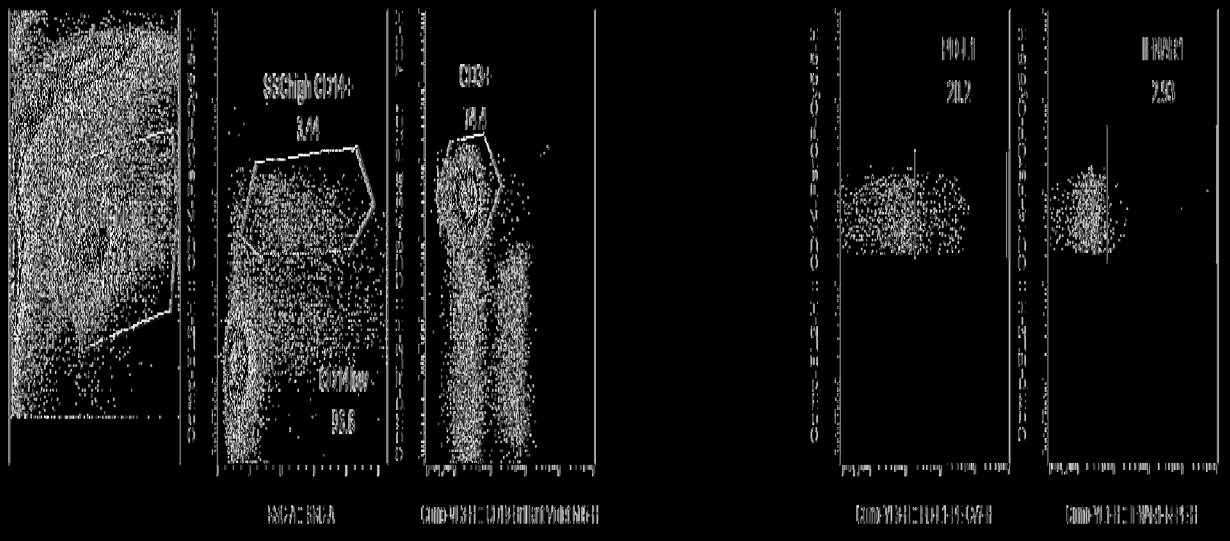


(圖 29)

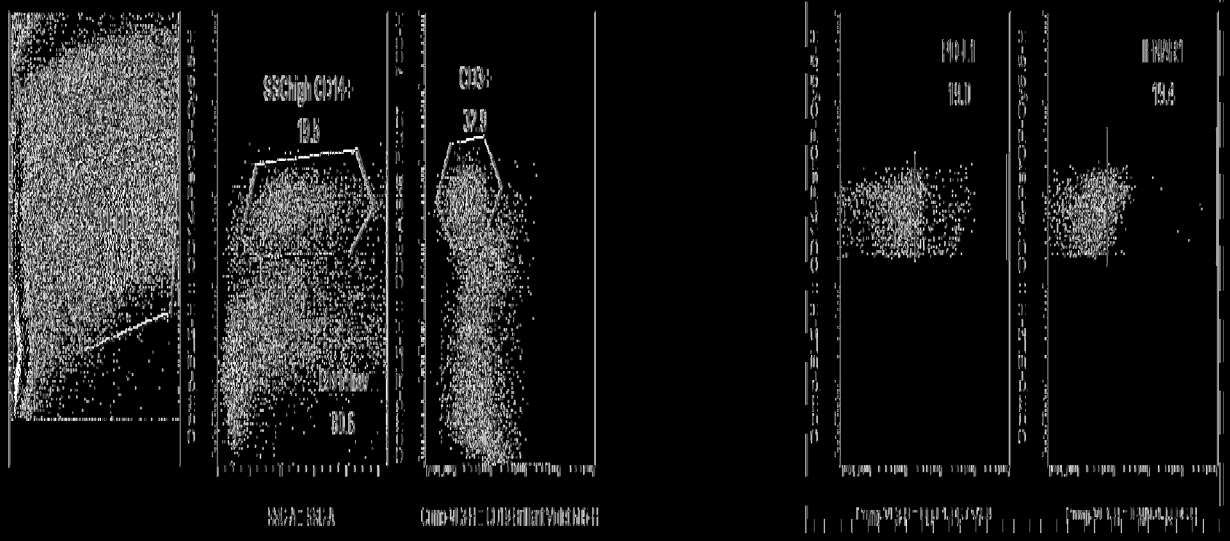

健康供體PBMC
髓系細胞
SSC-A
SSC-A
SSChigh CD14+
79.5
CD14-
70.5
CD14+
41.1
CD16+
3.000
CD16+
0.150

(圖 30)

患者之PBMC

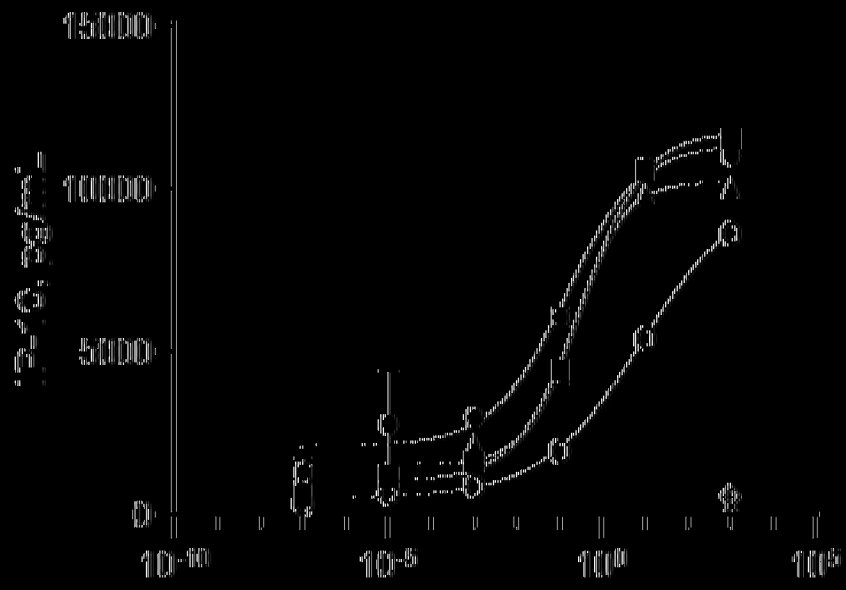


患者之經分離的腫瘤



[(圖 30)](續)

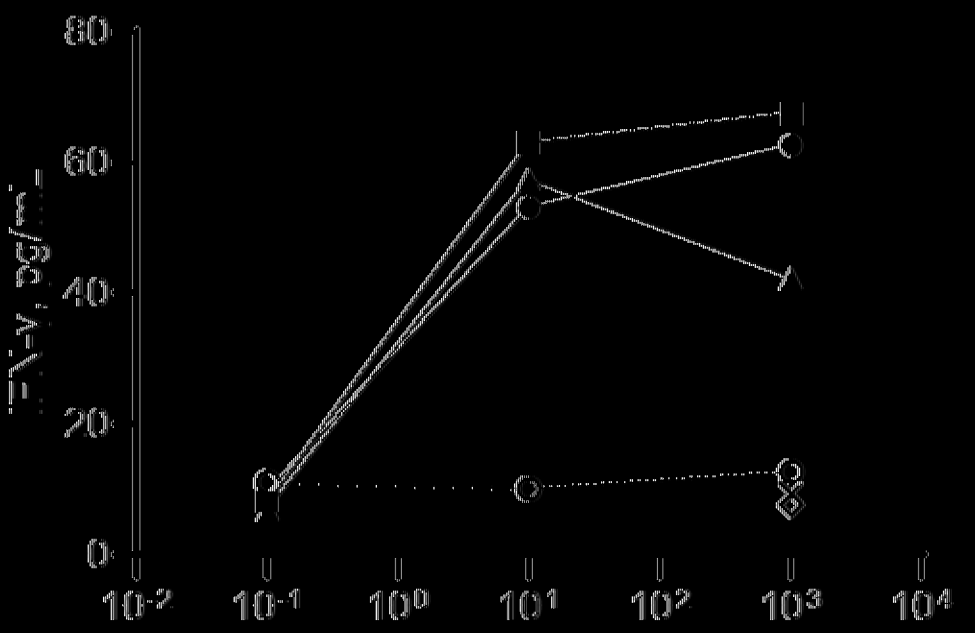
健康供體 PBMC (IFN-γ)



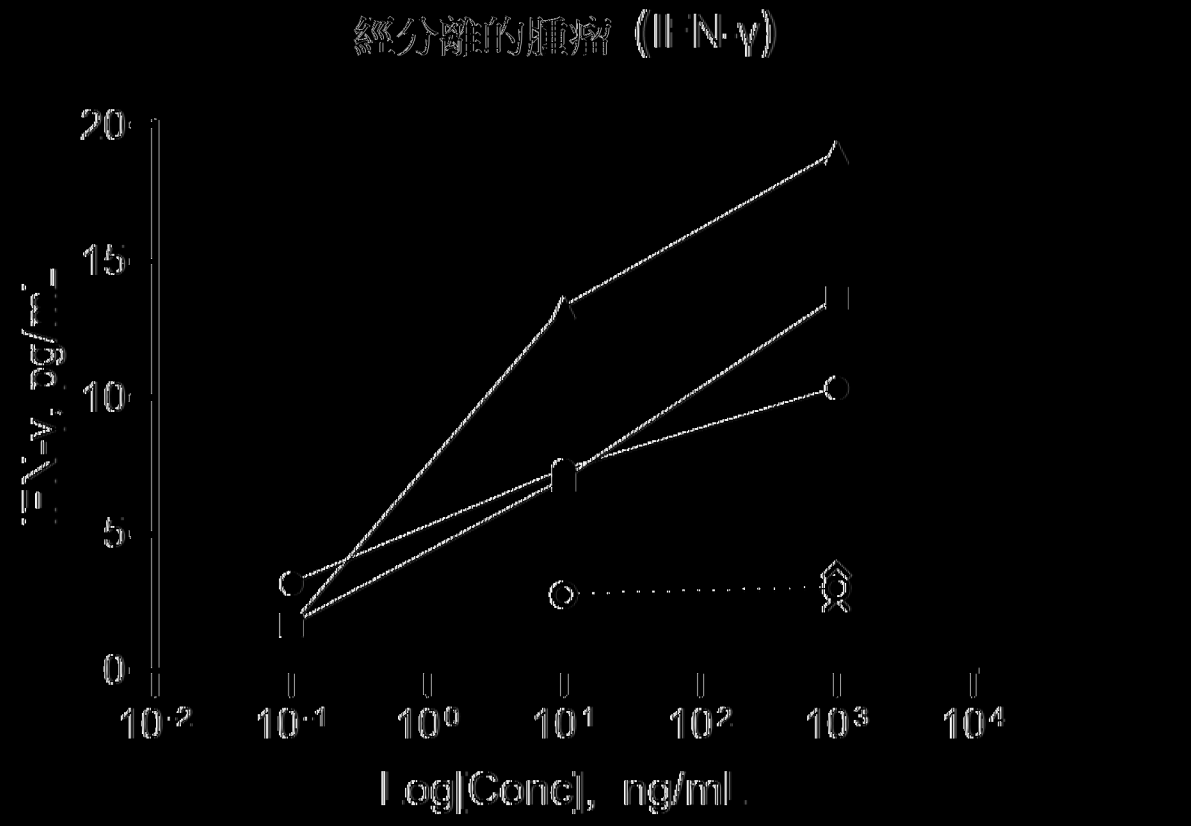
- 單獨之Sylatron
- 經變性的 Pro-II Nab
- 未經處理的
- 經天然的 Pro-II Nab
- aPD-L1, 10 ug/ml
- 經天然的 Pro-II Nab + aPD-L1

圖 31

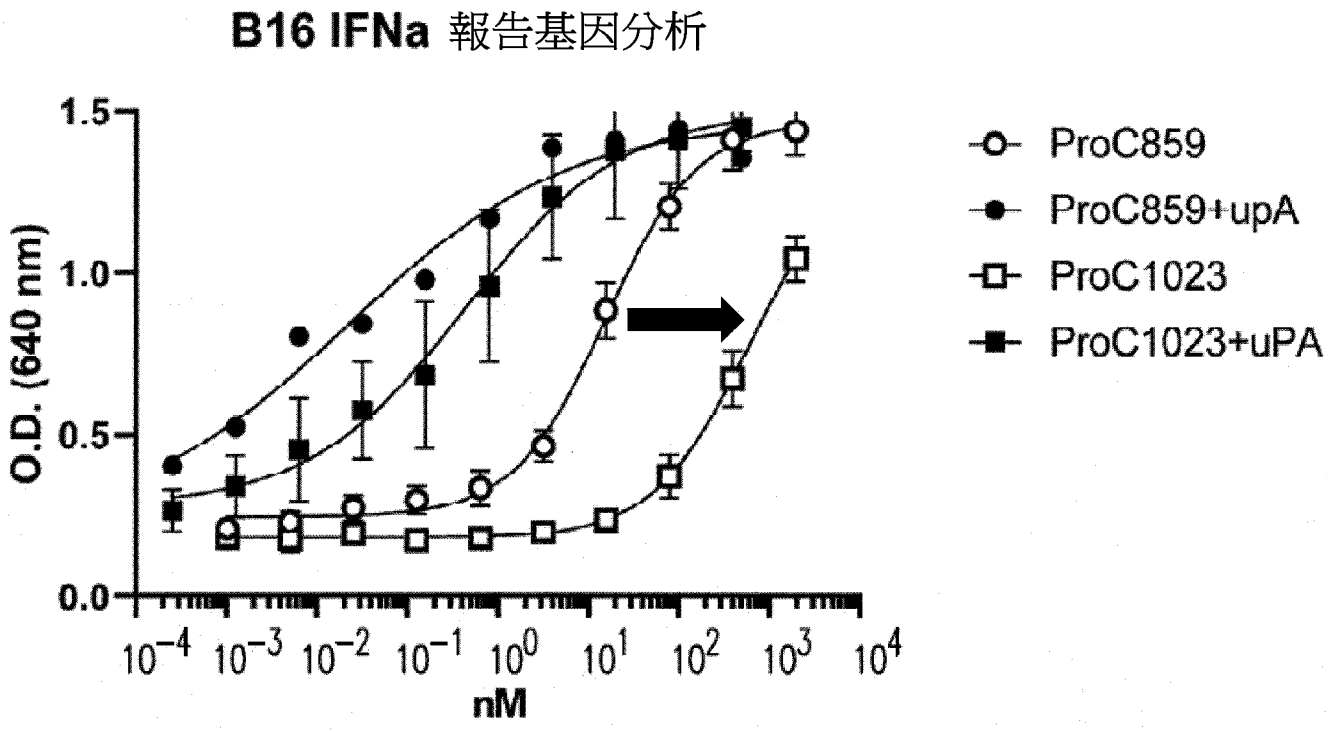
患者之 PBMC (IFN-γ)



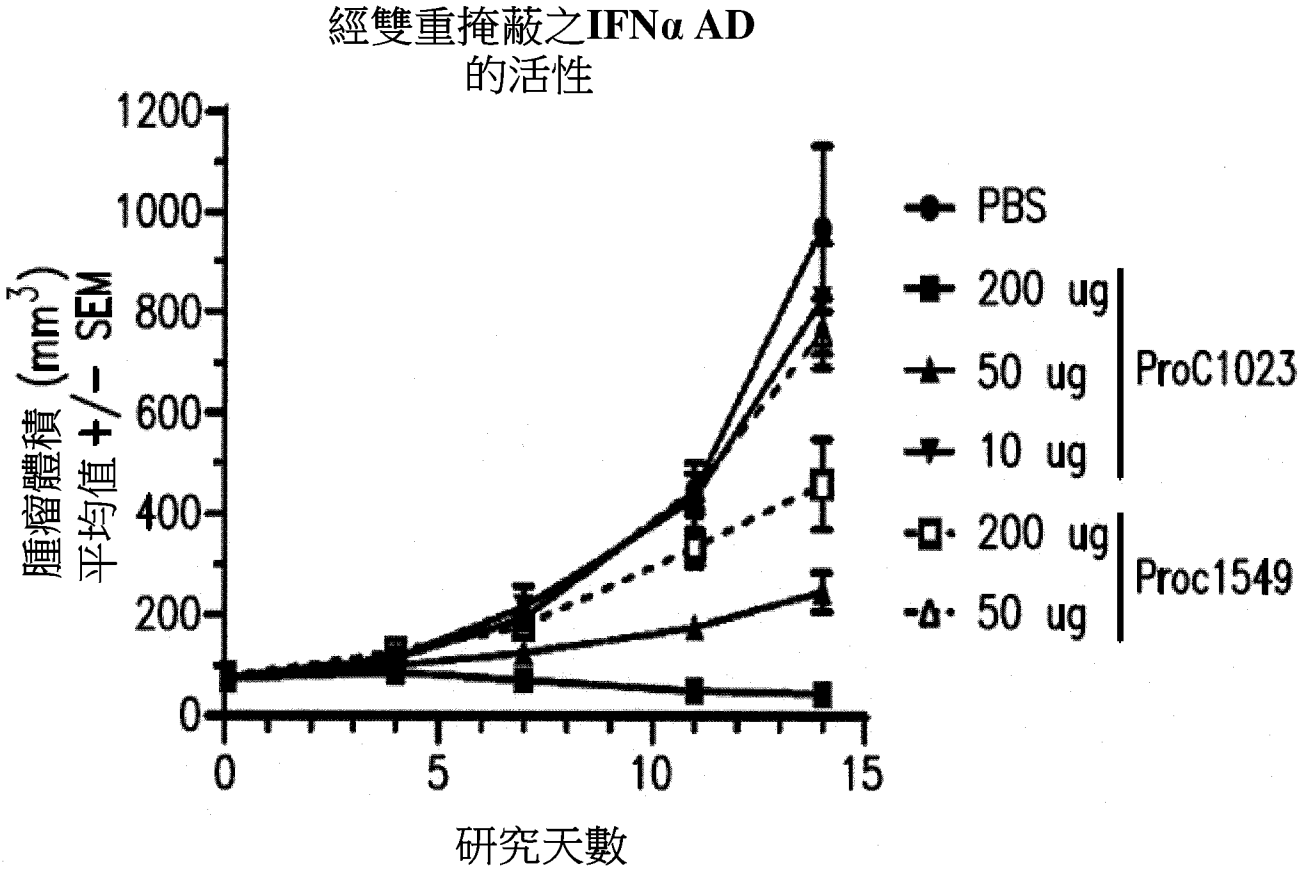
圖(圖 31) (續)


經分離的腫瘤 (II N-Y)
20
15
10
5
0
10-2
10-1
10⁰
10¹
10²
10³
10⁴
Log[Conc], ng/ml
單獨之Sylatron
經雙重抽激的II N-a2b
未經處理的
經活化的Pro-II N-a2b
aPD-L1, 10 ug/ml
經活化的II A-a2b +aPD-L1

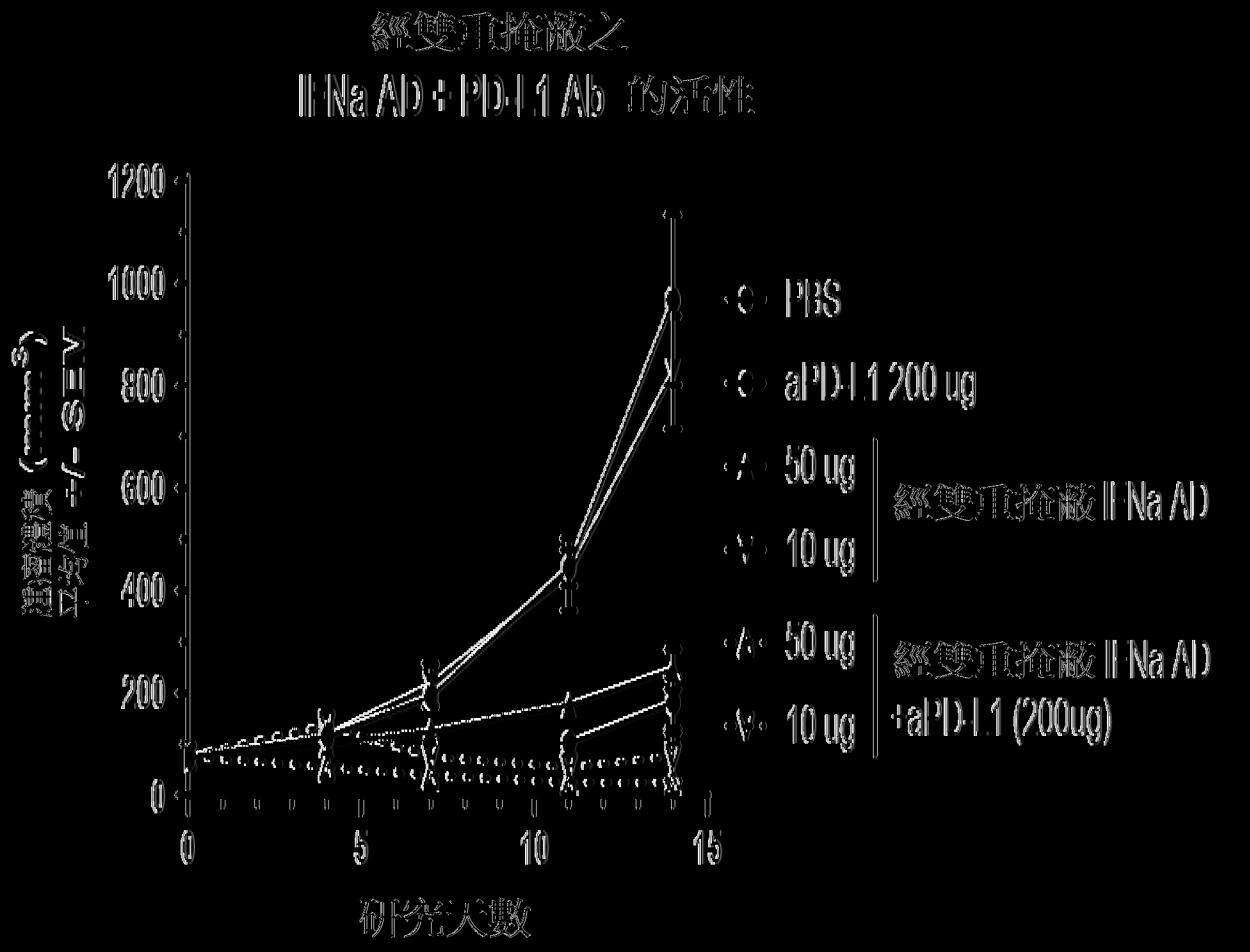
(圖 31) (續)


B16 IFNa 報告基因分析
O.D. (640 nm)
1.5
1.0
0.5
0.0
10^{-4} 10^{-3} 10^{-2} 10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4}
nM
ProC859
ProC859+upA
ProC1023
ProC1023+uPA

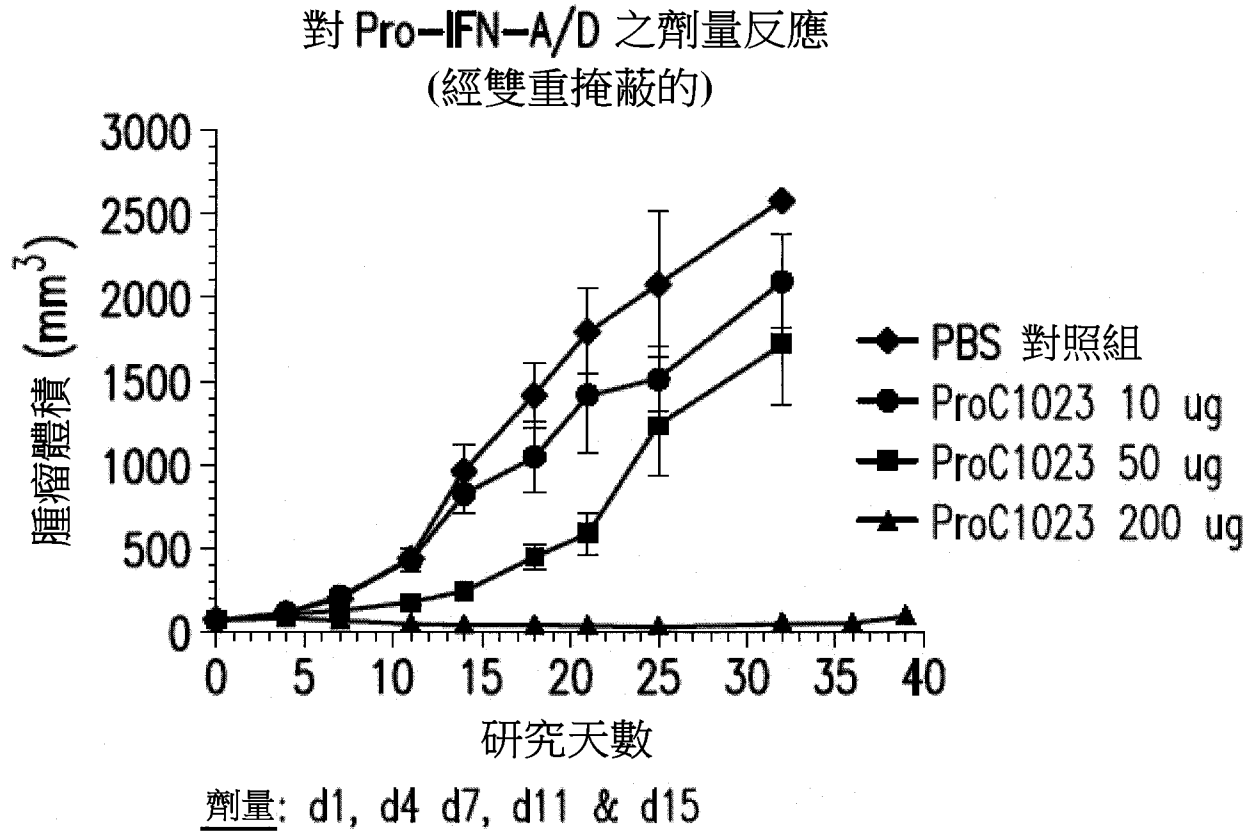
【圖 32】


經雙重掩蔽之IFNα AD
的活性
腫瘤體積 (mm3)
平均值 +/- SEM
1200
1000
800
600
400
200
0
0
5
10
15
研究天數
PBS
200 ug
50 ug
10 ug
ProC1023
200 ug
50 ug
Proc1549

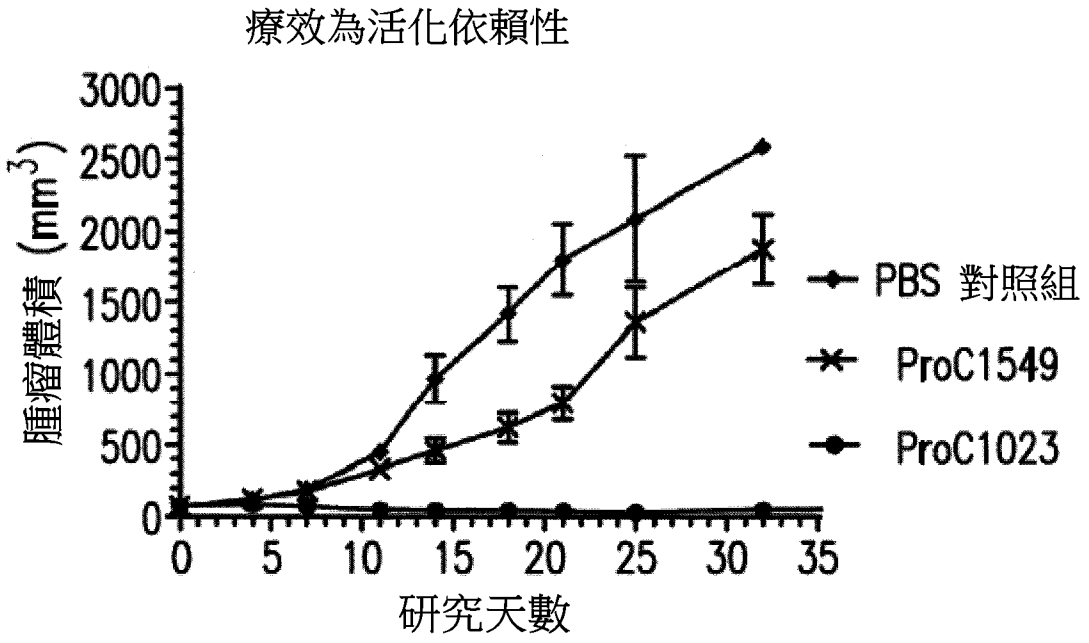
【圖 33A】


經雙重抗敵之
Ⅱ Na Al) + PD-L1 Ab 的活性
腫瘤體積 (mm3)
1200
1000
800
600
400
200
0
0
5
10
15
研究天數
PBS
aPD-L1 200 ug
50 ug
10 ug
經雙重抗敵Ⅱ Na Al)
50 ug
10 ug
經雙重抗敵Ⅱ Na Al)
+aPD-L1 (200ug)

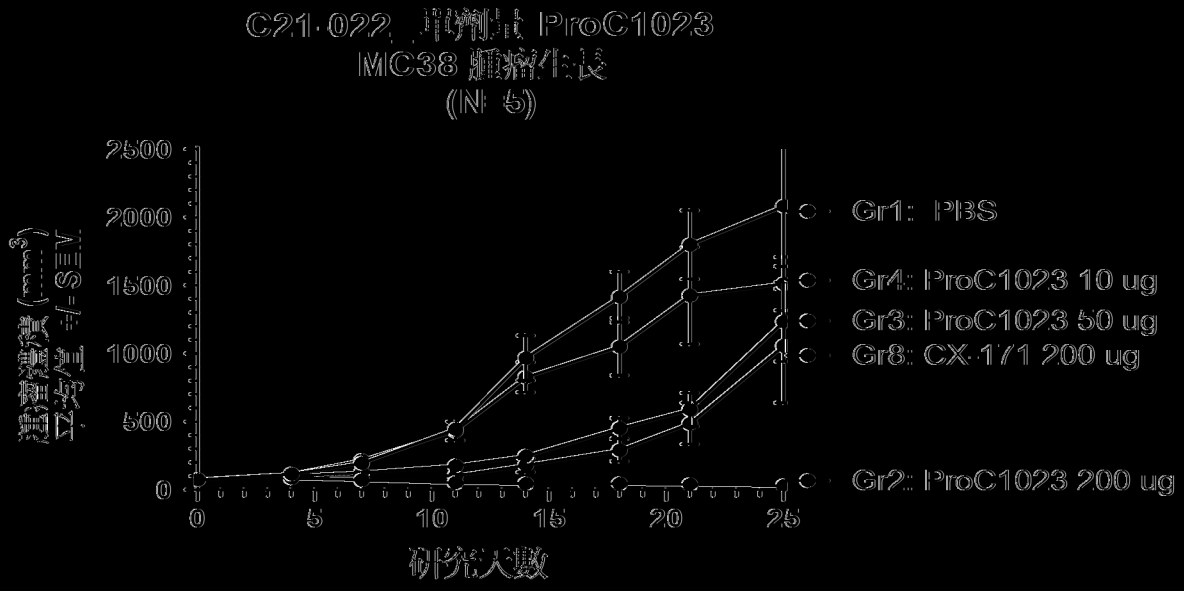
[圖 33B]


對 Pro-IFN-A/D 之劑量反應
(經雙重掩蔽的)
腫瘤體積 (mm3)
3000
2500
2000
1500
1000
500
0
0 5 10 15 20 25 30 35 40
研究天數
PBS 對照組
ProC1023 10 ug
ProC1023 50 ug
ProC1023 200 ug
劑量: d1, d4 d7, d11 & d15

【圖 34A】

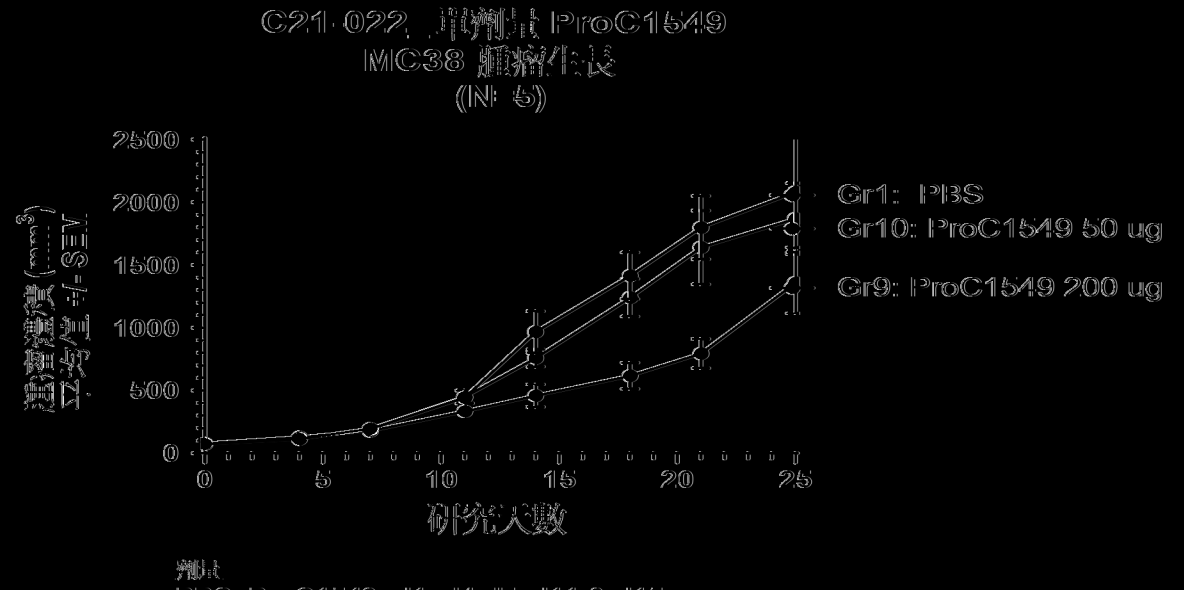

療效為活化依賴性
腫瘤體積 (mm3)
3000
2500
2000
1500
1000
500
0
0 5 10 15 20 25 30 35
研究天數
PBS 對照組
ProC1549
ProC1023

【圖 34B】



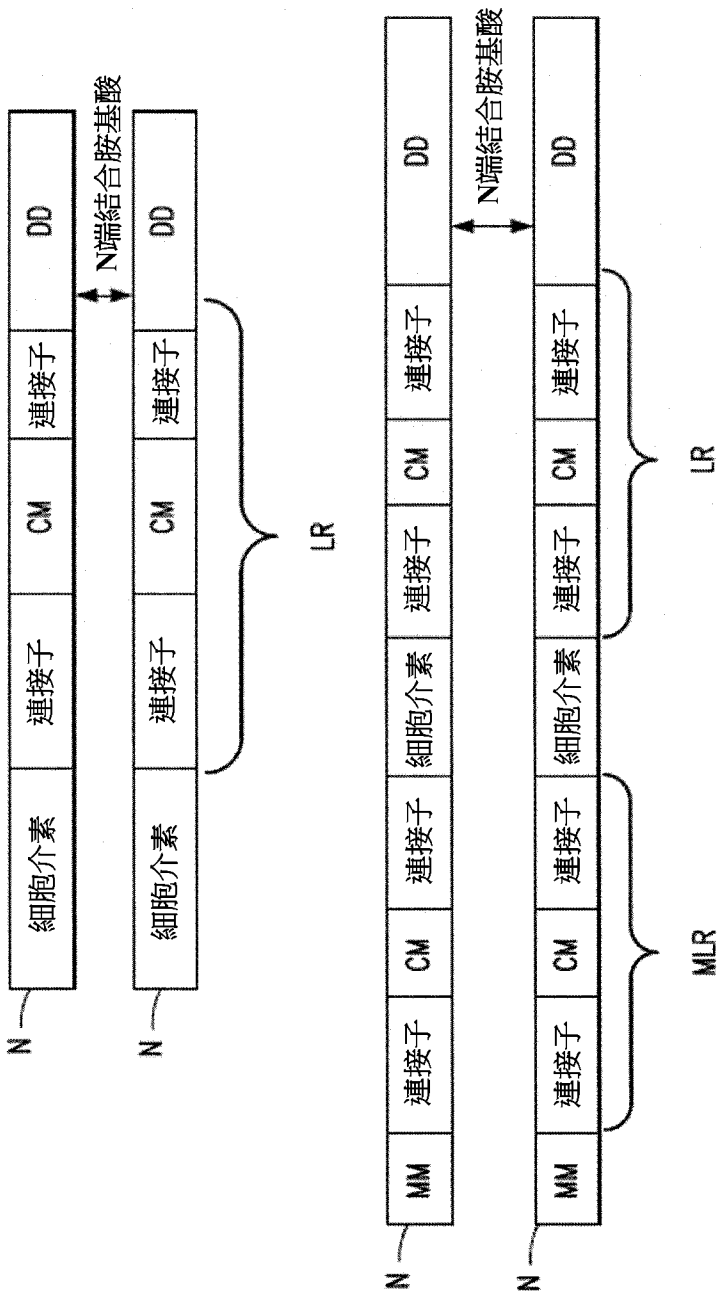
劑量
PBS, ProC1023: d1, d4 d7, d11 & d15
CX-171: d1, d7 & d15

|(圖 35A)|



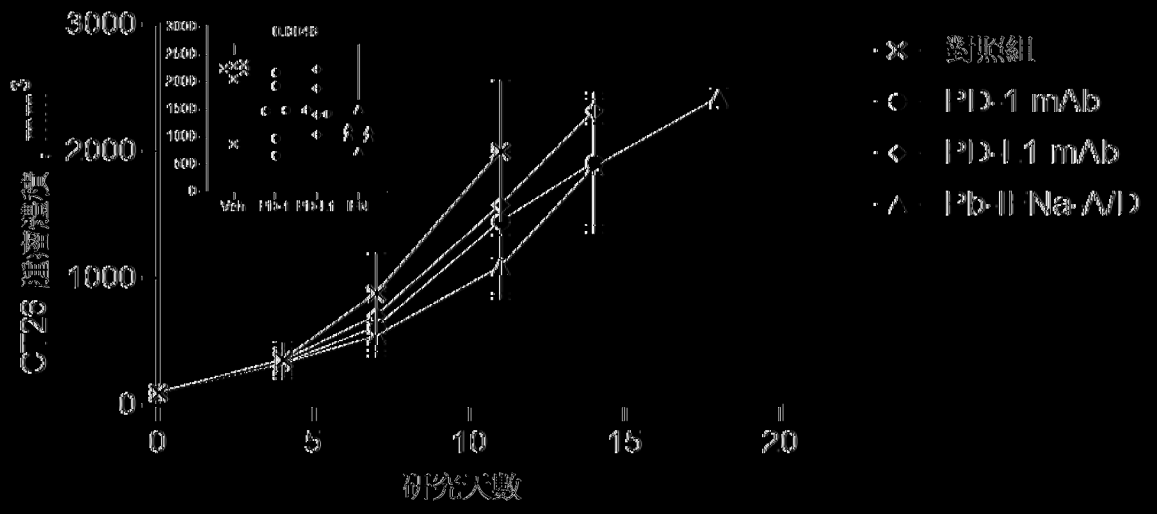
劑量
PBS, ProC1549: d1, d4 d7, d11 & d15

|(圖 35B)|

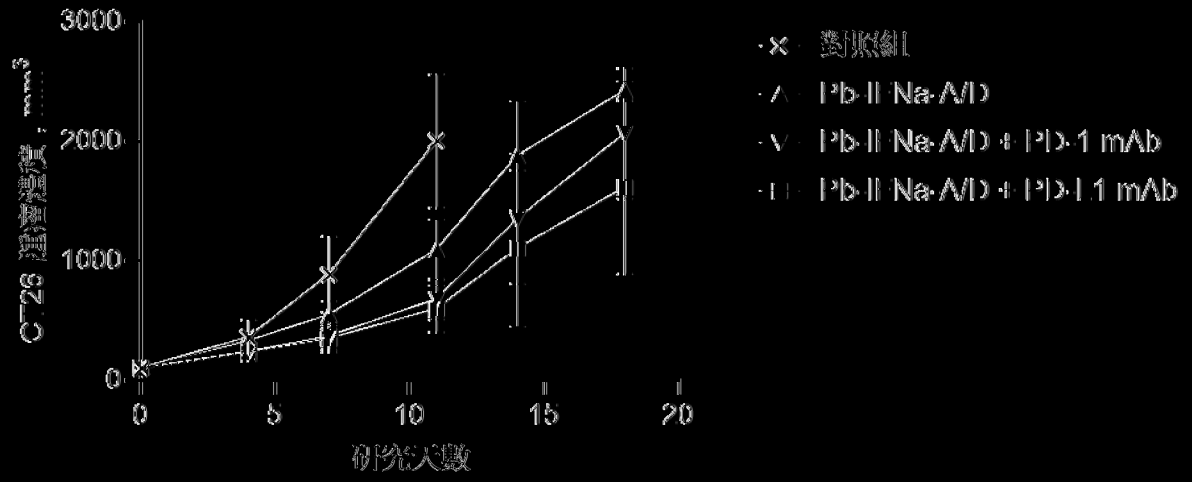

N
細胞介素
連接子
CM
連接子
DD
N端結合胺基酸
N
細胞介素
連接子
CM
連接子
DD
LR
N
MM
連接子
CM
連接子
細胞介素
連接子
CM
連接子
DD
N端結合胺基酸
N
MM
連接子
CM
連接子
細胞介素
連接子
CM
連接子
DD
MLR
LR

【圖 36】

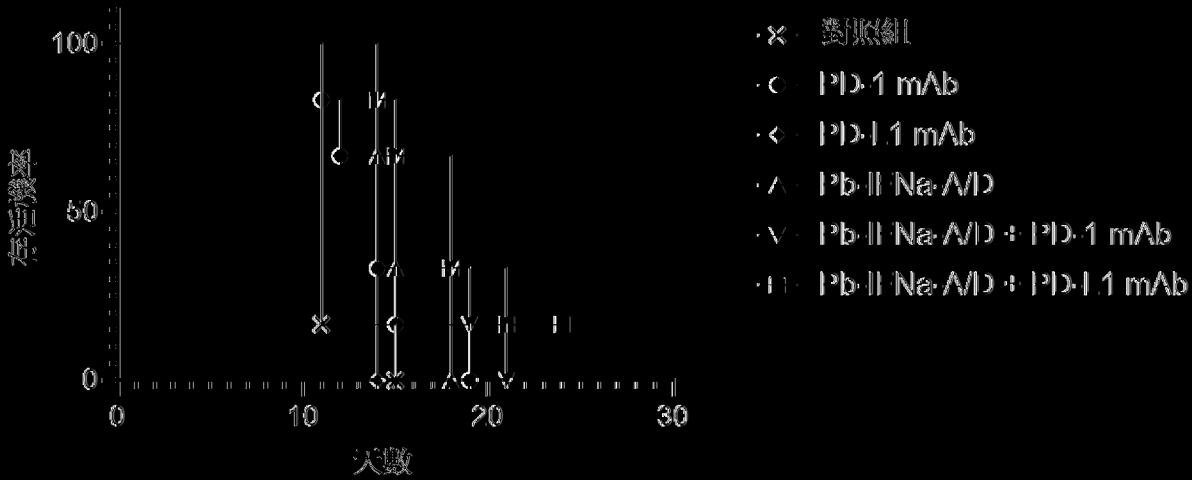
C126 單一療法



C126: Pb-II Na + PD-(L)1 組合

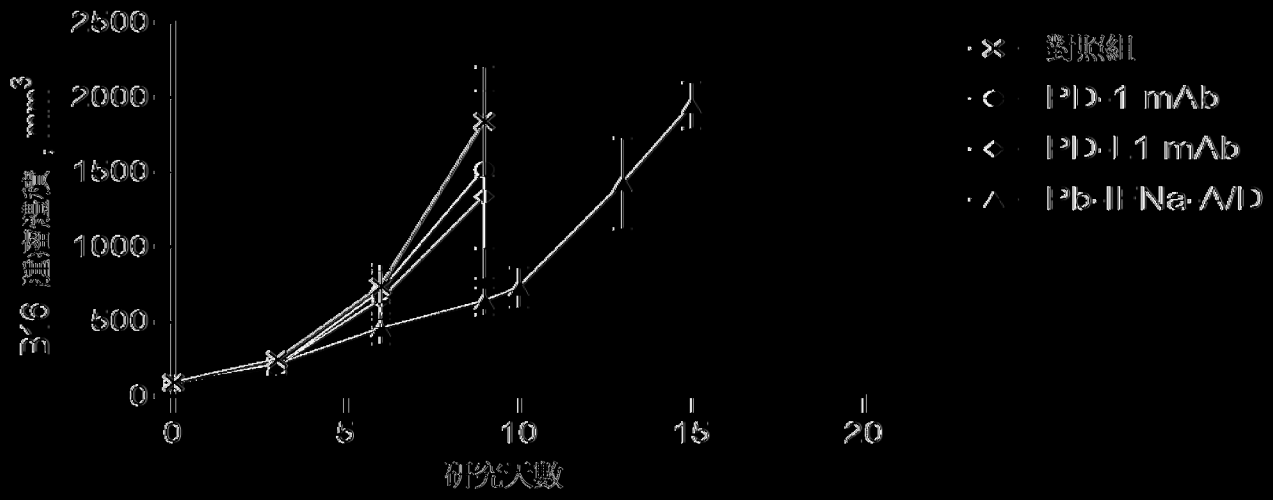


C126: 存活的

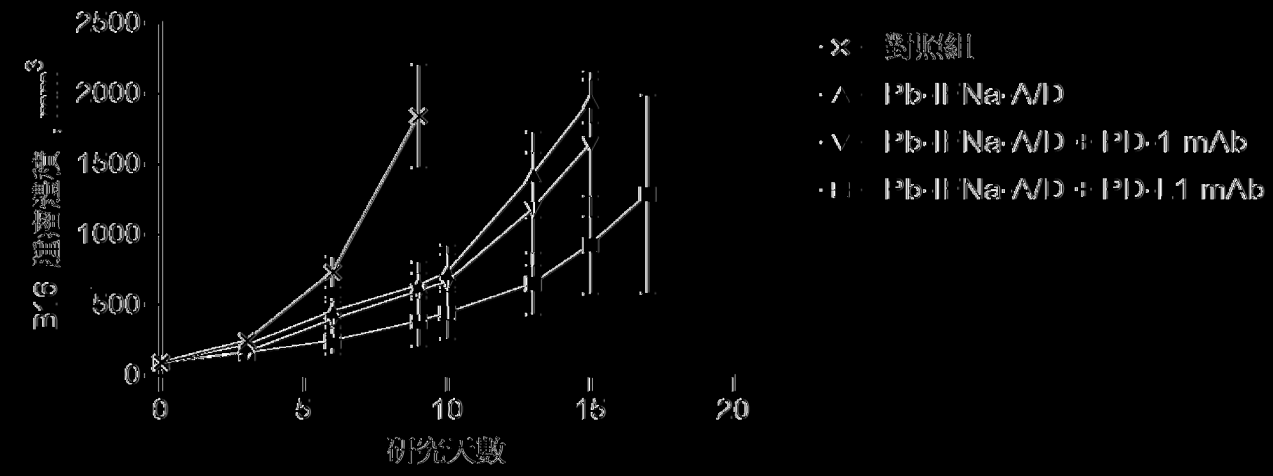


[圖 37]

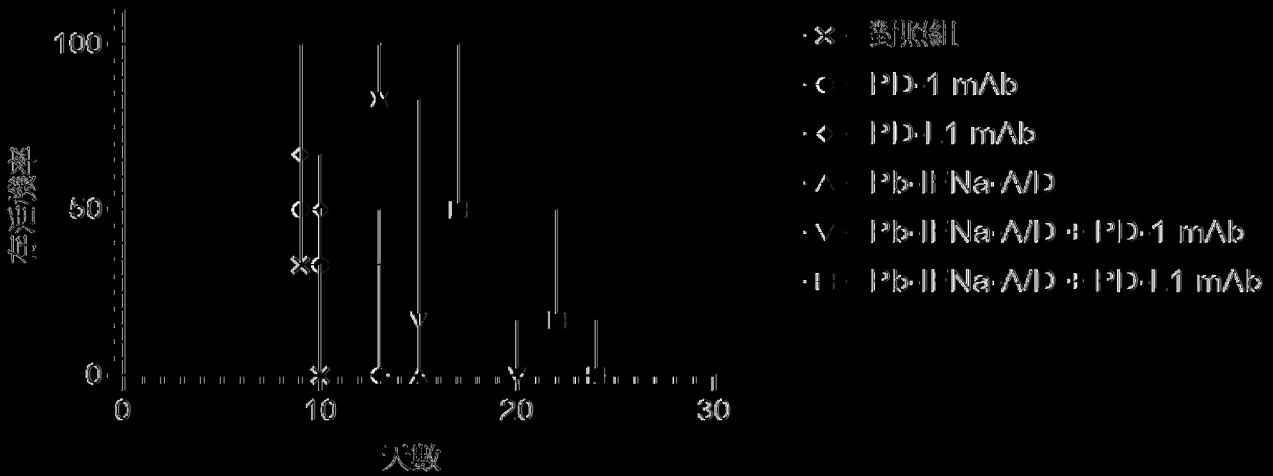
B16 單一療法



B16: Pb-II Na + PD-(L)1 組合



B16: 存活的



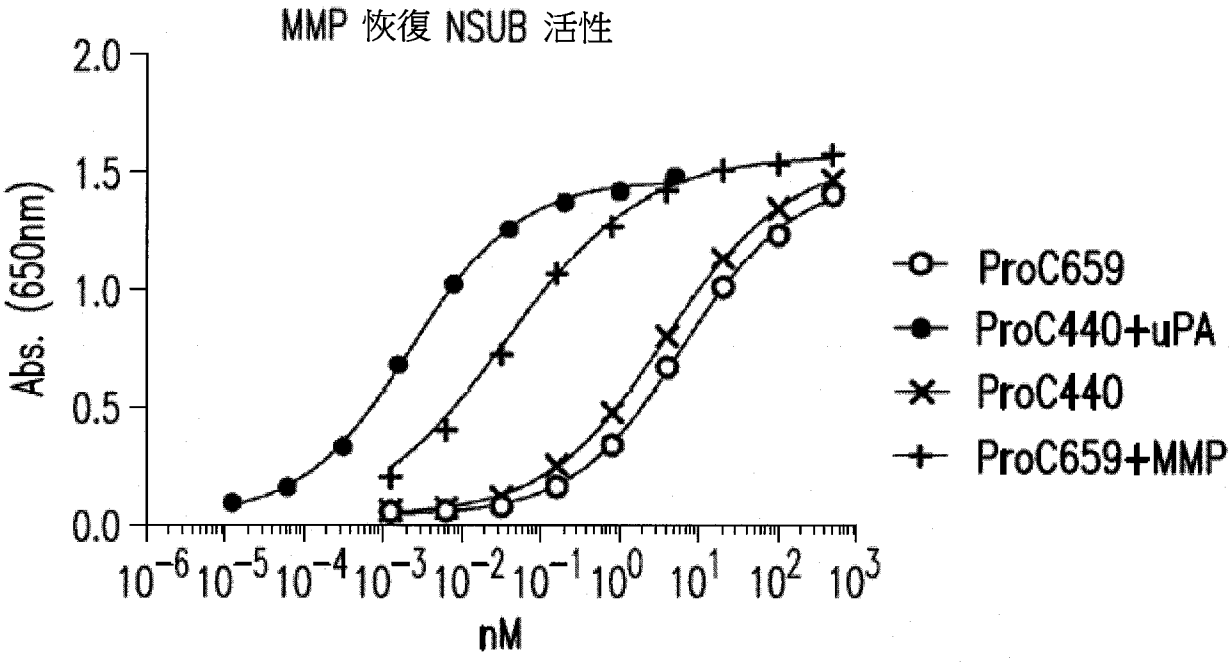
[圖 37] (續)

（第 38A）

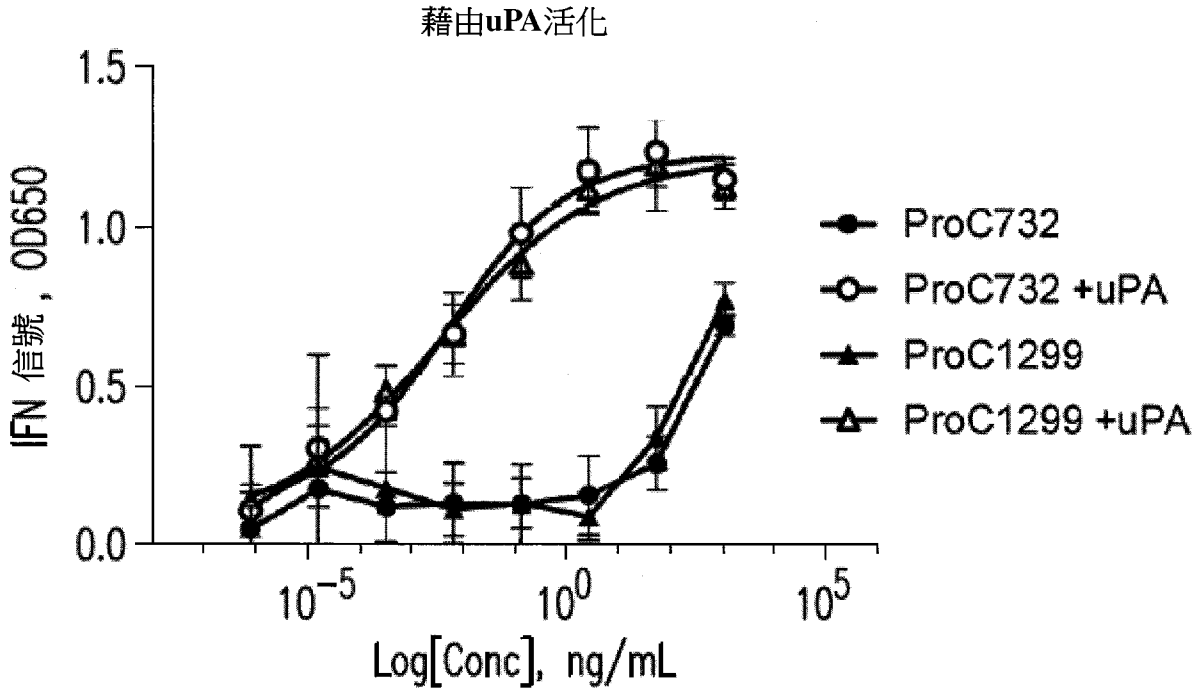
(383)
(試驗物)
(試驗物)
(試驗物

(圖3B)
(圖3A)
分子量
相對豐度
分子量
相對豐度

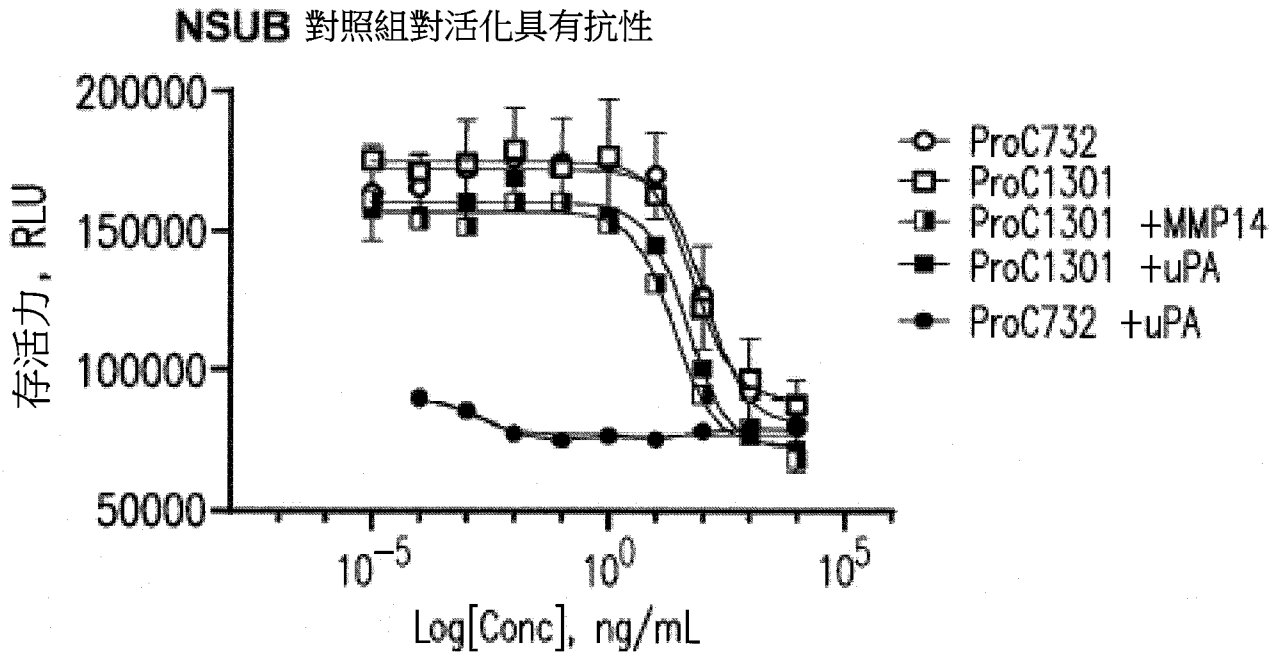
(式3)
(式3)
(式3)


MMP 恢復 NSUB 活性
Abs. (650nm)
2.0
1.5
1.0
0.5
0.0
10^{-6} 10^{-5} 10^{-4} 10^{-3} 10^{-2} 10^{-1} 10^{0} 10^{1} 10^{2} 10^{3}
nM
ProC659
ProC440+uPA
ProC440
ProC659+MMP

【圖 39A】


藉由uPA活化
IFN 信號，OD650
1.5
1.0
0.5
0.0
10^{-5}
10^{0}
10^{5}
Log[Conc], ng/mL
ProC732
ProC732 +uPA
ProC1299
ProC1299 +uPA

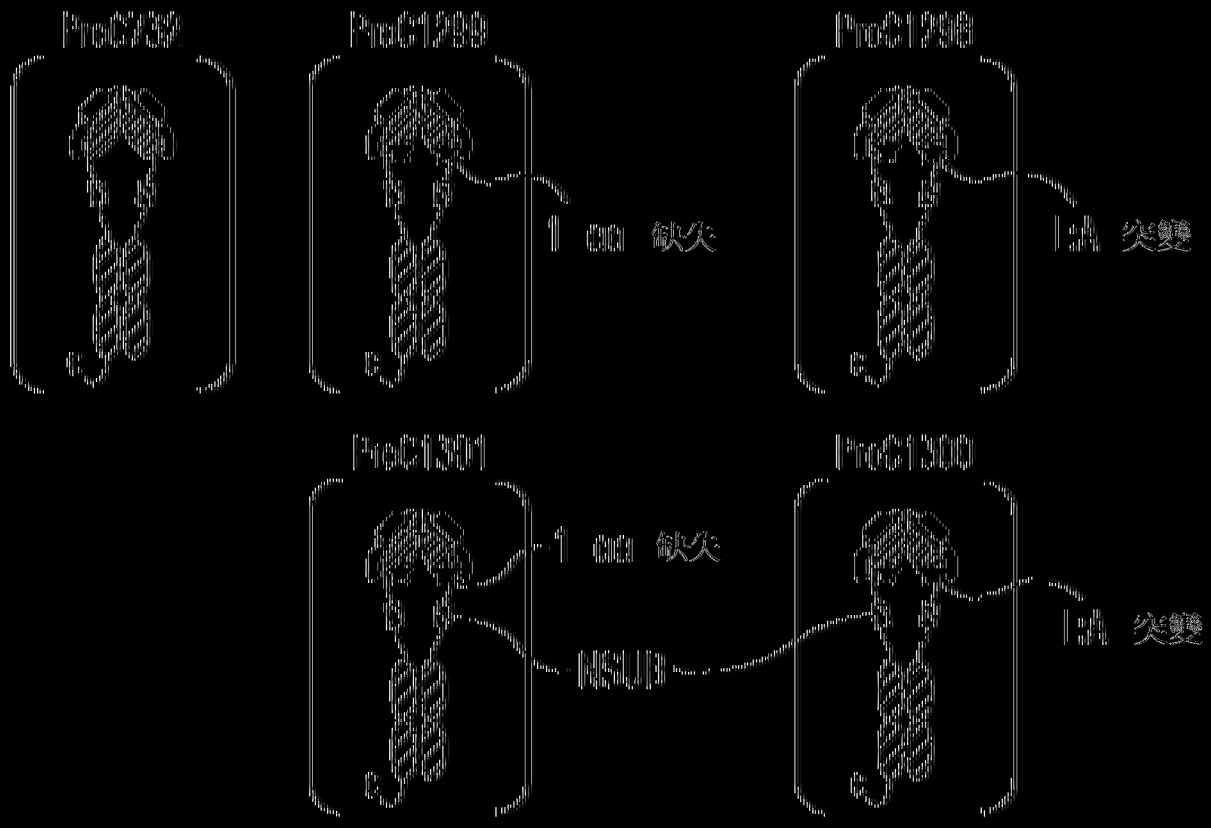
【圖 39B】




```
IFNa2b  1    CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMI  60
             CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMI
IFNaAD  1    CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMI  60

IFNa2b  61   QQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVR  120
             QQIFNLF+TKDSSAAWDE LLDKF TELYQQLNDLEACV+Q   V ETPLM  DSILAV+
IFNaAD  61   QQIFNLFTTKDSSAAWDEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMNVDSILAVK  120
                                                    |   |L161 (MMP14 裂解 )
IFNa2b  121  KYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE  165
             KYF+RITLYL EKKYSPCAWEVVRAEIMRS SLSTNLQE LR KE
IFNaAD  121  KYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE  165
                                                    |   |
                                                    L157 & 161 ( 預測之 MMP12 裂解 )
```

【圖 39C】


ProC39
ProC1298
1 aa 缺失
ProC1296
插入 突變
ProC1301
1 aa 缺失
HSUP
ProC1300
插入 突變

|(Pro 39C)| (續)

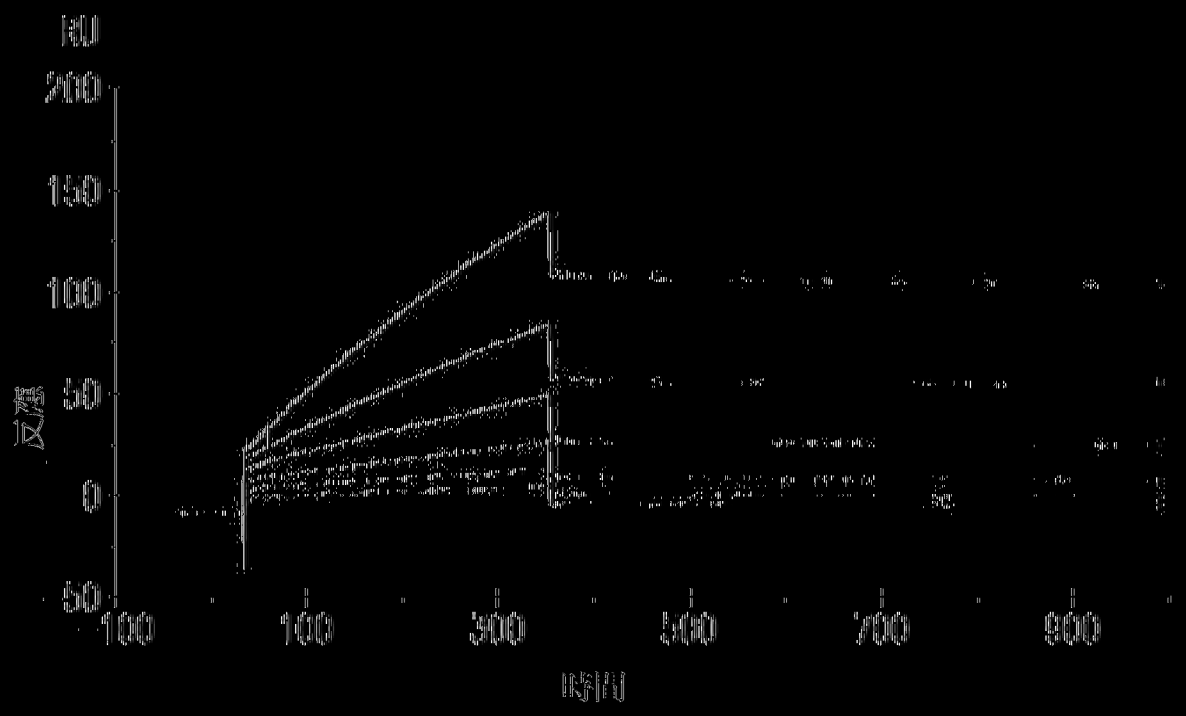

60
200
150
100
50
0
-50
100
100
300
500
700
900
時間

圖 40A

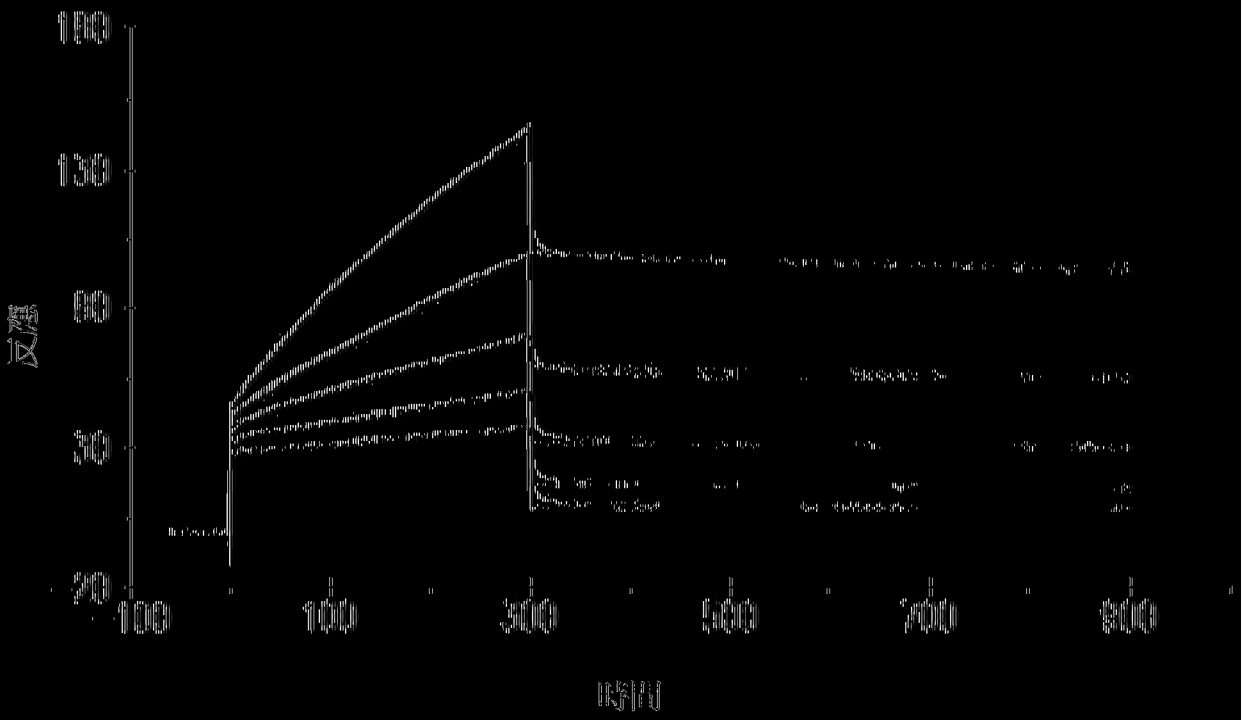

110
130
90
70
50
30
10
100
100
300
500
700
900
時間

圖 40B

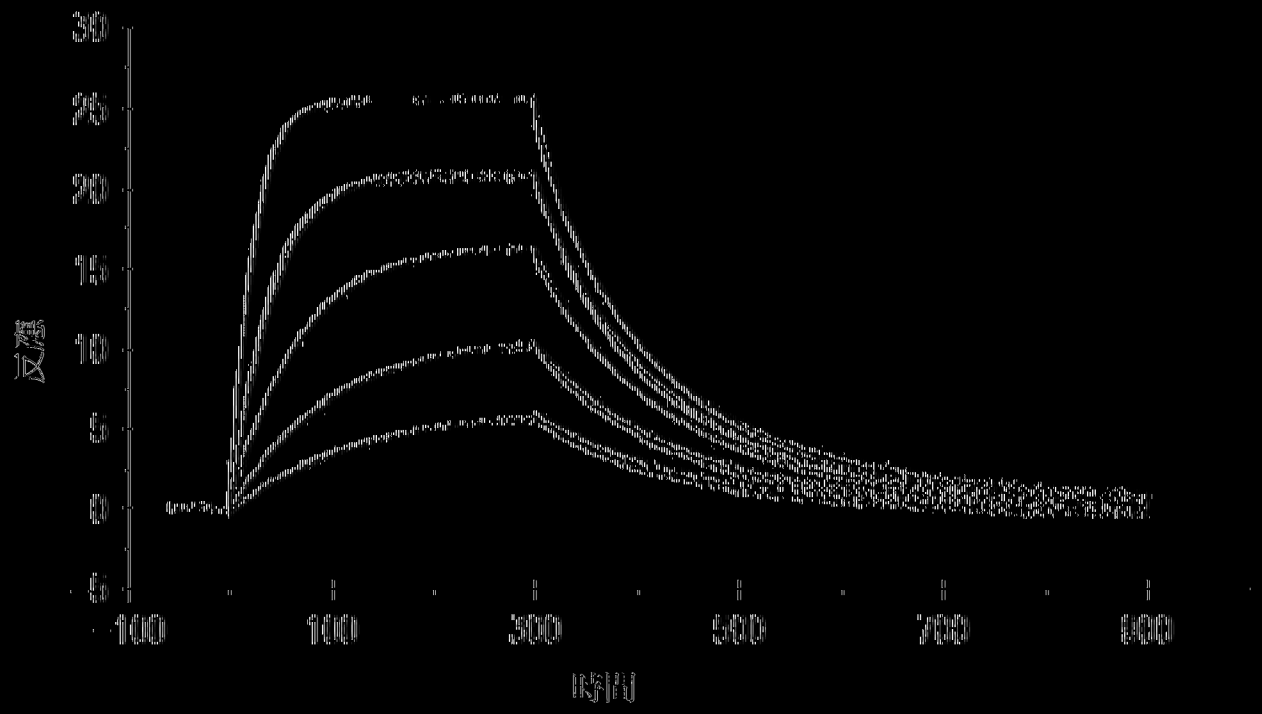

30
25
20
15
10
5
0
-5
100
100
300
500
700
900
時間

圖 40C

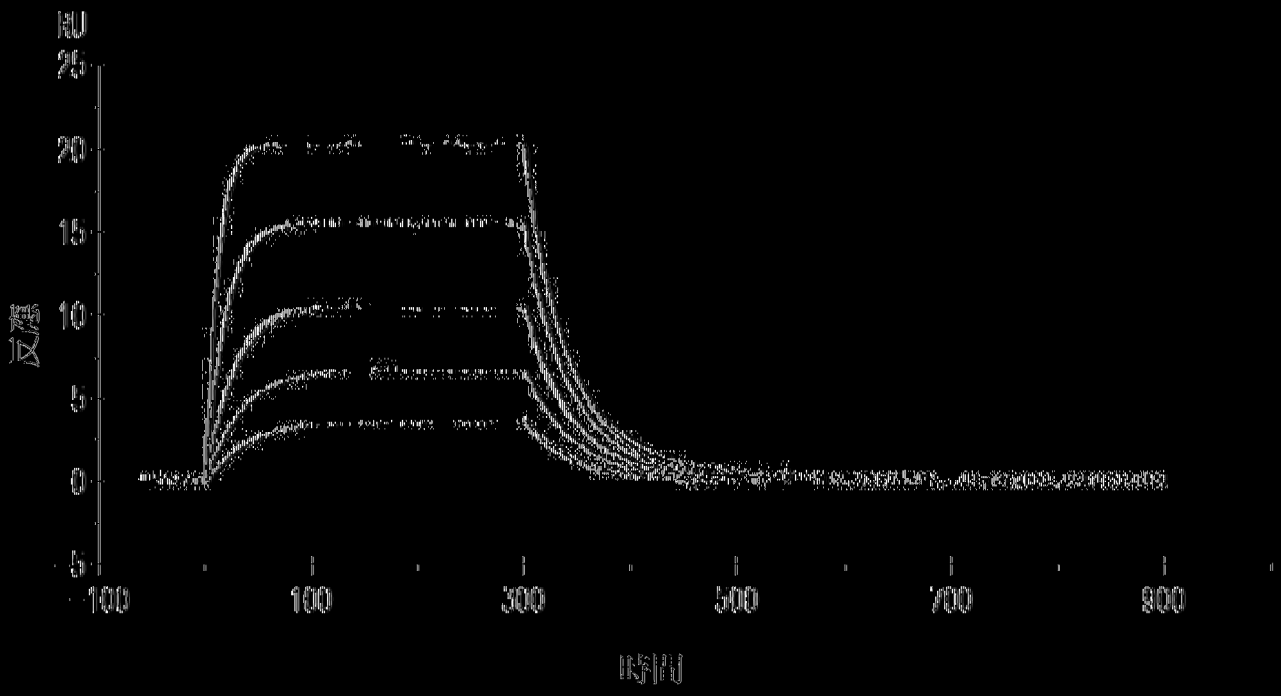
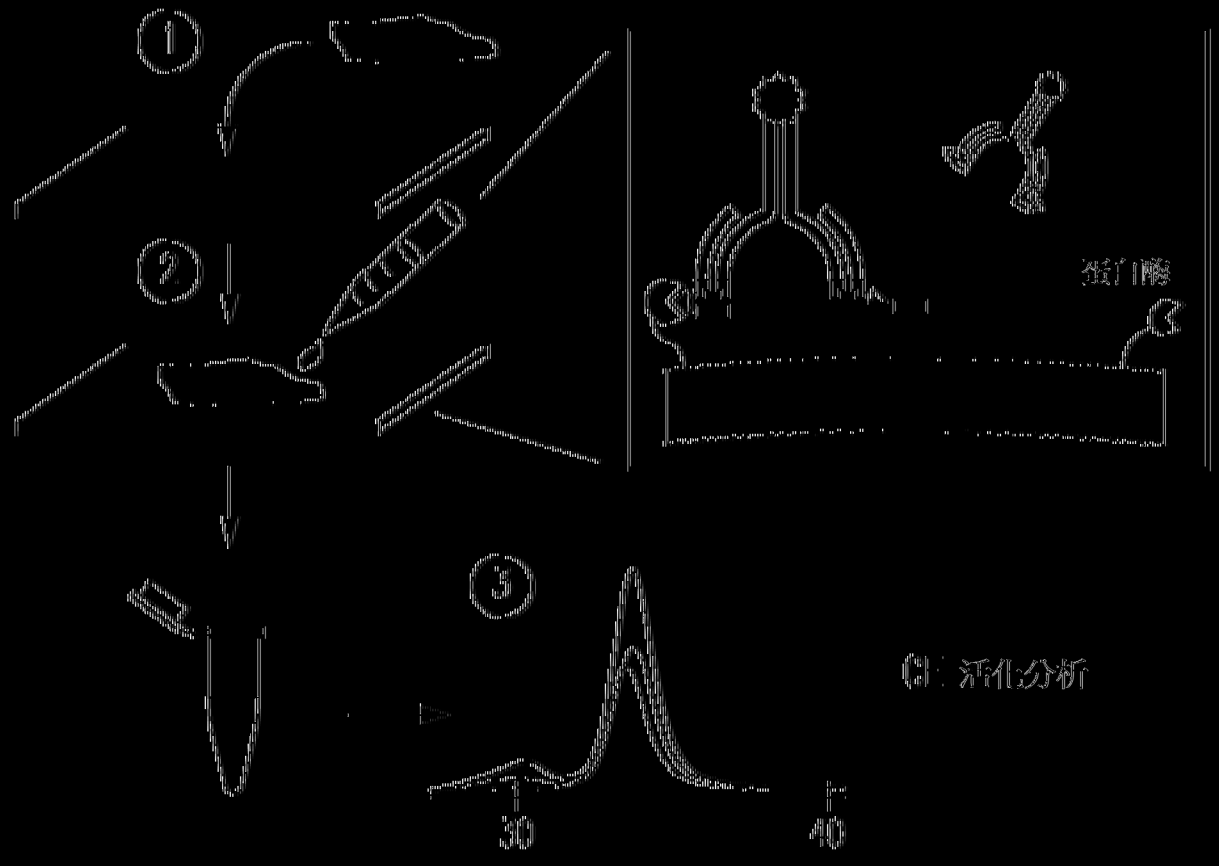
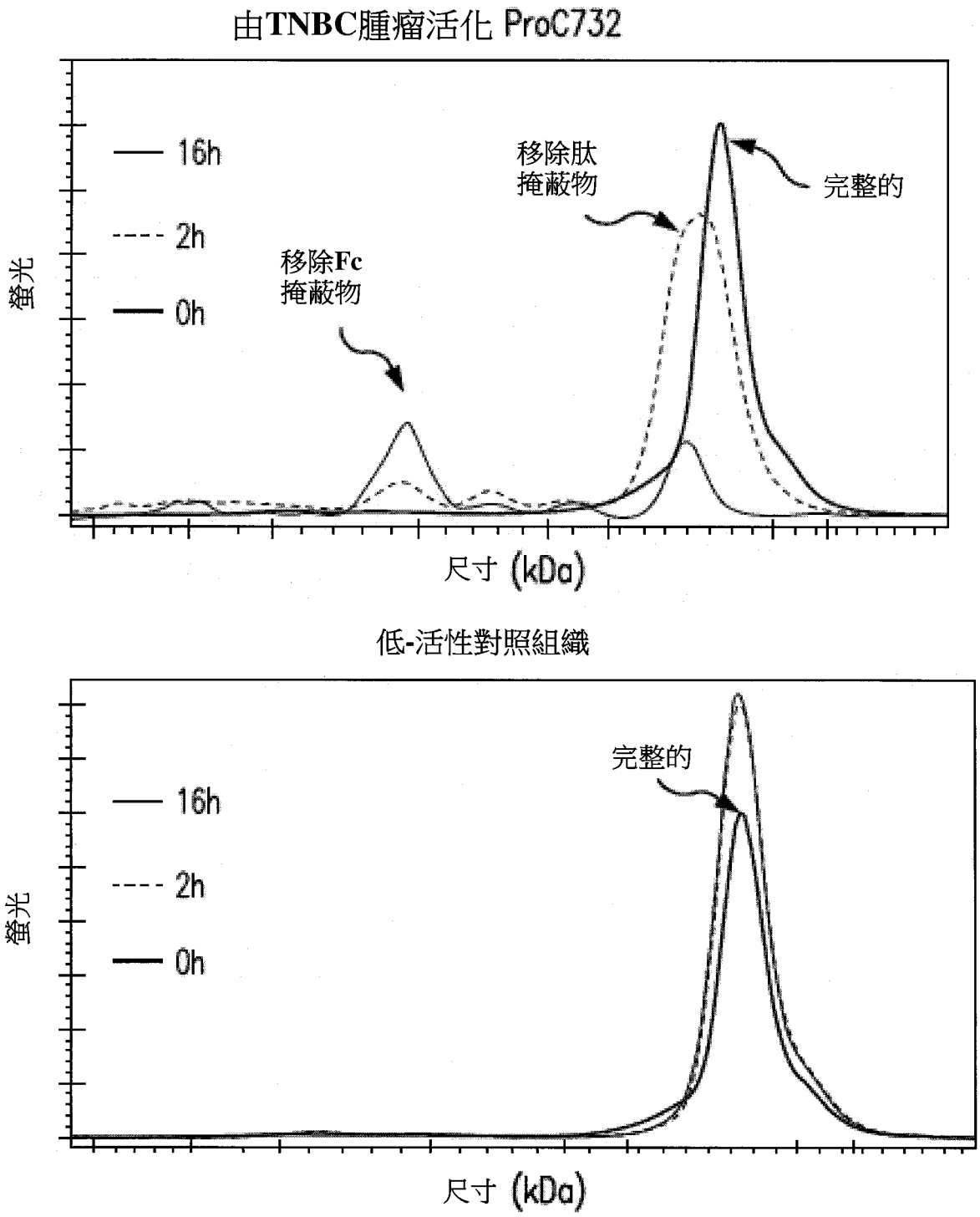

RU
25
20
15
10
5
0
-5
100
100
300
500
700
900
時間

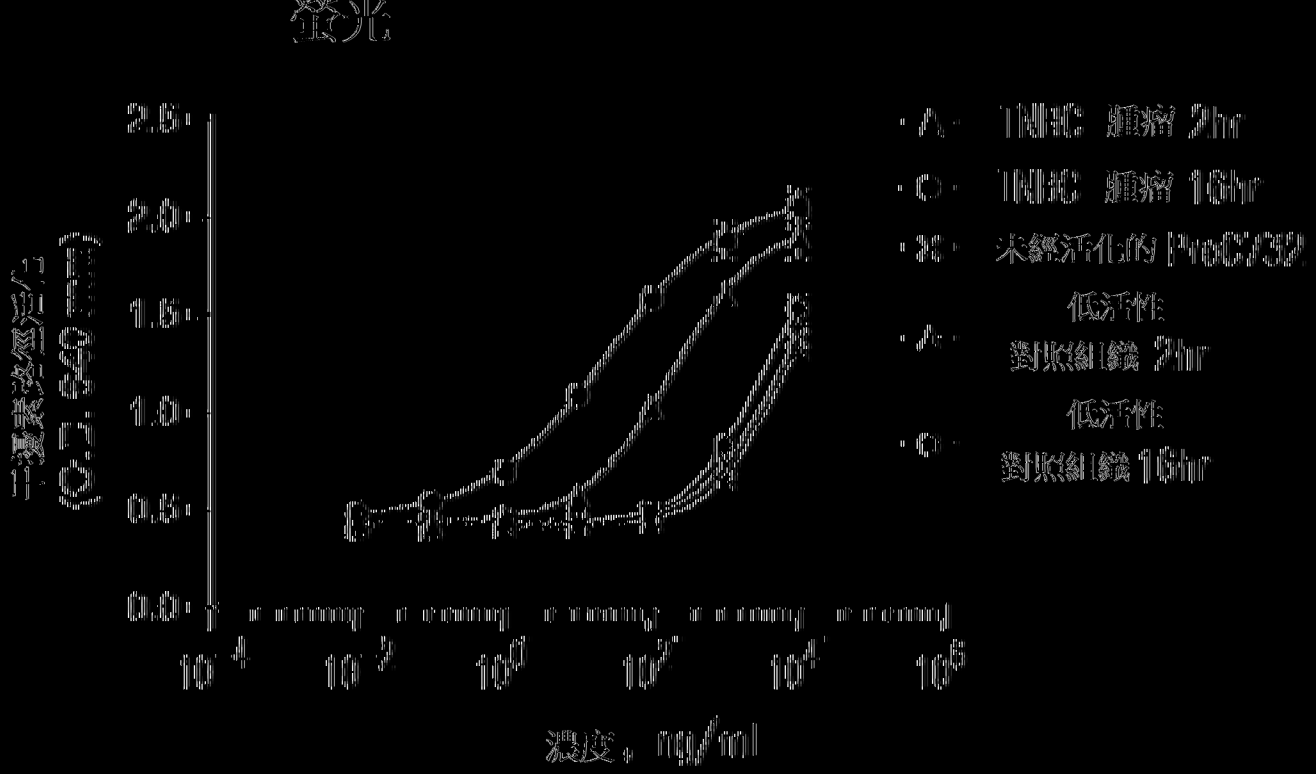
圖 40D



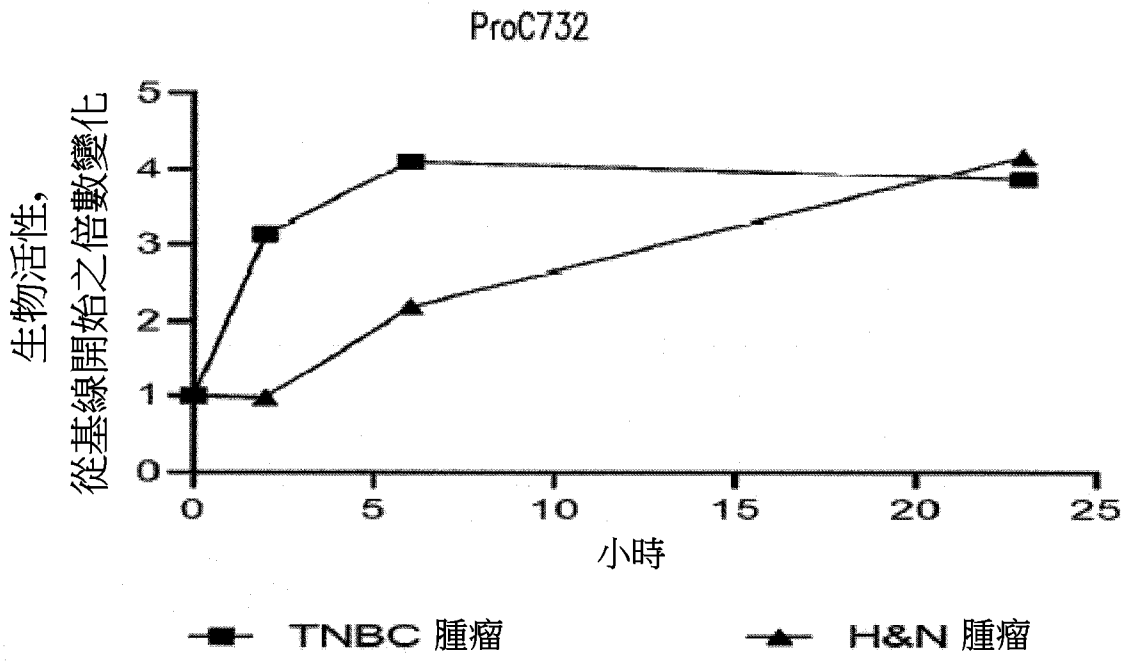
(圖 41A)


由TNBC腫瘤活化 ProC732
16h
2h
0h
螢光
移除Fc
掩蔽物
移除肽
掩蔽物
完整的
尺寸 (kDa)
低-活性對照組織
16h
2h
0h
螢光
完整的
尺寸 (kDa)

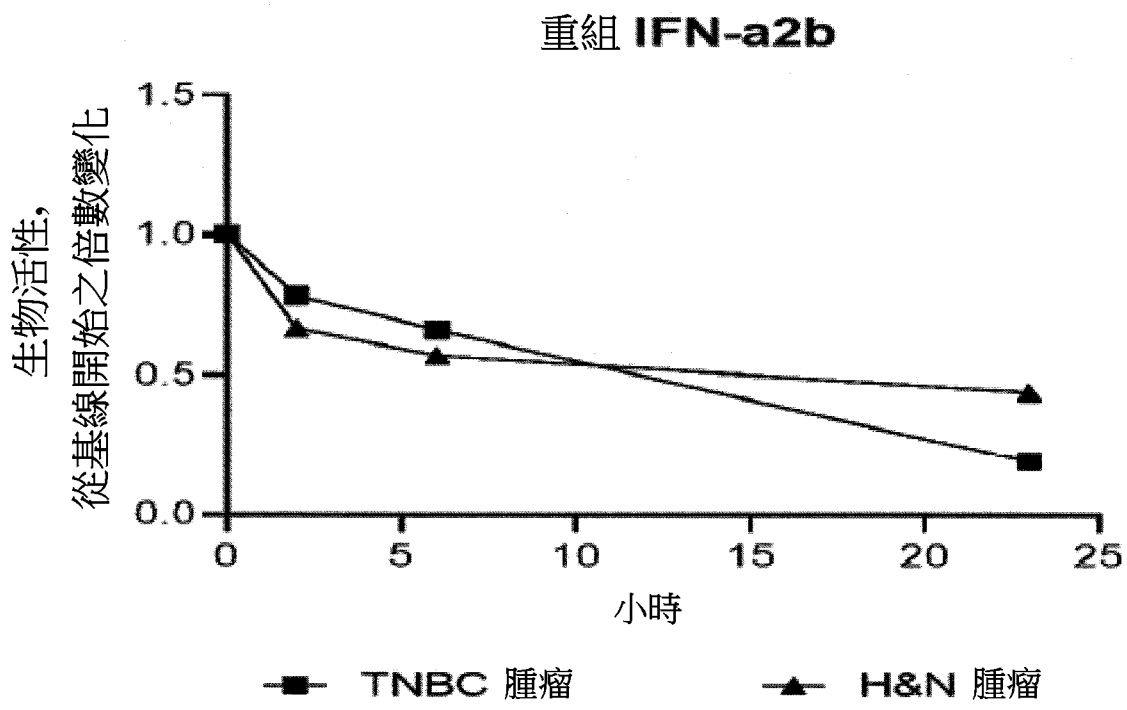
【圖 41B】


螢光
2.5
2.0
1.5
1.0
0.5
0.0
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
濃度，ng/ml
A：THC 浸漬 2hr
C：THC 浸漬 16hr
X：未經活化的 Pro62
低活性
A：對照組織 2hr
低活性
C：對照組織 16hr

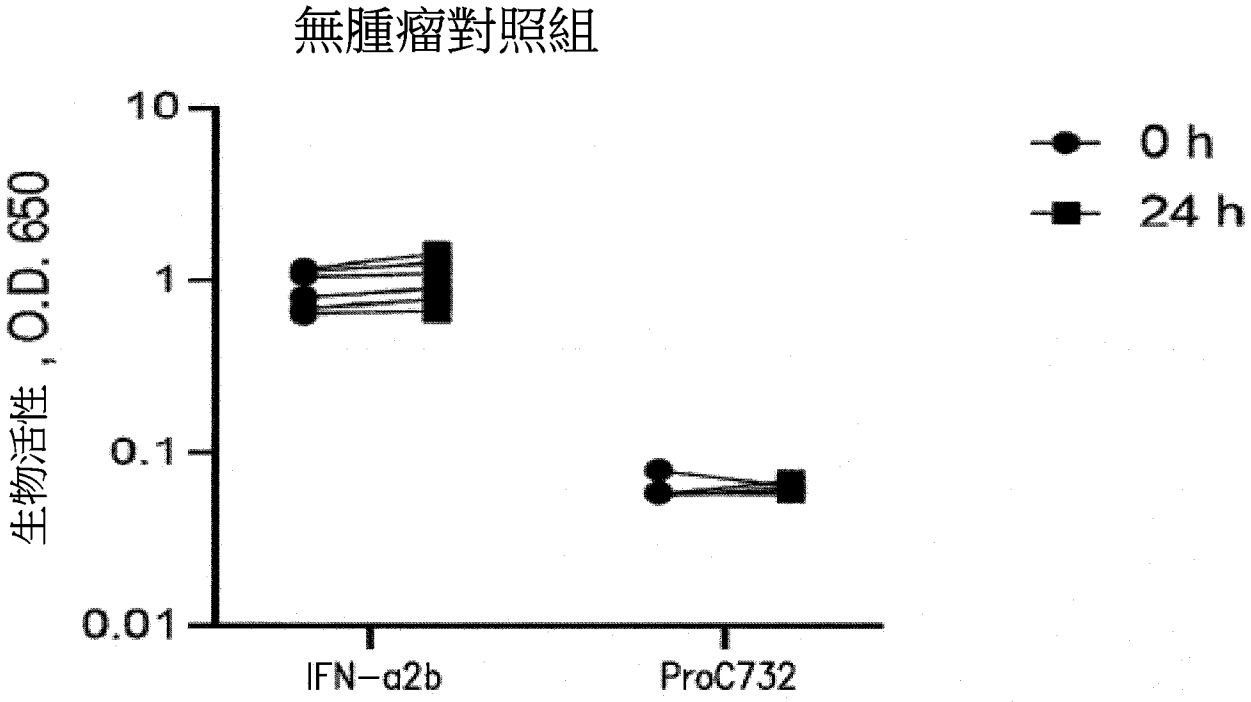
|(圖 41C)|


ProC732
生物活性，
從基線開始之倍數變化
0
1
2
3
4
5
0
5
10
15
20
25
小時
TNBC 腫瘤
H&N 腫瘤

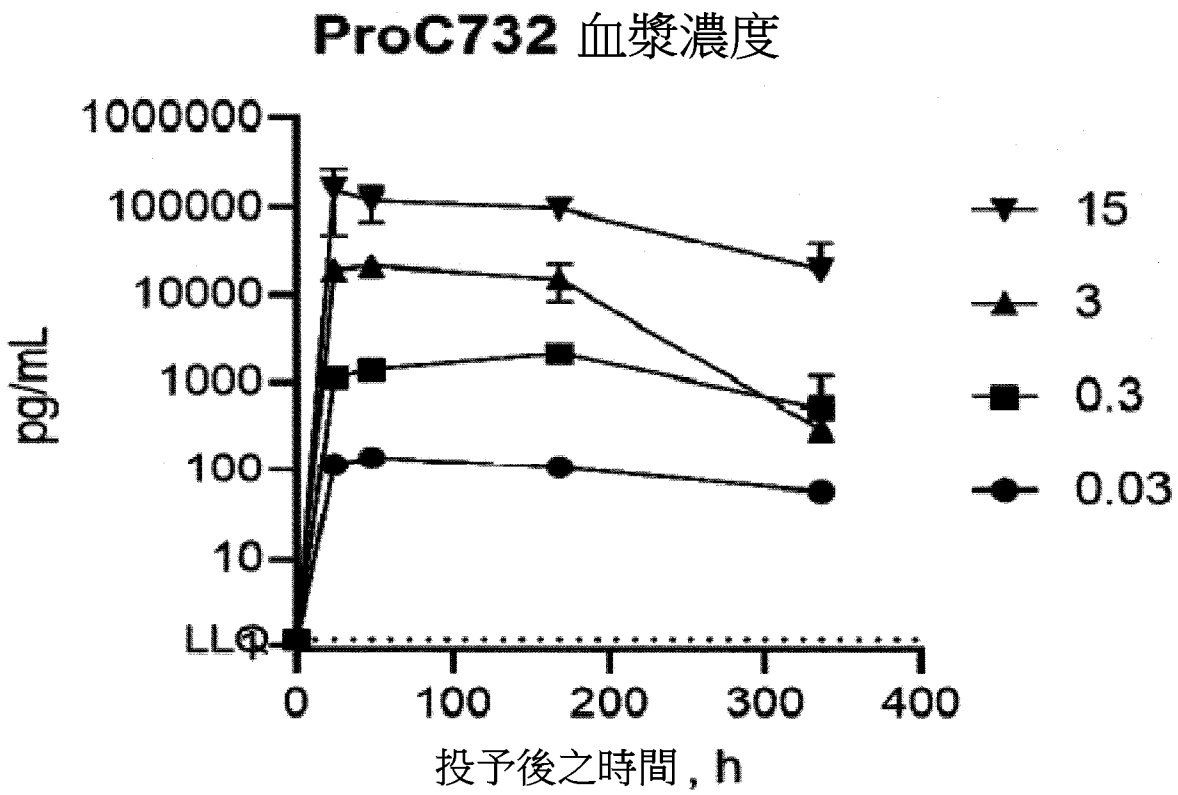
【圖 42A】


重組 IFN-a2b
生物活性，
從基線開始之倍數變化
0.0
0.5
1.0
1.5
0
5
10
15
20
25
小時
TNBC 腫瘤
H&N 腫瘤

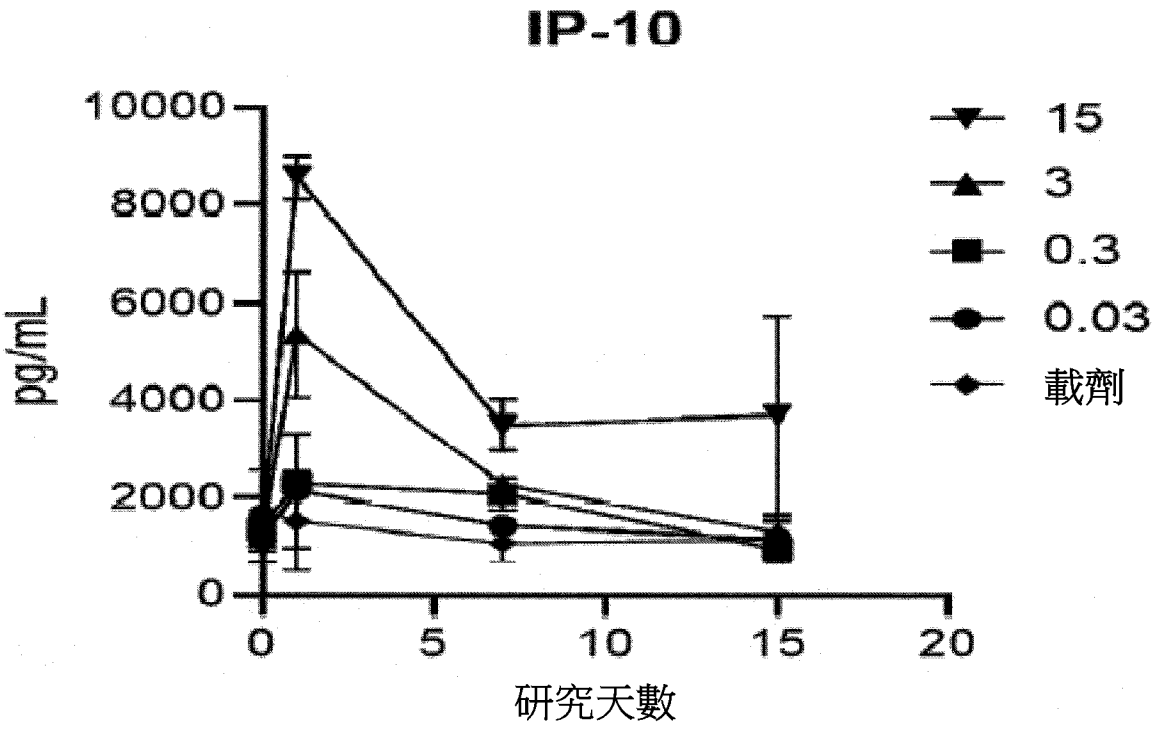
【圖 42B】


無腫瘤對照組
10
1
0.1
0.01
生物活性，O.D. 650
0 h
24 h
IFN−α2b
ProC732

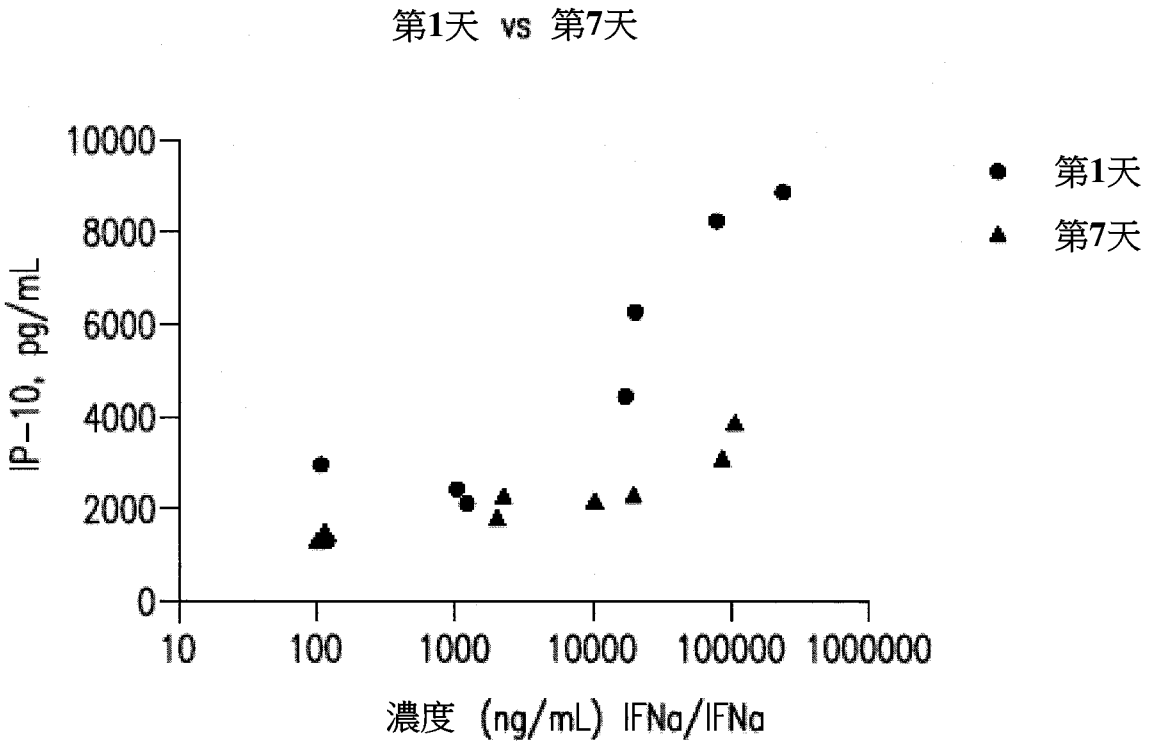
【圖 42C】


ProC732 血漿濃度
1000000
100000
10000
1000
100
10
LLQ
pg/mL
0
100
200
300
400
投予後之時間，h
15
3
0.3
0.03

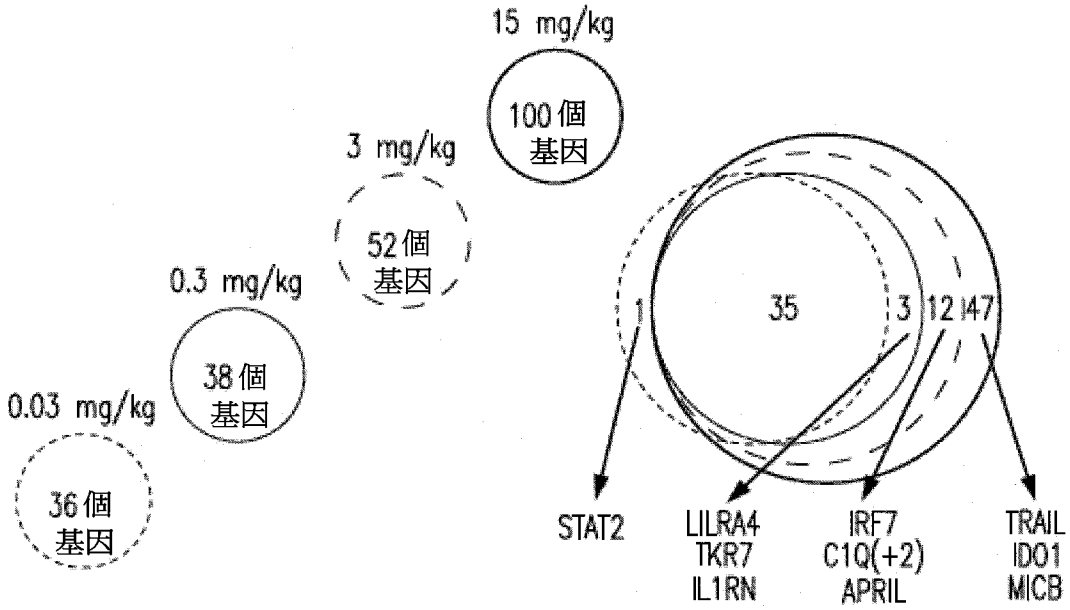
【圖 43】


IP-10
10000
8000
6000
4000
2000
0
pg/mL
0
5
10
15
20
研究天數
15
3
0.3
0.03
載劑

【圖 44A】


第1天 vs 第7天
10000
8000
6000
4000
2000
0
IP-10, pg/mL
10
100
1000
10000
100000
1000000
濃度 (ng/mL) IFNa/IFNa
第1天
第7天

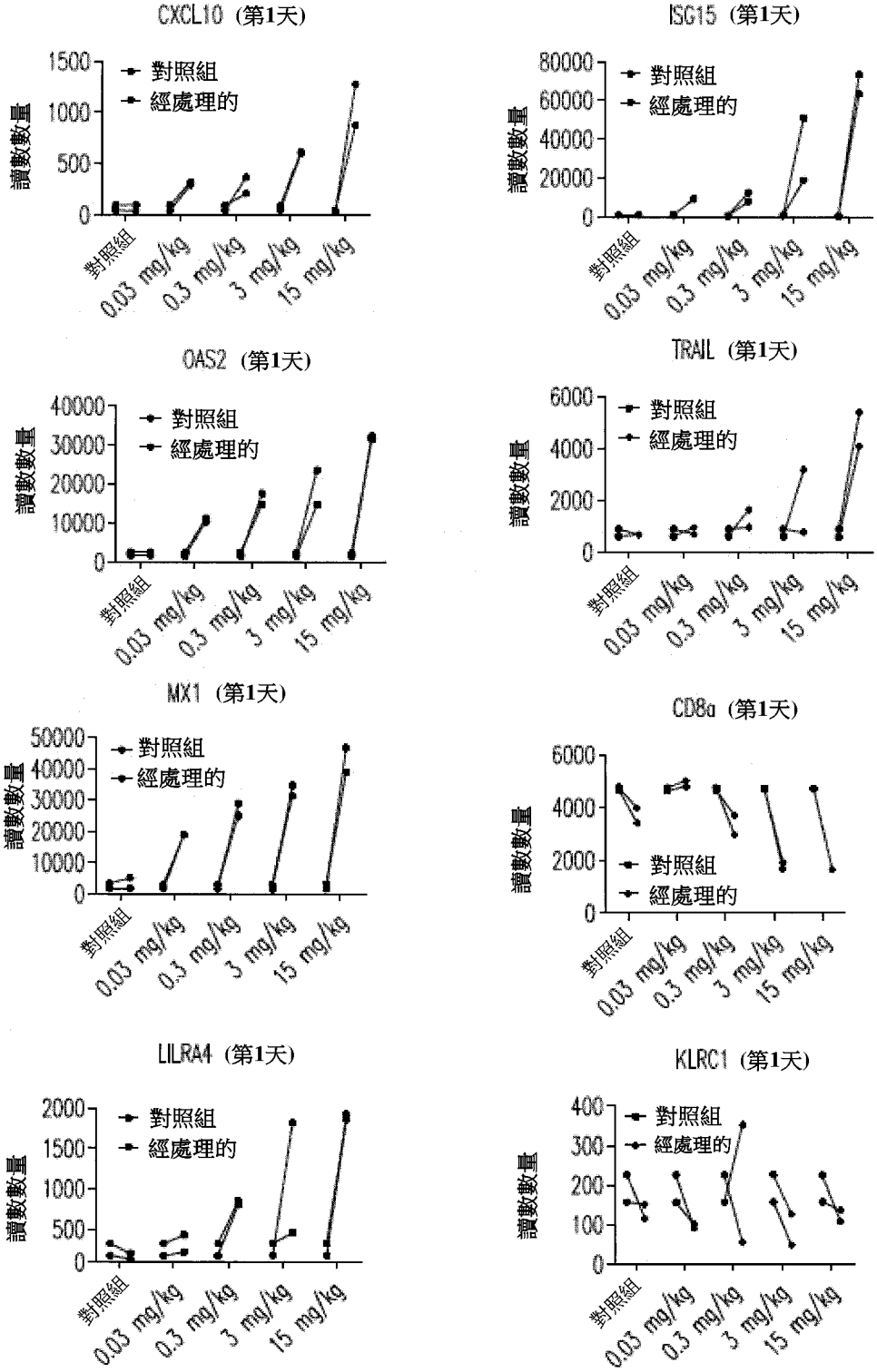
【圖 44B】



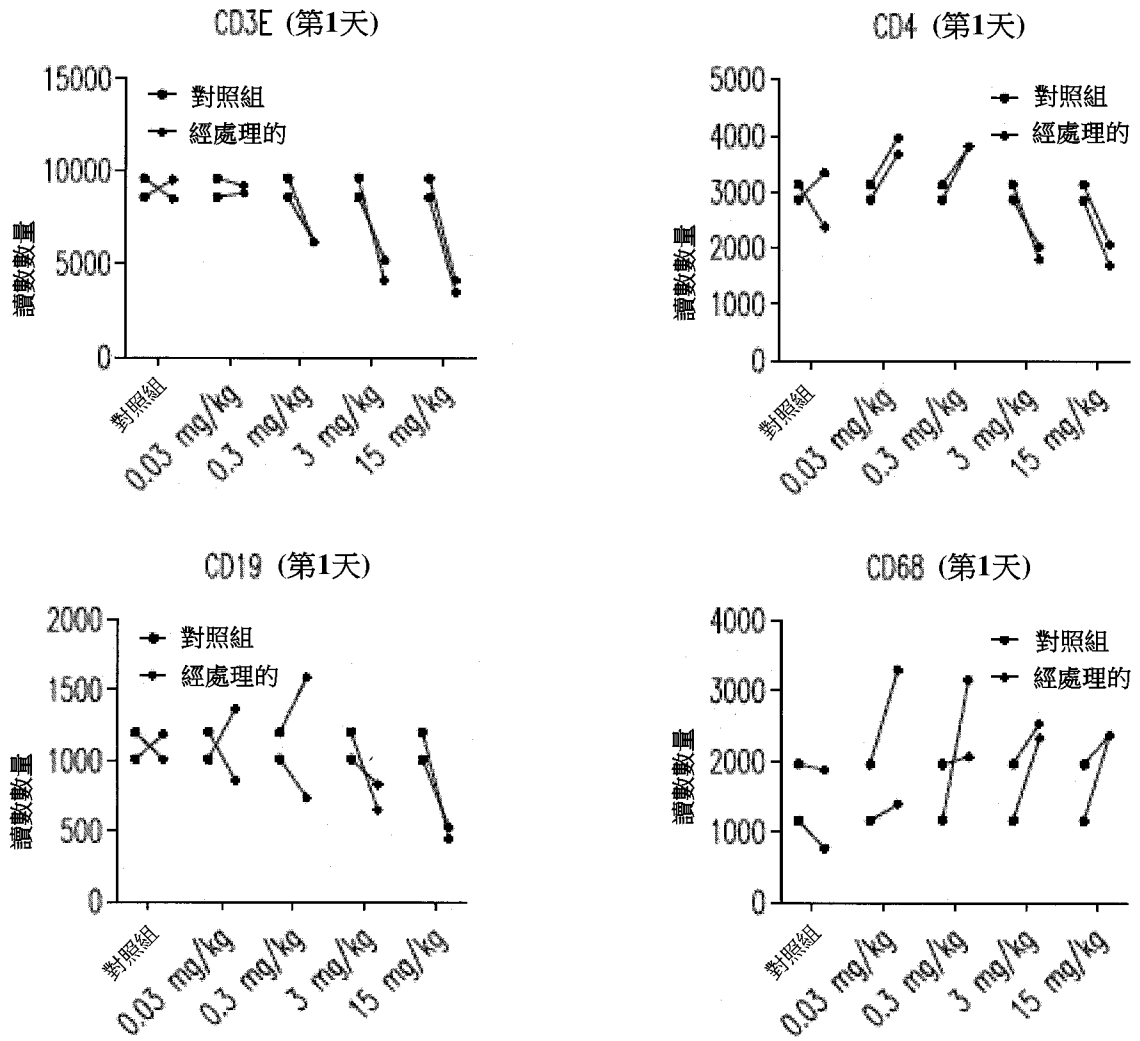
共通之35個基因

SIGLEC1	OASL
RSAD2	IFI27
OAS1	MX2
CMPK2	OAS2
IFIT1B	APOBEC3A
ISG15	OAS3
HERC5	PLA2C4C
IFI44L	DDX60
IFIT2	IFIT5
IFIT1	HERC6
XAF1	RAB44
IFI44	TMPRSS2
MX1	CXCL 10
USP18	EPSTI1
IFI6	APOBEC3B
IFIT3	DDX58
DHX58	CMKLR1
SLFN13	

【圖 45】


CXCL10 (第1天)
讀數數量
1500
1000
500
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
ISG15 (第1天)
讀數數量
80000
60000
40000
20000
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
OAS2 (第1天)
讀數數量
40000
30000
20000
10000
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
TRAIL (第1天)
讀數數量
6000
4000
2000
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
MX1 (第1天)
讀數數量
50000
40000
30000
20000
10000
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
CD8a (第1天)
讀數數量
6000
4000
2000
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
LILRA4 (第1天)
讀數數量
2000
1500
1000
500
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
KLRC1 (第1天)
讀數數量
400
300
200
100
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg

【圖 46】


CD3E (第1天)
讀數數量
15000
10000
5000
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
CD4 (第1天)
讀數數量
5000
4000
3000
2000
1000
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
CD19 (第1天)
讀數數量
2000
1500
1000
500
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg
CD68 (第1天)
讀數數量
4000
3000
2000
1000
0
對照組
經處理的
對照組
0.03 mg/kg
0.3 mg/kg
3 mg/kg
15 mg/kg

【圖 46】(續)

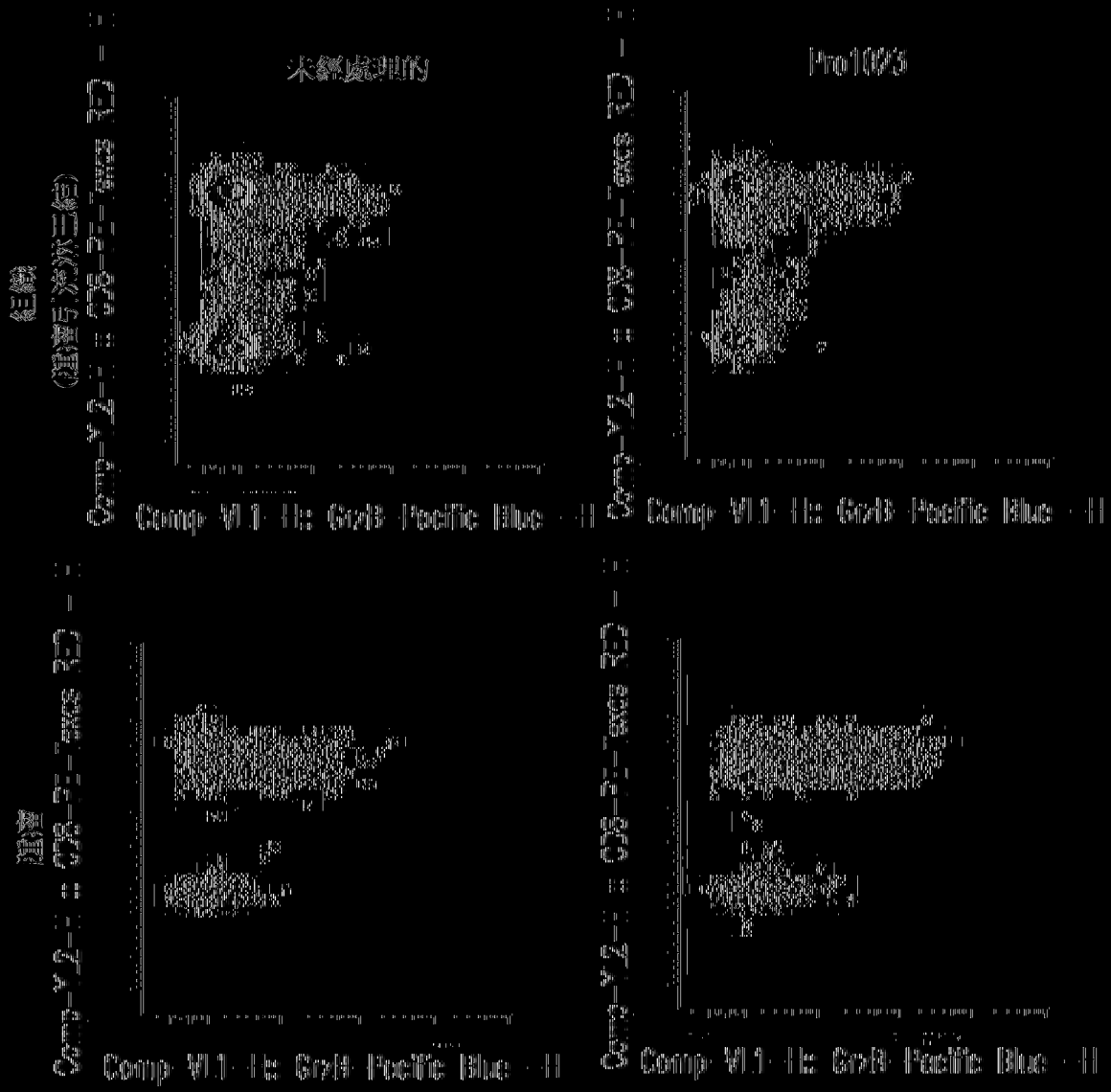
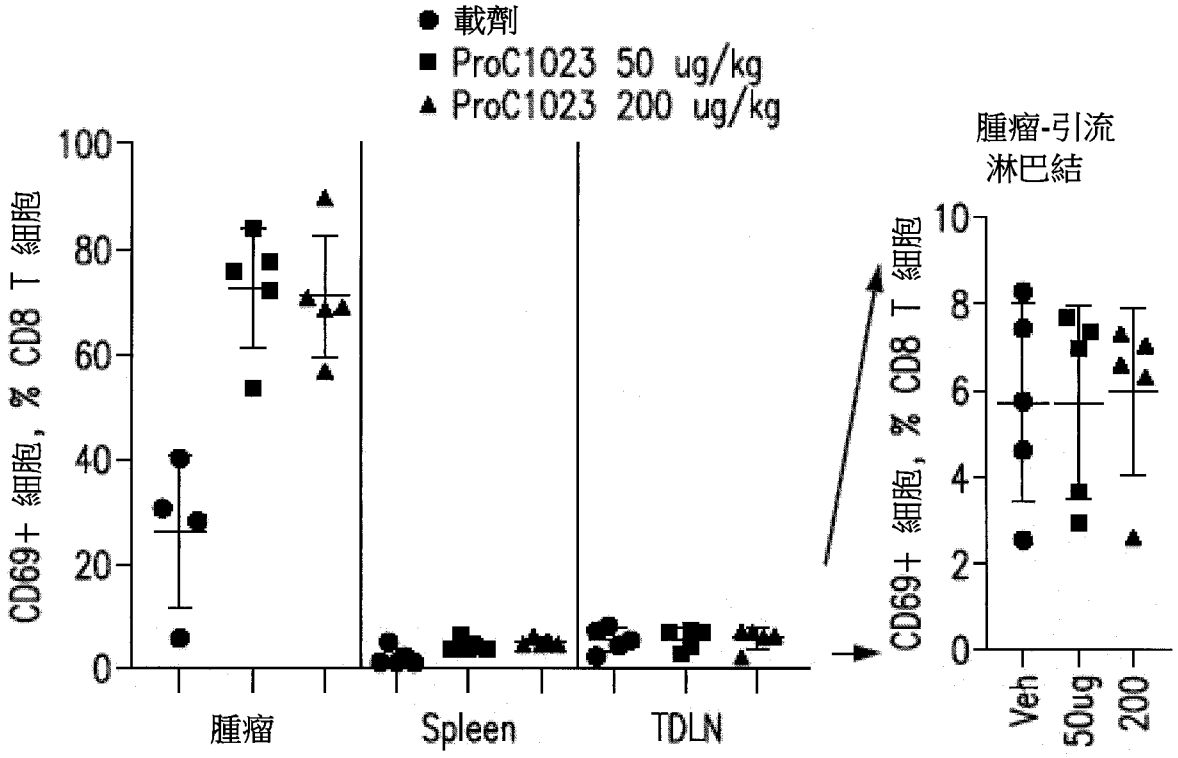
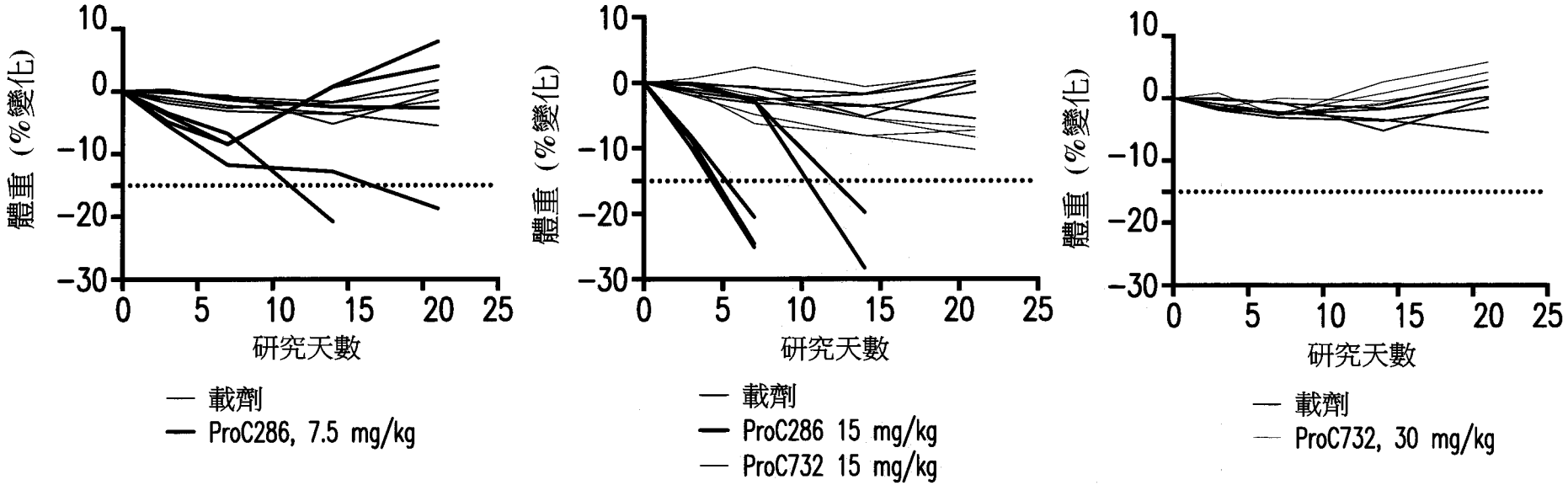

未經處理的
Pro10/3
Comp V1 · II: Grb Pacific Blue · II
Comp V1 · II: Grb Pacific Blue · II
Comp V1 · II: Grb Pacific Blue · II
Comp V1 · II: Grb Pacific Blue · II

圖 47

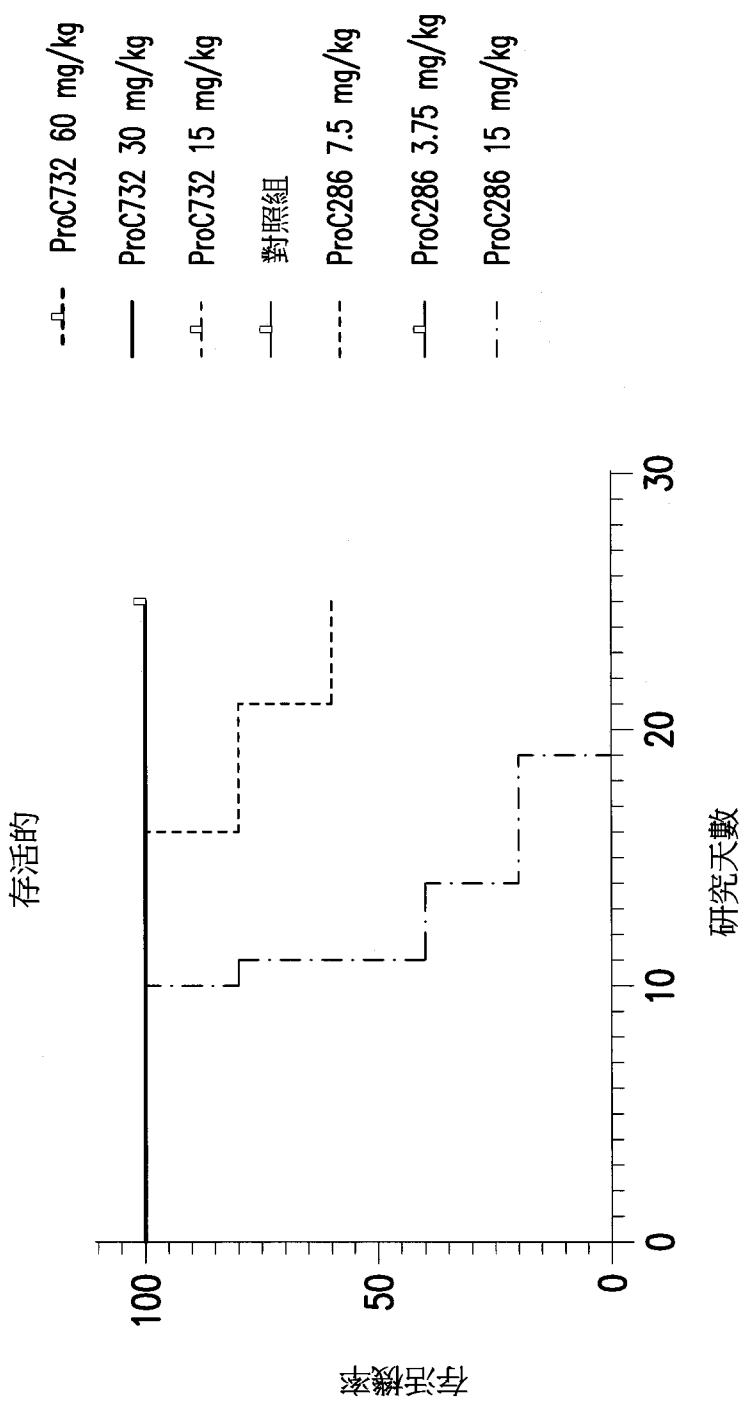

載劑
ProC1023 50 ug/kg
ProC1023 200 ug/kg
CD69+ 細胞, % CD8 T 細胞
腫瘤
Spleen
TDLN
腫瘤-引流
淋巴結
Veh
50ug
200

【圖 47】(續)

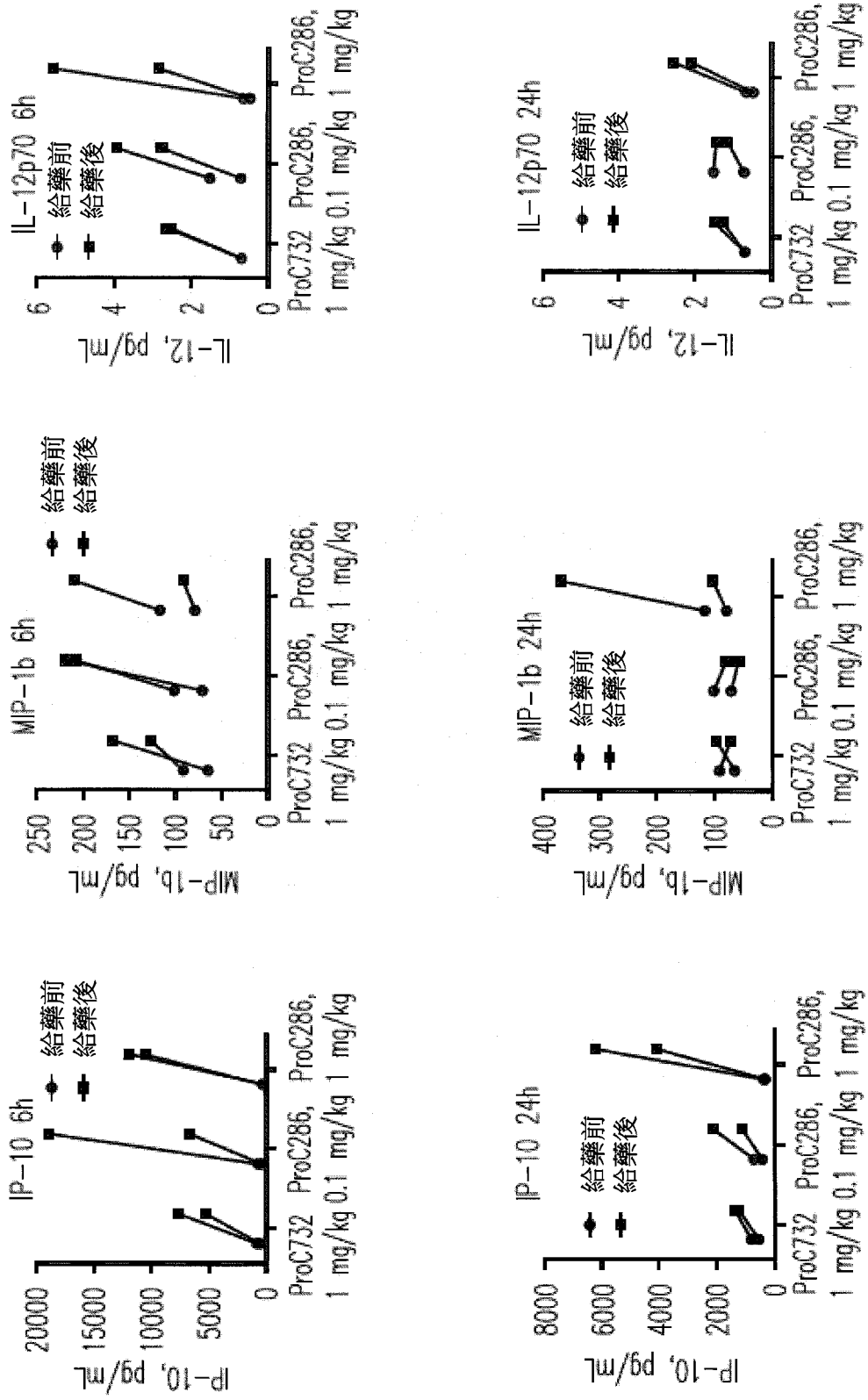
	3.75mg/kg	7.5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
ProC732 (經掩蔽的)			耐受的	耐受的	耐受的
ProC286 (未經掩蔽的)	耐受的	3/5 存活的	0/5 存活的		



【圖 48】


ProC732 60 mg/kg
ProC732 30 mg/kg
ProC732 15 mg/kg
對照組
ProC286 7.5 mg/kg
ProC286 3.75 mg/kg
ProC286 15 mg/kg
存活的
存活機率
100
50
0
0
10
20
30
研究天數

【圖 48】(續)


IP-10 6h
給藥前
給藥後
IP-10, pg/mL
20000
15000
10000
5000
0
ProC732 ProC286, ProC286,
1 mg/kg 0.1 mg/kg 1 mg/kg
MIP-1b 6h
給藥前
給藥後
MIP-1b, pg/mL
250
200
150
100
50
0
ProC732 ProC286, ProC286,
1 mg/kg 0.1 mg/kg 1 mg/kg
IL-12p70 6h
給藥前
給藥後
IL-12, pg/mL
6
4
2
0
ProC732 ProC286, ProC286,
1 mg/kg 0.1 mg/kg 1 mg/kg
IP-10 24h
給藥前
給藥後
IP-10, pg/mL
8000
6000
4000
2000
0
ProC732 ProC286, ProC286,
1 mg/kg 0.1 mg/kg 1 mg/kg
MIP-1b 24h
給藥前
給藥後
MIP-1b, pg/mL
400
300
200
100
0
ProC732 ProC286, ProC286,
1 mg/kg 0.1 mg/kg 1 mg/kg
IL-12p70 24h
給藥前
給藥後
IL-12, pg/mL
6
4
2
0
ProC732 ProC286, ProC286,
1 mg/kg 0.1 mg/kg 1 mg/kg

【圖 49】

圖 (5)
0
5000
10000
15000
20000
降雨強度 (mm/h)
0
3
7
10
13
16
19
22
時間
- 20 m/s
15 m/s
10 m/s
5 m/s
0 m/s

絶縁抵抗 (mm³)
サイズ小 ⇒ 大
500
1000
1500
2000
2500
3000
高温保存 (K)
0
5
10
15
20
25
30
35
40
K
K
K

0.02 mg/kg
0.1 mg/kg
0.5 mg/kg
血漿 PreC/32, ng/ml
0.000
0.000
0.00
0.0
0
100
200
300
400
時間 (分)

図2

濃度 (μg/ml)
時間 (分)
完整活體物
完整立體活體物
30mA, SC
濃度 (μg/ml)
時間 (分)
完整活體物
完整立體活體物
7.5mA, SC
濃度 (μg/ml)
時間 (分)
完整活體物
完整立體活體物
30mA, V
濃度 (μg/ml)
時間 (分)
完整活體物
完整立體活體物

圖 (38)

濃度 (μg/ml)
時間
75 min
5 min
30 min
30 min
60 min
0
100
200
300
400
500
10000
5000
1000
500
0

濃度 (μg/ml)
時間
60 min
完整抗體藥物
所釋出的酵素
所釋出的藥物
0
100
200
300
400
500
2000
1500
1000
500
0

圖 5B