之生物體培養物可在使群體不偏向表現產物被宿主細胞良好耐受之編碼序列的非誘導條件下擴增。除啟動子之外，其他調節元件亦可為抗CDH6抗體鏈或片段之有效表現所必需或需要的。此等元件典型地包括ATG起始密碼子及相鄰的核糖體結合位點或其他序列。另外，表現效率可藉由包括適於所用細胞系統之增強子來增強(參見例如Scharf等人, Results Probl. Cell Differ. 20:125, 1994；及Bittner等人, Meth. Enzymol., 153:516, 1987)。舉例而言，SV40增強子或CMV增強子可用於增強哺乳動物宿主細胞中之表現。

表現載體亦可提供分泌信號序列位置以與由所插入之抗CDH6抗體序列編碼之多肽形成融合蛋白。更通常，所插入之抗CDH6抗體序列在包含於載體中之前連接至信號序列。接收編碼抗CDH6抗體輕鏈及重鏈可變域之序列所用的載體有時亦編碼恆定區或其一部分。此類載體允許可變區以與恆定區形成之融合蛋白形式表現，從而產生完整抗體或其片段。典型地，此類恆定區為人類恆定區。

含有及表現抗CDH6抗體鏈之宿主細胞可為原核或真核細胞。大腸桿菌為一種適用於選殖及表現本發明聚核苷酸之原核宿主。適用之其他微生物宿主包括桿菌(諸如枯草桿菌(Bacillus subtilis))，及其他腸內菌科(諸如沙門氏菌(Salmonella)、沙雷氏菌(Serratia))，及多種假單胞菌種。在此等原核宿主中，亦可產生表現載體，其典型地含有與宿主細胞相容之表現控制序列(例如複製起點)。另外，將存在任何數目之多種熟知啟動子，諸如乳糖啟動子系統、色胺酸(trp)啟動子系統、β-內醯胺酶啟動子系統或來自噬菌體λ之啟動子系統。啟動子典型地控制表現(視情況與操縱序列一起控制表現)，且具有用於起始且完成轉錄及轉譯之核糖體結合位點序列及其類似序列。諸如酵母之其他微生物亦可用於表現抗CDH6多肽。亦可使用昆蟲細胞與桿狀病毒載體之組合。

OnCusp
Ex. 1002

在其他態樣中，哺乳動物宿主細胞用於表現及產生本發明之抗CDH6多肽。舉例而言，其可為表現內源性免疫球蛋白基因的融合瘤細胞株(例如骨髓瘤融合瘤純系)或含有外源性表現載體的哺乳動物細胞株(例如SP2/0骨髓瘤細胞)。此等細胞包括任何正常死亡或正常或異常永生動物或人類細胞。舉例而言，已開發出能夠分泌完整免疫球蛋白之多種適合宿主細胞株，包括CHO細胞株、各種COS細胞株、海拉細胞(HeLa cells)、骨髓瘤細胞株、經轉形之B細胞及融合瘤。哺乳動物組織細胞培養物用於表現多肽之用途一般性論述於例如Winnacker, From Genes to Clones, VCH Publishers, N.Y., N.Y., 1987中。哺乳動物宿主細胞之表現載體可包括表現控制序列，諸如複製起點、啟動子及增強子(參見例如Queen等人, Immunol. Rev. 89:49-68, 1986)，及必需的處理資訊位點，諸如核糖體結合位點、RNA拼接位點、聚腺苷酸化位點，及轉錄終止子序列。此等表現載體通常含有源於哺乳動物基因或源於哺乳動物病毒之啟動子。適合啟動子可為組成性、細胞類型特異性、階段特異性及/或可調節或可調控的。適用啟動子包括(但不限於)金屬硫蛋白啟動子、組成性腺病毒主要晚期啟動子、地塞米松(dexamethasone)誘導性MMTV啟動子、SV40啟動子、MRP polIII啟動子、組成性MPSV啟動子、四環素(tetracycline)誘導性CMV啟動子(諸如人類即刻早期CMV啟動子)、組成性CMV啟動子及此項技術中已知之啟動子-增強子組合。

引入含有所關注之聚核苷酸序列之表現載體的方法視細胞宿主之類型而變化。舉例而言，氯化鈣轉染通常用於原核細胞，而磷酸鈣處理或電穿孔可用於其他細胞宿主(一般參見Sambrook等人，同上)。其他方法包括例如電穿孔、磷酸鈣處理、脂質體介導轉形、注射及顯微注射、衝擊法、病毒顆粒(virosome)、免疫脂質體、聚陽離子:核酸結合物、裸DNA、人工病毒粒子、與疱疹病毒結構蛋白VP22融合

(Elliot及O'Hare, Cell 88:223, 1997)、DNA之藥劑增強性吸收，及離體轉導。就長期高產量生產重組蛋白質而言，通常需要穩定的表現。舉例而言，穩定表現抗CDH6抗體鏈或結合片段之細胞株可使用本發明之表現載體製備，該表現載體含有病毒複製起點或內源性表現元件及可選標記基因。在引入載體之後，可允許細胞在豐富培養基中生長1-2天，隨後將其與選擇性培養基交換。可選標記之目的為賦予抗選擇性，且其存在允許成功表現所引入序列的細胞在選擇性培養基中生長。經穩定轉染之耐藥性細胞可使用適合於該細胞類型之組織培養技術增殖。

治療及診斷用途

本發明之抗體、抗體片段(例如抗原結合片段)及抗體藥結合物適用於多種應用，包括(但不限於)治療癌症，諸如實體癌症。在某些態樣中，抗體、抗體片段(例如抗原結合片段)及抗體藥結合物適用於抑制腫瘤生長、誘導分化、減小腫瘤體積及/或降低腫瘤致瘤性。使用方法可為活體外、離體或活體內方法。

在一個態樣中，抗體、抗體片段(例如抗原結合片段)及抗體藥結合物適用於偵測生物樣品中CDH6之存在。如本文所用，術語「偵測」包含定量或定性偵測。在某些態樣中，生物樣品包含細胞或組織。在某些態樣中，此類組織包括相對於其他組織以較高含量表現CDH6的正常及/或癌性組織。

在一個態樣中，本發明提供一種偵測生物樣品中CDH6之存在的方法。在某些態樣中，方法包含在允許抗體結合至抗原的條件下使生物樣品與抗CDH6抗體接觸及偵測抗體與抗原之間是否形成複合物。

亦包括一種診斷與CDH6之表現增強相關之病症的方法。在某些態樣中，方法包含使測試細胞與抗CDH6抗體接觸；藉由偵測抗CDH6抗體對CDH6抗原的結合來測定測試細胞上之CDH6表現量(定量或定

性)；及比較測試細胞中之CDH6表現量與對照細胞(例如組織來源與測試細胞相同的正常細胞或表現CDH6之量類似於此正常細胞的細胞)中之CDH6表現量，其中測試細胞上之CDH6表現量高於對照細胞表示存在與CDH6之表現增強相關的病症。在某些態樣中，測試細胞獲自懷疑患有與CDH6之表現增強相關之病症的個體。在某些態樣中，病症為細胞增殖性病症，諸如癌症或腫瘤。

在某些態樣中，診斷或偵測方法(諸如上述方法)包含偵測抗CDH6抗體對細胞表面上或獲自表面上表現CDH6之細胞之膜製劑中所表現之CDH6的結合。用於偵測抗CDH6抗體對細胞表面上所表現之CDH6之結合的例示性分析為「FACS」分析。

某些其他方法可用於偵測抗CDH6抗體對CDH6的結合。此類方法包括(但不限於)此項技術中熟知的抗原結合分析，諸如西方墨點法、放射免疫分析、ELISA (酶聯免疫吸附分析)、「夾心」免疫分析、免疫沈澱分析、螢光免疫分析、蛋白質A免疫分析及免疫組織化學(IHC)。

在某些態樣中，抗CDH6抗體經標記。標記包括(但不限於)直接偵測之標記或部分(諸如螢光、發色、電子緻密、化學發光及放射性標記)，以及例如經由酶促反應或分子相互作用間接偵測之部分(諸如酶或配位體)。

在某些態樣中，抗CDH6抗體固著於不溶性基質上。固著需要將抗CDH6抗體與在溶液中保持游離的任何CDH6蛋白質分離。此習知地如下達成：在分析程序之前，藉由吸附於水不溶性基質或表面(Bennich等人，美國專利第3,720,760號)或藉由共價偶合(例如使用戊二醛交聯)而使抗CDH6抗體不溶解，或在抗CDH6抗體與CDH6蛋白質之間形成複合物之後，藉由例如免疫沈澱而使抗CDH6抗體不溶解。

替代或除抗CDH6抗體之外，可使用本發明之免疫結合物實施任

一種上述診斷或偵測態樣。

在一個態樣中，本發明提供一種治療、預防或改善疾病的方法，包含向患者投與抗體、抗體片段(例如抗原結合片段)及抗體藥結合物，從而治療該疾病。在某些態樣中，用抗體、抗體片段(例如抗原結合片段)及抗體藥結合物治療的疾病為癌症。可加以治療及/或預防之疾病之實例包括(但不限於)卵巢癌、腎及甲狀腺癌。在某些態樣中，癌症的特徵為表現CDH6之細胞，抗體、抗體片段(例如抗原結合片段)及抗體藥結合物可特異性結合至該等細胞。

本發明提供治療癌症之方法，包含投與治療有效量之抗體、抗體片段(例如抗原結合片段)或抗體藥結合物。在某些態樣中，癌症為實體癌症。在某些態樣中，個體為人類。

在某些態樣中，抑制腫瘤生長的方法包含向個體投與治療有效量之抗體、抗體片段(例如抗原結合片段)或抗體藥結合物。在某些態樣中，個體為人類。在某些態樣中，個體患有腫瘤或所患腫瘤已移除。

在某些態樣中，腫瘤表現抗CDH6抗體所結合的CDH6。在某些態樣中，腫瘤過度表現人類CDH6。

治療疾病時，抗體、抗體片段(例如抗原結合片段)或抗體藥結合物之適當劑量視多種因素而定，諸如所治療之疾病類型、疾病之嚴重程度及病程、疾病之反應性、先前療法、患者臨床病史等。抗體或藥劑可一次性投與或在持續數日至數月的一系列治療期間投與，或直至實現治癒或達成疾病病況之減弱(例如腫瘤尺寸減小)。最佳給藥時程可依據患者體內之藥物聚積量測結果來計算且將根據個別抗體、抗體片段(例如抗原結合片段)或抗體藥結合物之相對效能來變化。在某些態樣中，劑量為每公斤體重0.01 mg至10 mg (例如0.01 mg、0.05 mg、0.1 mg、0.5 mg、1 mg、2 mg、3 mg、4 mg、5 mg、7 mg、8 mg、9

mg或10 mg)，且可每天、每週、每月或每年給予一次或多次。在某些態樣中，本發明之抗體、抗體片段(例如抗原結合片段)或抗體藥結合物每兩週給予一次或每三週給予一次。治療醫師可根據藥物在體液或組織中之所測滯留時間及濃度估算重複給藥率。

組合療法

在某些情況下，本發明之抗體、抗體片段(例如抗原結合片段)或抗體藥結合物係與其他治療劑組合，諸如其他抗癌劑、抗過敏劑、抗噁心劑(或抗嘔吐劑)、疼痛舒解劑、細胞保護劑及其組合。

考慮用於組合療法中之通用化學治療劑包括阿那曲唑(anastrozole)(Arimidex®)、比卡魯胺(bicalutamide)(Casodex®)、硫酸博萊黴素(bleomycin sulfate)(Blenoxane®)、白消安(busulfan)(Myleran®)、白消安注射劑(Busulfex®)、卡培他濱(capecitabine)(Xeloda®)；N4-戊氧基羰基-5-去氧-5-氟胞嘧啶核苷、卡鉑(carboplatin)(Paraplatin®)；卡莫司汀(carmustine)(BiCNU®)、苯丁酸氮芥(chlorambucil)(Leukeran®)、順鉑(cisplatin)(Platinol®)、克拉屈濱(cladribine)(Leustatin®)、環磷醯胺(cyclophosphamide)(Cytoxan®或Neosar®)；阿糖胞苷(cytarabine)，胞嘧啶阿拉伯糖苷(cytosine arabinoside)(Cytosar-U®)；阿糖胞苷脂質體注射劑(DepoCyt®)、達卡巴嗪(dacarbazine)(DTIC-Dome®)、放線菌素d (放線菌素D，Cosmegan)、鹽酸道諾黴素(Cerubidine®)、檸檬酸道諾黴素脂質體注射劑(DaunoXome®)；地塞米松(dexamethasone)、多西他賽(docetaxel)(Taxotere®)；鹽酸阿黴素(Adriamycin®，Rubex®)、依託泊苷(etoposide)(Vepesid®)、磷酸氟達拉濱(fludarabine phosphate)(Fludara®)、5-氟尿嘧啶(5-fluorouracil)(Adrucil®，Efudex®)、氟他胺(flutamide)(Eulexin®)；替紮他濱(tezacitibine)、吉西他濱(Gemcitabine)(二氟去氧胞苷)；羥脲(Hydrea®)、艾達黴素

(Idarubicin)(Idamycin®)、異環磷醯胺(ifosfamide)(IFEX®)、伊立替康(irinotecan)(Camptosar®)、L-天冬醯胺酶(ELSPAR®)；甲醯四氫葉酸鈣(leucovorin calcium)，美法侖(melphalan)(Alkeran®)；6-巰基嘌呤(Purinethol®)、甲胺喋呤(methotrexate)(Folex®)、米托蒽醌(mitoxantrone)(Novantrone®)；麥羅塔(mylotarg)、太平洋紫杉醇(paclitaxel)(Taxol®)；菲尼克斯(phoenix)(Yttrium90/MX-DTPA)；噴司他汀(pentostatin)、植入卡莫司汀(carmustine)的聚苯丙生20(polifeprosan 20)(Gliadel®)；檸檬酸他莫昔芬(tamoxifen citrate)(Nolvadex®)、替尼泊甙(teniposide)(Vumon®)；6-硫鳥嘌呤(6-thioguanine)、噻替派(thiotepa)、替拉紮明(tirapazamine)(Tirazone®)；注射用之鹽酸拓朴替康(topotecan hydrochloride)(Hycamptin®)、長春鹼(vinblastine)(Velban®)、長春新鹼(vincristine)(Oncovin®)及長春瑞賓(vinorelbine)(Navelbine®)。

在一個態樣中，本發明之抗體、抗體片段(例如抗原結合片段)或抗體藥結合物與具有抗癌特性之第二化合物在醫藥組合調配物中組合，或在作為組合療法之給藥方案中組合。醫藥組合調配物或給藥方案中之第二化合物可具有該組合中之抗體或免疫結合物的互補活性，使得其彼此間無不利影響。舉例而言，本發明之抗體、抗體片段(例如抗原結合片段)或抗體藥結合物可與(但不限於)化學治療劑、酪胺酸激酶抑制劑(例如伊馬替尼(Imatinib))組合投與。

如本文所用，術語「醫藥組合」係指呈一種單位劑型之固定組合，或非固定組合或分裝部分之套組用於組合投與，其中兩個或超過兩個治療劑可同時獨立地投與或在時間間隔內分別投與，尤其其中此等時間間隔允許組合搭配物顯示協作效應，例如協同效應。

術語「組合療法」係指投與兩種或兩種以上治療劑來治療本發明中所述之治療學病狀或病症。此類投藥包含此等治療劑以實質性同

時方式共投與，諸如具有固定比率之活性成分的單一膠囊。或者，此類投藥包含各種活性成分在多個或各別容器(例如膠囊、粉末及液體)中共投與。粉末及/或液體在投與之前可復原或稀釋至所要劑量。另外，此類投藥亦包含在大致相同的時間或在不同時間依序使用各類型治療劑。在任一情況下，治療方案將提供藥物組合在治療本文所述之病狀或病症方面的有益作用。

組合療法可提供「協同作用」且證實「協同性」，亦即當活性成分一起使用時所達成之效應大於由分開使用化合物所產生之效應的總和。協同效應可在活性成分如下時獲得：(1)於經組合之單位劑量調配物中同時共調配及投與或遞送；(2)以各別調配物形式交替或並行遞送；或(3)藉由一些其他方案。當以交替療法遞送時，協同效應可在化合物依序(例如藉由各別注射器中之不同注射)投與或遞送時獲得。一般而言，在交替療法期間，依序(亦即連續)投與有效劑量之各活性成分，而在組合療法中，有效劑量之兩種或兩種以上活性成分一起投與。

在一個態樣中，本發明提供一種治療癌症之方法，係藉由向有需要之個體投與抗體藥結合物與一或多種酪胺酸激酶抑制劑(包括(但不限於)EGFR抑制劑、Her2抑制劑、Her3抑制劑、IGFR抑制劑及Met抑制劑)之組合。

舉例而言，酪胺酸激酶抑制劑包括(但不限於)鹽酸埃羅替尼(Erlotinib hydrochloride)(Tarceva®)；立尼法尼(Linifanib)(N-[4-(3-胺基-1H-吲唑-4-基)苯基]-N'-(2-氟-5-甲基苯基)脲，亦稱為ABT 869，獲自Genentech)；蘋果酸舒尼替尼(Sunitinib malate)(Sutent®)；伯舒替尼(Bosutinib)(4-[(2,4-二氯-5-甲氧基苯基)胺基]-6-甲氧基-7-[3-(4-甲基哌嗪-1-基)丙氧基]喹啉-3-甲腈，亦稱為SKI-606，且描述於美國專利第6,780,996號中)；達沙替尼(Dasatinib)(Sprycel®)；帕唑帕尼

(Pazopanib)(Votrient®)；索拉非尼(Sorafenib)(Nexavar®)；紮克替馬(Zactima)(ZD6474)；尼羅替尼(nilotinib)(Tasigna®)；瑞戈非尼(Regorafenib)(Stivarga®)及伊馬替尼(Imatinib)或甲磺酸伊馬替尼(Gilvec®及Gleevec®)。

表皮生長因子受體(EGFR)抑制劑包括(但不限於)鹽酸埃羅替尼(Tarceva®)、吉非替尼(Gefitnib)(Iressa®)；N-[4-[(3-氯-4-氟苯基)胺基]-7-[[(3"S")-四氫-3-呋喃基]氧基]-6-喹唑啉基]-4(二甲基胺基)-2-丁烯醯胺，Tovok®)；凡德他尼(Vandetanib)(Caprelsa®)；拉帕替尼(Lapatinib)(Tykerb®)；(3R,4R)-4-胺基-1-((4-((3-甲氧基苯基)胺基)吡咯并[2,1-f][1,2,4]三嗪-5-基)甲基)哌啶-3-醇(BMS690514)；卡奈替尼二鹽酸鹽(Canertinib dihydrochloride)(CI-1033)；6-[4-[(4-乙基-1-哌嗪基)甲基]苯基]-N-[(1R)-1-苯基乙基]-7H-吡咯并[2,3-d]嘧啶-4-胺(AEE788，CAS 497839-62-0)；木利替尼(Mubritinib)(TAK165)；培利替尼(Pelitinib)(EKB569)；阿法替尼(Afatinib)(BIBW2992)；來那替尼(Neratinib)(HKI-272)；N-[4-[[1-[(3-氟苯基)甲基]-1H-吲唑-5-基]胺基]-5-甲基吡咯并[2,1-f][1,2,4]三嗪-6-基]-胺基甲酸(3S)-3-嗎啉基甲基酯(BMS599626)；N-(3,4-二氯-2-氟苯基)-6-甲氧基-7-[[(3aα,5β,6aα)-八氫-2-甲基環戊并[c]吡咯-5-基]甲氧基]-4-喹唑啉胺(XL647，CAS 781613-23-8)；及4-[4-[[(1R)-1-苯基乙基]胺基]-7H-吡咯并[2,3-d]嘧啶-6-基]-酚(PKI166，CAS 187724-61 -4)。

EGFR抗體包括(但不限於)西妥昔單抗(Cetuximab)(Erbitux®)；帕尼單抗(Panitumumab)(Vectibix®)；馬妥珠單抗(Matuzumab)(EMD-72000)；尼妥珠單抗(Nimotuzumab)(hR3)；紮魯姆單抗(Zalutumumab)；TheraCIM h-R3；MDX0447 (CAS 339151-96 -1)；及ch806 (mAb-806，CAS 946414-09 -1)。

人類表皮生長因子受體2 (HER2受體)(亦稱為Neu、ErbB-2、

CD340 或 p185) 抑制劑包括(但不限於)曲妥珠單抗(Trastuzumab)(Herceptin®)；帕妥珠單抗(Pertuzumab)(Omnitarg®)；來那替尼(HKI-272，(2E)-N-[4-[[3-氯-4-[(吡啶-2-基)甲氧基]苯基]胺基]-3-氰基-7-乙氧基喹啉-6-基]-4-(二甲基胺基)丁-2-烯醯胺，且描述於PCT公開案第WO 05/028443號中)；拉帕替尼或二甲苯磺酸拉帕替尼(Tykerb®)；(3R,4R)-4-胺基-1-((4-((3-甲氧基苯基)胺基)吡咯并[2,1-f][1,2,4]三嗪-5-基)甲基)哌啶-3-醇(BMS690514)；(2E)-N-[4-[(3-氯-4-氟苯基)胺基]-7-[[(3S)-四氫-3-呋喃基]氧基]-6-喹唑啉基]-4-(二甲基胺基)-2-丁烯醯胺(BIBW-2992，CAS 850140-72 -6)；N-[4-[[1-[(3-氟苯基)甲基]-1H-吲唑-5-基]胺基]-5-甲基吡咯并[2,1-f][1,2,4]三嗪-6-基]-胺基甲酸(3S)-3-嗎啉基甲基酯(BMS 599626，CAS 714971-09 -2)；卡奈替尼二鹽酸鹽(PD183805或CI-1033)；及N-(3,4-二氯-2-氟苯基)-6-甲氧基-7-[[(3aα,5β,6aα)-八氫-2-甲基環戊并[c]吡咯-5-基]甲氧基]-4-喹唑啉胺(XL647，CAS 781613-23-8)。

HER3抑制劑包括(但不限於)LJM716、MM-121、AMG-888、RG7116、REGN-1400、AV-203、MP-RM-1、MM-111及MEHD-7945A。

MET抑制劑包括(但不限於)卡博替尼(Cabozantinib)(XL184，CAS 849217-68 -1)；弗雷替尼(Foretinib)(GSK1363089，先前為XL880，CAS 849217-64 -7)；提瓦替尼(Tivantinib)(ARQ197，CAS 1000873-98-2)；1-(2-羥基-2-甲基丙基)-*N*-(5-(7-甲氧基喹啉-4-基氧基)吡啶-2-基)-5-甲基-3-側氧基-2-苯基-2,3-二氫-1*H*-吡唑-4-甲醯胺(AMG 458)；克卓替尼(Cryzotinib)(Xalkori®，PF-02341066)；(3Z)-5-(2,3-二氫-1H-吲哚-1-基磺醯基)-3-({3,5-二甲基-4-[(4-甲基哌嗪-1-基)羰基]-1H-吡咯-2-基}亞甲基)-1,3-二氫-2H-吲哚-2-酮(SU11271)；(3Z)-N-(3-氯苯基)-3-({3,5-二甲基-4-[(4-甲基哌嗪 -1-基)羰基]-1H-吡咯-2-基}亞甲基)-N-

甲基-2-側氧基吲哚啉-5-磺醯胺(SU11274)；(3Z)-N-(3-氯苯基)-3-{[3,5-二甲基-4-(3-嗎啉-4-基丙基)-1H-吡咯-2-基]亞甲基}-N-甲基-2-側氧基吲哚啉-5-磺醯胺(SU11606)；6-[二氟[6-(1-甲基-1H-吡唑-4-基)-1,2,4-三唑并[4,3-b]噠嗪-3-基]甲基]-喹啉(JNJ38877605，CAS 943540-75-8)；2-[4-[1-(喹啉-6-基甲基)-1H-[1,2,3]三唑并[4,5-b]吡嗪-6-基]-1H-吡唑-1-基]乙醇(PF04217903，CAS 956905-27-4)；N-((2R)-1,4-二噁烷-2-基甲基)-N-甲基-N'-[3-(1-甲基-1H-吡唑-4-基)-5-側氧基-5H-苯并[4,5]環庚并[1,2-b]吡啶-7-基]磺醯胺(MK2461，CAS 917879-39-1)；6-[[6-(1-甲基-1H-吡唑-4-基)-1,2,4-三唑并[4,3-b]噠嗪-3-基]硫基]-喹啉(SGX523，CAS 1022150-57-7)；及(3*Z*)-5-[[(2,6-二氯苯基)甲基]磺醯基]-3-[[3,5-二甲基-4-[[(2*R*)-2-(1-吡咯啶基甲基)-1-吡咯啶基]羰基]-1*H*-吡咯-2-基]亞甲基]-1,3-二氫-2*H*-吲哚-2-酮(PHA665752，CAS 477575-56-7)。

IGF1R抑制劑包括(但不限於) BMS-754807、XL-228、OSI-906、GSK0904529A、A-928605、AXL1717、KW-2450、MK0646、AMG479、IMCA12、MEDI-573及BI836845。欲回顧，參見例如Yee, JNCI, 104; 975 (2012)。

在另一態樣中，本發明提供一種治療癌症之方法，其係藉由將抗體藥結合物與一或多種FGF下游信號傳導路徑抑制劑(包括(但不限於)MEK抑制劑、Braf抑制劑、PI3K/Akt抑制劑、SHP2抑制劑以及mTor抑制劑)組合投與有需要之個體。

舉例而言，有絲分裂原活化蛋白激酶(MEK)抑制劑包括(但不限於) XL-518 (亦稱為GDC-0973，CAS編號1029872-29-4，獲自ACC Corp.)；2-[(2-氯-4-碘苯基)胺基]-N-(環丙基甲氧基)-3,4-二氟-苯甲醯胺(亦稱為CI-1040或PD184352且描述於PCT公開案第WO2000035436號中)；N-[(2R)-2,3-二羥基丙氧基]-3,4-二氟-2-[(2-氟-4-碘苯基)胺基]-

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苯甲醯胺(亦稱為PD0325901且描述於PCT公開案第WO2002006213號中)；2,3-雙[胺基[(2-胺基苯基)硫基]亞甲基]-丁二腈(亦稱為U0126且描述於美國專利第2,779,780號中)；N-[3,4-二氟-2-[(2-氟-4-碘苯基)胺基]-6-甲氧基苯基]-1-[(2R)-2,3-二羥丙基]-環丙烷磺醯胺(亦稱為RDEA119或BAY869766且描述於PCT公開案第WO2007014011號中)；(3S,4R,5Z,8S,9S,11E)-14-(乙胺基)-8,9,16-三羥基-3,4-二甲基-3,4,9,19-四氫-1H-2-苯并氧雜環十四烷-1,7(8H)-二酮](亦稱為E6201且描述於PCT公開案第WO2003076424號中)；2'-胺基-3'-甲氧基黃酮(亦稱為PD98059，獲自Biaffin GmbH & Co., KG, Germany)；維羅非尼(Vemurafenib)(PLX-4032，CAS 918504-65 -1)；(R)-3-(2,3-二羥丙基)-6-氟-5-(2-氟-4-碘苯基胺基)-8-甲基吡啶并[2,3-d]嘧啶-4,7(3H,8H)-二酮(TAK-733，CAS 1035555-63-5)；皮馬瑟替(Pimasertib)(AS-703026，CAS 1204531-26 -9)；及曲美替尼二甲亞碸(Trametinib dimethyl sulfoxide)(GSK-1120212，CAS 1204531-25-80)。

磷酸肌醇3-激酶(PI3K)抑制劑包括(但不限於) 4-[2-(1H-吲唑-4-基)-6-[[4-(甲基磺醯基)哌嗪-1-基]甲基]噻吩并[3,2-d]嘧啶-4-基]嗎啉(亦稱為GDC 0941且描述於PCT公開案第WO 09/036082及WO 09/055730號中)；2-甲基-2-[4-[3-甲基-2-側氧基-8-(喹啉-3-基)-2,3-二氫咪唑并[4,5-c]喹啉-1-基]苯基]丙腈(亦稱為BEZ 235或NVP-235，且描述於PCT公開案第WO 06/122806號中)；4-(三氟甲基)-5-(2,6-二嗎啉基嘧啶-4-基)吡啶-2-胺(亦稱為BKM120或NVP-BKM120，且描述於PCT公開案第WO2007/084786號中)；陶紮色替(Tozasertib)(VX680或MK-0457，CAS 639089-54-6)；(5Z)-5-[[4-(4-吡啶基)-6-喹啉基]亞甲基]-2,4-噻唑啶二酮(GSK1059615，CAS 958852-01 -2)；(1E,4S,4aR,5R,6aS,9aR)-5-(乙醯氧基)-1-[(二-2-丙烯基胺基)亞甲基]-4,4a,5,6,6a,8,9,9a-八氫-11-羥基-4-(甲氧基甲基)-4a,6a-二甲基-環戊并

[5,6]蒽并[1,2-c]哌喃-2,7,10(1H)-三酮(PX866，CAS 502632-66-8)；及8-苯基-2-(嗎啉-4-基)-吃烯-4-酮(LY294002，CAS 154447-36 -6)。

mTor抑制劑包括(但不限於)坦羅莫司(Torisel®)；地磷莫司(正式地稱為迪福莫司，(*1R,2R*,4*S*)-4-[(2*R*)-2[(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*Z*,30*S*,32*S*,35*R*)-1,18-二羥基-19,30-二甲氧基-15,17,21,23,29,35-六甲基-2,3,10,14,20-五側氧基-11,36-二氧雜-4-氮雜三環[30.3.1.$0^{4,9}$]三十六基-16,24,26,28-四烯-12-基]丙基]-2-甲氧基環己基二甲基次膦酸酯，亦稱為AP23573及MK8669，且描述於PCT公開案第WO 03/064383號中)；依維莫司(Everolimus)(Afinitor®或RAD001)；雷帕黴素(Rapamycin)(AY22989，Sirolimus®)；斯馬匹莫(Simapimod)(CAS 164301-51 -3)；(5-{2,4-雙[(3S)-3-甲基嗎啉-4-基]吡啶并[2,3-d]嘧啶-7-基}-2-甲氧基苯基)甲醇(AZD8055)；2-胺基-8-[反-4-(2-羥基乙氧基)環己基]-6-(6-甲氧基-3-吡啶基)-4-甲基-吡啶并[2,3-d]嘧啶-7(8*H*)-酮(PF04691502，CAS 1013101-36 -4)；及N^2-[1,4-二側氧基-4-[[4-(4-側氧基-8-苯基-*4H*-1-苯并哌喃-2-基)嗎啉鎓-4-基]甲氧基]丁基]-L-精胺醯甘胺醯基-L-α-天冬胺醯基L-絲胺酸-，內鹽(SF1126，CAS-67 -1)。

在又一態樣中，本發明提供一種治療癌症的方法，係藉由將抗體藥結合物與一或多種促細胞凋亡劑(包括(但不限於) IAP抑制劑、Bcl2抑制劑、MCl1抑制劑、Trail劑、Chk抑制劑)組合投與有需要之個體。

舉例而言，IAP抑制劑包括(但不限於) NVP-LCL161、GDC-0917、AEG-35156、AT406及TL32711。IAP抑制劑之其他實例包括(但不限於) WO04/005284、WO 04/007529、WO05/097791、WO 05/069894、WO 05/069888、WO 05/094818、US2006/0014700、US2006/0025347、WO 06/069063、WO 06/010118、WO 06/017295及

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WO08/134679中所揭示之彼等物，該等文獻皆以引用的方式併入本文中。

BCL-2抑制劑包括(但不限於) 4-[4-[[2-(4-氯苯基)-5,5-二甲基-1-環己-1-基]甲基]-1-哌嗪基]-N-[[4-[[(1R)-3-(4-嗎啉基)-1-[(苯硫基)甲基]丙基]胺基]-3-[(三氟甲基)磺醯基]苯基]磺醯基]苯甲醯胺(亦稱為ABT-263且描述於PCT公開案第WO 09/155386號中)；替曲卡星A (Tetrocarcin A)；抗黴素(Antimycin)；棉籽酚(Gossypol)((-)BL-193)；奧巴拉西(Obatoclax)；2-胺基-6-環戊基-4-(1-氰基-2-乙氧基-2-側氧基乙基)-4H色酮-3-甲酸乙酯(HA14-1)；奧利默森(Oblimersen)(G3139，Genasense®)；Bak BH3肽；(-)-棉籽酚乙酸(AT-101)；4-[4-[(4'-氯[1,1'-聯苯]-2-基)甲基]-1-哌嗪基]-N-[[4-[[(1R)-3-(二甲基胺基)-1-[(苯硫基)甲基]丙基]胺基]-3-硝基苯基]磺醯基]-苯甲醯胺(ABT-737，CAS 852808-04-9)；及納維克拉斯(Navitoclax)(ABT-263，CAS 923564-51-6)。

促細胞凋亡受體促效劑(PARAs)包括DR4 (TRAILR1)及DR5 (TRAILR2)，包括(但不限於)杜拉樂明(Dulanermin)(AMG-951，RhApo2L/TRAIL)；瑪帕單抗(Mapatumumab)(HRS-ETR1，CAS 658052-09-6)；來沙木單抗(Lexatumumab)(HGS-ETR2，CAS 845816-02-6)；阿撲單抗(Apomab)(Apomab®)；康納木單抗(Conatumumab)(AMG655，CAS 896731-82-1)；及替加珠單抗(Tigatuzumab)(CS1008，CAS 946415-34-5，獲自Daiichi Sankyo)。

檢查點激酶(CHK)抑制劑包括(但不限於) 7-羥基星孢菌素(7-Hydroxystaurosporine)(UCN-01)；6-溴-3-(1-甲基-1*H*-吡唑-4-基)-5-(3*R*)-3-哌啶基-吡唑并[1,5-a]嘧啶-7-胺(SCH900776，891494-63-6)；5-(3-氟苯基)-3-脲基噻吩-2-甲酸N-[(S)-哌啶-3-基]醯胺(AZD7762，CAS 860352-01-8)；4-[((3S)-1-氮雜雙環[2.2.2]辛-3-基)胺基]-3-(1H-苯

并咪唑-2-基)-6-氯喹啉-2(1H)-酮(CHIR 124，CAS 405168-58 -3)；7-胺基放線菌素d (7-AAD)、異格魯醯胺(Isogranulatimide)、去溴已炔二醇(debromohymenialdisine)；N-[5-溴-4-甲基-2-[2S)-2-嗎啉基甲氧基]苯基]-N'-(5-甲基-2-吡嗪基)脲(LY2603618，CAS 911222-45 -2)；蘿蔔硫素(Sulforaphane)(CAS 4478-93 -7,4-甲基亞磺醯基丁基異硫氰酸酯)；9,10,11,12-四氫-9,12-環氧基-1H-二吲哚并1,2,3-*fg*:3',2',1'-*kl*]吡咯并[3,4-*i*][1,6]苯并二吖 -1,3(2H)-二酮(SB-218078，CAS 135897-06-2)；及TAT-S216A (Sha等人, Mol. Cancer. Ther 2007; 6(1):147-153)及CBP501。

在一個態樣中，本發明提供一種治療癌症之方法，係藉由將抗體藥結合物與一或多種FGFR抑制劑組合投與有需要之個體。舉例而言，FGFR抑制劑包括(但不限於)布立尼布丙胺酸酯(Brivanib alaninate)(BMS-582664，(S)-((R)-1-(4-(4-氟-2-甲基-*1H*-吲哚-5-基氧基)-5-甲基吡咯并[2,1-*f*][1,2,4]三嗪-6-基氧基)丙-2-基)2-胺基丙酸酯)；瓦格特氟(Vargatef)(BIBF1120，CAS 928326-83-4)；多韋替尼二乳酸(Dovitinib dilactic)(TKI258，CAS 852433-84-2)；3-(2,6-二氯-3,5-二甲氧基-苯基)-1-{6-[4-(4-乙基-哌嗪-1-基)-苯基胺基]-嘧啶-4-基}-1-甲基-脲(BGJ398，CAS 872511-34 -7)；達魯舍替(Danusertib)(PHA-739358)；及(PD173074，CAS 219580-11-7)。在一個特定態樣中，本發明提供一種治療癌症的方法，係藉由將抗體藥結合物與FGFR2抑制劑組合投與有需要之個體，FGFR2抑制劑諸如3-(2,6-二氯-3,5-二甲氧基苯基)-1-(6((4-(4-乙基哌嗪-1-基)苯基)胺基)嘧啶-4-基)-1-甲基脲(亦稱為BGJ-398)；或4-胺基-5-氟-3-(5-(4-甲基哌嗪-1-基)-1H-苯并[d]咪唑-2-基)喹啉-2(1H)-酮(亦稱為多韋替尼(dovitinib)或TKI-258)；AZD4547 (Gavine等人, 2012, Cancer Research 72, 2045-56, N-[5-[2-(3,5-二甲氧基苯基)乙基]-2H-吡唑-3-基]-4-(3R,5S)-二甲基哌嗪-1-基)

苯甲醯胺)；波納替尼(Ponatinib)(AP24534；Gozgit等人，2012, Mol Cancer Ther., 11; 690-99；3-[2-(咪唑并[1,2-b]噠嗪-3-基)乙炔基]-4-甲基-N-{4-[(4-甲基哌嗪-1-基)甲基]-3-(三氟甲基)苯基}苯甲醯胺，CAS 943319-70-8)。

醫藥組合物

為製備including免疫結合物的醫藥或無菌組合物，將本發明之免疫結合物與醫藥學上可接受之載劑或賦形劑混合。組合物另外可含有一或多種適於治療或預防癌症(例如卵巢癌、腎癌、肝癌及甲狀腺癌)的其他治療劑。

治療劑及診斷劑之調配物可藉由與生理學上可接受之載劑、賦形劑或穩定劑混合、以例如凍乾粉末、漿液、水溶液、洗劑或懸浮液形式製備(參見例如Hardman等人，Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y., 2001；Gennaro, Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y., 2000；Avis等人，(編), Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY, 1993；Lieberman等人，(編), Pharmaceutical Dosage Forms: Tablets, Marcel Dekker, NY, 1990；Lieberman等人，(編) Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, NY, 1990；Weiner及Kotkoskie, Excipient Toxicity and Safety, Marcel Dekker, Inc., New York, N.Y., 2000)。

在一個特定態樣中，本發明之抗體藥結合物的臨床使用形式(CSF)為含有ADC、丁二酸鈉及聚山梨醇酯20之小瓶中的凍乾物。凍乾物可用注射用水復原，溶液包含ADC、丁二酸鈉、蔗糖及聚山梨醇酯20，pH為約5.0。為了隨後靜脈內投與，所得溶液通常在載劑溶液中進一步稀釋。

選擇用於治療之投與方案視若干因素而定，包括實體之血清或組織周轉率、症狀程度、實體之免疫原性及生物基質中之靶細胞之可接近性。在某些態樣中，投藥方案根據副作用之可接受程度來使遞送至患者之治療量最大化。因此，所遞送之生物制劑量部分地視特定實體及所治療之病狀嚴重程度而定。關於選擇抗體、細胞激素及小分子之適當劑量之指導可獲得(參見例如Wawrzynczak, Antibody Therapy, Bios Scientific Pub. Ltd, Oxfordshire, UK, 1996；Kresina (編), Monoclonal Antibodies, Cytokines and Arthritis, Marcel Dekker, New York, N.Y., 1991；Bach (編), Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases, Marcel Dekker, New York, N.Y., 1993；Baert等人, New Engl. J. Med. 348:601-608, 2003；Milgrom等人, New Engl. J. Med. 341:1966-1973, 1999；Slamon等人, New Engl. J. Med. 344:783-792, 2001；Beniaminovitz等人, New Engl. J. Med. 342:613-619, 2000；Ghosh等人, New Engl. J. Med. 348:24-32, 2003；Lipsky等人, New Engl. J. Med. 343:1594-1602, 2000)。

適當劑量由臨床師例如使用此項技術中已知或懷疑影響治療或預測影響治療之參數或因素來確定。一般而言，初始劑量為稍微小於最佳劑量的量，且隨後以較小增量遞增，直至達成所要或最佳作用(相對於任何負面的副作用而言)。重要診斷度量包括症狀(例如發炎)之度量或發炎性細胞激素之產生量。

可改變醫藥組合物抗體藥結合物中活性成分的實際劑量水準，以便使得活性成分的量有效達成針對特定患者、組合物及投藥模式之所要治療反應，而不會對患者產生毒性。所選劑量水準將視多種藥物動力學因素而定，包括本發明所用特定組合物或其酯、鹽或醯胺之活性；投藥途徑；投藥時間；所用特定化合物之排泄速率；治療持續時間；與所用特定組合物組合使用之其他藥物、化合物及/或物質；所

治療患者之年齡、性別、體重、病狀、一般健康及先前病史；及醫學技術中已知之類似因素。

包含抗體或其片段的組合物可藉由連續輸注提供，或藉由在例如一天、一週之時間間隔或每週1-7次給藥來提供。劑量可以靜脈內、皮下、表面、經口、經鼻、直腸、肌肉內、顱內方式或藉由吸入來提供。特定劑量方案為包括避免顯著不良副作用之最大劑量或給藥頻率的劑量方案。

對於本發明之免疫結合物而言，投與患者之劑量可為每公斤患者體重0.0001 mg至100 mg。劑量可為每公斤患者體重0.0001 mg至20 mg、0.0001 mg至10 mg、0.0001 mg至5 mg、0.0001 mg至2 mg、0.0001 mg至1 mg、0.0001 mg至0.75 mg、0.0001 mg至0.5 mg、0.0001 mg至0.25 mg、0.0001 mg至0.15 mg、0.0001 mg至0.10 mg、0.001 mg至0.5 mg、0.01 mg至0.25 mg，或0.01 mg至0.10 mg。抗體或其片段之劑量可使用患者體重(千克(kg))乘以所投劑量(mg/kg)來計算。

免疫結合物可重複給予且投藥間隔時間可為至少1天、2天、3天、5天、10天、15天、30天、45天、2個月、75天、3個月或至少6個月。在一個特定態樣中，本發明之免疫結合物每3週重複給予。

特定患者之有效量可根據以下因素而變化：諸如所治療之病狀、患者之總體健康狀況、投藥方法、途徑及劑量，以及副作用之嚴重程度(參見例如Maynard等人, A Handbook of SOPs for Good Clinical Practice, Interpharm Press, Boca Raton, Fla., 1996; Dent, Good Laboratory and Good Clinical Practice, Urch Publ., London, UK, 2001)。

投藥途徑可為例如局部或皮膚施用、藉由靜脈內、腹膜內、腦內、肌肉內、眼內、動脈內、腦脊髓內、病灶內注射或輸注，或持續釋放系統或植入(參見例如Sidman等人, Biopolymers 22:547-556,

1983；Langer等人, J. Biomed. Mater. Res. 15:167-277, 1981；Langer, Chem. Tech. 12:98-105, 1982；Epstein等人, Proc. Natl. Acad. Sci. USA 82:3688-3692, 1985；Hwang等人, Proc. Natl. Acad. Sci. USA 77:4030-4034, 1980；美國專利第6,350,466號及第6,316,024號)。必要時，組合物亦可包括助溶劑或局部麻醉劑(諸如利多卡因)以減輕注射部位之疼痛，或兩者。另外，亦可使用肺部投藥，例如使用吸入器或噴霧器及具有氣霧劑之調配物。參見例如美國專利第6,019,968號、第5,985,320號、第5,985,309號、第5,934,272號、第5,874,064號、第5,855,913號、第5,290,540號及第4,880,078號；及PCT公開案第WO 92/19244號、第WO 97/32572號、第WO 97/44013號、第WO 98/31346號及第WO 99/66903號，其各自以全文引用之方式併入本文中。

本發明之組合物亦可經由一或多種投藥途徑、使用此項技術中已知之多種方法中之一或多者來投與。如熟習此項技術者所瞭解，投藥途徑及/或模式將視所要結果而變化。免疫結合物之所選投與途徑包括靜脈內、肌肉內、皮內、腹膜內、皮下、脊髓或其他非經腸投與途徑，例如注射或輸注。非經腸投藥可代表除經腸及局部投藥外之投藥模式，其通常為注射，且包括(但不限於)靜脈內、肌肉內、動脈內、鞘內、囊內、眶內、心內、皮內、腹膜內、經氣管、皮下、表皮下、關節內、囊下、蛛網膜下、脊椎內、硬膜外及胸骨內注射及輸注。或者，本發明之組合物可經由非非經腸途徑投與，諸如局部、表皮或黏膜投與途徑，例如鼻內、經口、陰道、直腸、舌下或局部。在一個態樣中，本發明之免疫結合物藉由輸注投與。在另一態樣中，免疫結合物係皮下投與。

若本發明之免疫結合物係以控制釋放或持續釋放系統投與，可使用泵浦達成控制或持續釋放(參見Langer, 同上；Sefton, CRC Crit.

Ref Biomed. Eng. 14:20, 1987；Buchwald等人, Surgery 88:507, 1980；Saudek等人, N. Engl. J. Med. 321:574, 1989)。聚合物材料可用於達成免疫結合物療法之控制或持續釋放(參見例如Medical Applications of Controlled Release, Langer及Wise (編), CRC Pres., Boca Raton, Fla., 1974; Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen及Ball (編), Wiley, New York, 1984; Ranger及Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61, 1983；亦參見Levy等人, Science 228:190, 1985; During等人, Ann. Neurol. 25:351, 1989；Howard等人, J. Neurosurg. 7 1:105, 1989；美國專利第5,679,377號；美國專利第5,916,597號；美國專利第5,912,015號；美國專利第5,989,463號；美國專利第5,128,326號；PCT公開案第WO 99/15154號；及PCT公開案第WO 99/20253號)。持續釋放型調配物中所用之聚合物之實例包括(但不限於)聚(甲基丙烯酸2-羥基乙酯)、聚(甲基丙烯酸甲酯)、聚(丙烯酸)、聚(乙烯-共-乙酸乙烯酯)、聚(甲基丙烯酸)、聚乙交酯(PLG)、聚酸酐、聚(N-乙烯吡咯啶酮)、聚(乙烯醇)、聚丙烯醯胺、聚(乙二醇)、聚乳酸交酯(PLA)、聚(丙交酯-共-乙交酯)(PLGA)及聚原酸酯。在一個態樣中，持續釋放型調配物中所用之聚合物呈惰性，不含可濾出雜質，儲存穩定，無菌且可生物降解。控制或持續釋放型系統可置放於預防或治療標靶附近，因此僅需要全身性劑量之一部分(參見例如Goodson, Medical Applications of Controlled Release, 同上, 第2卷, 第115-138頁, 1984)。

控制釋放型系統論述於Langer, Science 249:1527-1533, 1990之評述中。熟習此項技術者已知之任何技術可用於製造包含本發明之一或多種免疫結合物的持續釋放型調配物。參見例如美國專利第4,526,938號；PCT公開案WO 91/05548；PCT公開案WO 96/20698；Ning等人, Radiotherapy & Oncology 39:179-189, 1996；Song等人, PDA Journal

of Pharmaceutical Science & Technology 50:372-397, 1995；Cleek等人, Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, 1997；及Lam等人, Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, 1997，各文獻以全文引用的方式併入本文中。

若本發明之免疫結合物局部投與，則其可調配成以下形式：軟膏、乳膏、經皮貼片、乳液、凝膠、洗髮劑、噴霧劑、氣溶膠、溶液、乳液，或熟習此項技術者熟知的其他形式。參見例如Remington's Pharmaceutical Sciences and Introduction to Pharmaceutical Dosage Forms, 第19版, Mack Pub. Co., Easton, Pa. (1995)。對於不可噴霧的局部劑型而言，通常使用包含與局部施用相容之載劑或一或多種賦形劑且在一些情況下動態黏度大於水的黏稠至半固體或固體形式。適合調配物包括(但不限於)溶液、懸浮液、乳液、乳膏、軟膏、粉末、擦劑、油膏及其類似物，必要時，其經滅菌或與助劑(例如防腐劑、穩定劑、濕潤劑、緩衝劑或鹽)混合以影響各種特性，諸如滲透壓。其他適合的局部劑型包括可噴霧氣溶膠製劑，其中在一些情況下，與固體或液體惰性載劑組合之活性成分封裝於具有加壓揮發物(例如氣態推進劑，諸如氟利昂(freon))之混合物或擠壓瓶中。必要時，醫藥組合物及劑型中亦可添加增濕劑或保濕劑。此類其他成分之實例在此項技術中已熟知。

若包含免疫結合物之組合物係鼻內投與，則其可調配成氣溶膠形式、噴霧劑、霧狀或滴劑形式。特定言之，根據本發明使用的預防劑或治療劑可宜以自加壓包或噴霧器呈遞之氣溶膠噴霧形式遞送，其中使用適合推進劑(例如二氯二氟甲烷、三氯氟甲烷、二氯四氟乙烷、二氧化碳或其他適合氣體)。在加壓氣溶膠之情況下，劑量單位可藉由提供可遞送定量之量的閥來決定。吸入器或吹入器中所用的膠囊及藥筒(由例如明膠組成)可調配成含有化合物與適合粉末基質(諸如

乳糖或澱粉)之粉末混合物。

與第二治療劑(例如細胞激素、類固醇、化學治療劑、抗生素或輻射)共投與或用其治療的方法在此項技術中已知(參見例如Hardman等人, (編) (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10.sup.th ed., McGraw-Hill, New York, N.Y.；Poole及Peterson (編) (2001) Pharmacotherapeutics for Advanced Practice:A Practical Approach, Lippincott, Williams & Wilkins, Phila., Pa.；Chabner及Longo (編) (2001) Cancer Chemotherapy and Biotherapy, Lippincott, Williams & Wilkins, Phila., Pa.)。有效量之治療劑可使症狀減少至少10%、至少20%、至少約30%、至少40%或至少50%。

可為與免疫結合物組合投與之其他療法(例如預防劑或治療劑)可與本發明之免疫結合物相隔小於5分鐘投與，相隔小於30分鐘，相隔1小時，相隔約1小時，相隔約1至約2小時，相隔約2小時至約3小時，相隔約3小時至約4小時，相隔約4小時至約5小時，相隔約5小時至約6小時，相隔約6小時至約7小時，相隔約7小時至約8小時，相隔約8小時至約9小時，相隔約9小時至約10小時，相隔約10小時至約11小時，相隔約11小時至約12小時，相隔約12小時至18小時，相隔18小時至24小時，相隔24小時至36小時，相隔36小時至48小時，相隔48小時至52小時，相隔52小時至60小時，相隔60小時至72小時，相隔72小時至84小時，相隔84小時至96小時，或96小時至120小時。在一次相同患者的訪視內可投與兩種或兩種以上療法。

在某些態樣中，免疫結合物可經調配以保證正確的活體內分佈。舉例而言，血腦障壁(BBB)排除多種高度親水性化合物。為確保本發明之治療化合物越過BBB(必要時)，其可調配成例如脂質體。關於製造脂質體之方法，參見例如美國專利第4,522,811號；第5,374,548號；及第5,399,331號。脂質體可包含選擇性輸送至特定細胞或器官中

之一或多種部分，從而增強靶向藥物遞送(參見例如Ranade, (1989) J. Clin. Pharmacol. 29:685)。例示性靶向部分包括葉酸鹽或生物素(參見例如Low等人之美國專利第5,416,016號)；甘露糖苷(Umezawa等人, (1988) Biochem. Biophys. Res. Commun. 153:1038)；抗體(Bloeman等人, (1995) FEBS Lett. 357:140；Owais等人, (1995) Antimicrob. Agents Chemother. 39:180)；界面活性劑蛋白質A受體(Briscoe等人, (1995) Am. J. Physiol. 1233:134)；p 120 (Schreier等人, (1994) J. Biol. Chem. 269:9090)；亦參見K. Keinanen; M. L. Laukkanen (1994) FEBS Lett. 346:123; J. J. Killion; I. J. Fidler (1994) Immunomethods 4:273。

本發明提供將包含單獨或與其他療法組合之免疫結合物之醫藥組合物投與有需要之個體的方案。組合療法(例如預防劑或治療劑)可同時或依序投與個體。組合治療中之療法(例如預防劑或治療劑)亦可循環地投與。循環療法包括將第一療法(例如第一預防劑或治療劑)投與一段時間，隨後將第二療法(例如第二預防劑或治療劑)投與一段時間，及重複此依序投與(亦即循環)以便減小針對療法(例如藥劑)之一的抗藥性，避免或降低療法(例如藥劑)之一的副作用，及/或改良療法之功效。

本發明之組合療法中之療法(例如預防劑或治療劑)可同時投與個體。

術語「同時」不限於在恰好相同的時間投與療法(例如預防劑或治療劑)，而是意欲包含抗體或其片段的醫藥組合物依序及在時間間隔內投與個體，使得免疫結合物可與其他療法一起發揮作用以得到比其以其他方式投與更大的益處。舉例而言，各療法可同時或依任何次序在不同時間點依序投與個體；然而，若非同時投與，則其投與的時間應足夠接近以便提供所要的治療或預防作用。各療法可以任何適當形式且藉由任何適合途徑分別投與個體。在各種態樣中，可相隔小於

OnCusp
Ex. 1002

15分鐘、小於30分鐘、小於1小時、相隔約1小時、相隔約1小時至約2小時、相隔約2小時至約3小時、相隔約3小時至約4小時、相隔約4小時至約5小時、相隔約5小時至約6小時、相隔約6小時至約7小時、相隔約7小時至約8小時、相隔約8小時至約9小時、相隔約9小時至約10小時、相隔約10小時至約11小時、相隔約11小時至約12小時、相隔24小時、相隔48小時、相隔72小時或相隔1週向個體投與療法(例如預防劑或治療劑)。在其他態樣中，在相同的患者訪視內投與兩種或兩種以上療法(例如預防劑或治療劑)。

組合療法中之預防劑或治療劑可以相同醫藥組合物投與個體。或者，組合療法中之預防劑或治療劑可以各別醫藥組合物同時投與個體。預防劑或治療劑可藉由相同或不同投藥途徑投與個體。

實例

實例1：藉由噬菌體呈現技術鑑別CDH6抗體

HuCAL PLATINUM®淘選

藉由選擇結合至CDH6-ECD的純系來鑑別抗體。使用市售的噬菌體呈現文庫Morphosys HuCAL PLATINUM®文庫作為抗體變異體來源。噬菌質體文庫係基於HuCAL®概念(Knappik等人, J Mol Biol. 2000: 296(1):57-86；Prassler等人, J Mol Biol. 2011:413(1): 261-78 2011)且使用在噬菌體表面上呈現Fab的CysDisplayTM技術(Rothe等人, J Mol Biol. 2008: 376(4): 1182-200)。分離抗CDH6抗體時，使用固相及溶液淘選方法執行標準淘選策略。

淘選及篩選所用之抗原(重組蛋白質及細胞株)及抗體試劑之概述

針對多種形式的CDH6抗原完成淘選。作為抗原用於淘選及隨後篩選及表徵之重組CDH6蛋白質及表現CDH6之細胞株的概述明示於表1中。

根據GenBank或Uniprot資料庫之胺基酸序列(參見表1)對人類、

小鼠及大鼠CDH6細胞外域進行基因合成。根據使用來自多個食蟹獼猴組織之mRNA所產生的胺基酸序列及同源資訊(例如Zyagen Laboratories, San Diego, CA)對食蟹獼猴CDH6 cDNA模板進行基因合成。所合成的所有DNA片段選殖入具有允許純化之所列親和標記的適當表現載體或Zyagen Laboratories之用於哺乳動物細胞表面表現的表現載體中。

為了產生外源性表現人類CDH6的穩定CHO細胞株，根據製造商說明書使用TREX表現系統(Invitrogen, Carlsbad, CA)。簡言之，使CHO-TREx細胞(Invitrogen, R718-07, Carlsbad, CA)與10% FBS (Invitrogen, 10082-147, Carlsbad,CA)及10 μg/ml殺稻瘟菌素(Invitrogen A11139-02, Carlsbad, CA)一起在DMEM培養基(Invitrogen 11995-085)中生長。當細胞達成90%匯合時，在6孔盤中進行轉染。在一個艾本德無菌管(sterile Eppendorf tube)中將4 μg線性化CDH6質體DNA與100 μl DMEM培養基(無FBS)混合，在另一個艾本德無菌管中將12 μl Lipofectamine® 2000 (Invitrogen 11668-019, Carlsbad, CA)與100 μl DMEM培養基混合。將DNA與Lipofectamine®混合在一起且在室溫下培育15分鐘。對於各孔而言，將CHO-TREx細胞培養基更換為1 ml不含FBS的DMEM培養基；向各孔中添加一半的上述DNA/Lipofectamine®混合物，培育2小時。接著向各孔中添加2 ml生長培養基(具有FBS)，且細胞培育隔夜。次日，自6孔盤分離經轉染之細胞至T175燒瓶中，且在具有10% FBS、10 μg/ml殺稻瘟菌素、800-1000 μg/ml遺傳黴素(Invitrogen 10131-027)的選擇DMEM培養基中生長。在選擇培養基中使用最終1 μg/ml四環素誘導CDH6表現20至24小時。陽性細胞用最終5 μg/ml 抗CDH6一次單株抗體(MAB2715，得自R&D Systems, Minneapolis, MN)標記，接著用PE結合之抗小鼠二次抗體(目錄號12-4010-87, eBioscience, San Diego, CA)標記且藉由FACS分

選。

藉由選殖入哺乳動物表現載體(pcDNA6.1, Invitrogen, Carlsbad, CA)中之相應cDNAs轉染CHO-K1細胞(Invitrogen, Carlsbad, CA)來產生以外源性表現源於小鼠、大鼠及食蟹獼猴之CDH6為特徵的穩定CHO細胞株。當細胞達成90%匯合時，在6孔盤中進行轉染。在一個艾本德無菌管中將4 μg線性化CDH6質體DNA與100 μl不含FBS的DMEM培養基混合，在另一個艾本德無菌管中將12 μl Lipofectamine®2000 (Invitrogen 11668-019, Carlsbad, CA)與100 μl DMEM培養基混合。將DNA與Lipofectamine®溶液混合在一起，且在室溫下培育15分鐘。對於各孔而言，將CHO細胞培養基更換為1 ml不含FBS的DMEM培養基；向各孔中添加一半的上述DNA/Lipofectamine®混合物，培育2小時。接著向各孔中添加2 ml生長培養基(具有FBS)，且細胞培育隔夜。次日，自6孔盤分離經轉染之細胞至T175燒瓶中，且在具有10% FBS、10 μg/ml殺稻瘟菌素、800-1000 μg/ml遺傳黴素(Invitrogen 10131-027 Carlsbad, CA)的選擇DMEM培養基中生長。在選擇培養基中使用最終1 μg/ml四環素誘導CDH6表現20至24小時。陽性細胞用最終5 μg/ml 抗CDH6一次單株抗體(MAB2715，得自R&D Systems, Minneapolis, MN)標記，接著用PE結合之抗小鼠二次抗體(目錄號12-4010-87, eBioscience, San Diego, CA)標記且藉由FACS分選。替代的市售抗CDH6抗體為2B6抗體(#GWB-E8FDF3-Genway, San Diego, CA)。此抗體亦用於證實細胞中之CDH6表現。

表1

用於淘選及篩選之抗原、抗體及細胞株試劑之概述

抗原/抗體	寄存號/來源	描述	成熟序列
His6-SUMO-CDH6 aa54-260-APP-Avi	NM_004932.3	人類EC 1/2域變異體 (SEQ ID NO:3)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDGGGGSEFRHDSGLNDIFEAQK IEWHE
hCDH6aa54-615 APPavi	NM_004932.3	人類全長ECD (SEQ ID NO:4)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGENAEIEYSITDGEG LDMFDVITDQETQEGIITVKKLLDFEKKK VYTLKVEASNPYVEPRFLYLGPFKDSAT VRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLLWHNIT VIATEINNPKQSSRVPLYIKVLDVNDNAP EFAEFYETFVCEKAKADQLIQTLHAVDK DDPYSGHQFSFSLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCACDHHGNMQ SCHAEALIHPTGLSTGAGSEFRHDSGLND IFEAQKIEWHE
hCDH6aa54-615 APPavi-生物素	NM_004932.3	生物素化人類全長ECD (SEQ ID NO:5)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGENAEIEYSITDGEG LDMFDVITDQETQEGIITVKKLLDFEKKK VYTLKVEASNPYVEPRFLYLGPFKDSAT VRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLLWHNIT VIATEINNPKQSSRVPLYIKVLDVNDNAP EFAEFYETFVCEKAKADQLIQTLHAVDK DDPYSGHQFSFSLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCACDHHGNMQ SCHAEALIHPTGLSTGAGSEFRHDSGLND IFEAQK(BIOTIN)IEWHE

hCDH6aa54-615 Fc	NM_004932.3	二聚化人類全長ECD (SEQ ID NO:6)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGENAEIEYSITDGEG LDMFDVITDQETQEGIITVKKLLDFEKKK VYTLKVEASNPYVEPRFLYLGPFKDSAT VRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLLWHNIT VIATEINNPKQSSRVPLYIKVLDVNDNAP EFAEFYETFVCEKAKADQLIQTLHAVDK DDPYSGHQFSFSLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCACDHHGNMQ SCHAEALIHPTGLSTGAGSDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
cynoCDH6 FL	關於食蟹獼猴序列衍生，參見上述說明	食蟹獼猴(*Macaca fascicularis*)全長CDH6 (SEQ ID NO:7)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGENAEIEYSITDGEG LDMFDVITDQETQEGIITVKKLLDFEKKK VYTLKVEASNPHVEPRFLYLGPFKDSAT VRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLLWHNIT VIATEINNPKQSSRVPLYIKVLDVNDNAP EFAEFYETFVCEKAKADQLIQTLRAVDK DDPYSGHQFSFSLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCACDHHGNMQ SCHAEALIHPTGLSTGAGSEFRHDSGLND IFEAQKIEWHE
moCDH6 FL	NM_007666.3	小鼠(小家鼠(*Mus musculus*))全長CDH6 (SEQ ID NO:8)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAVNRRTGRP VEPESEFIIKIHDINDNEPIFTKDVYTATVP EMADVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP

			PGTPIGRIKASDADVGENAEIEYSITDGEG HEMFDVITDQETQEGIITVKKLLDFEKKK VYTLKVEASNPHVEPRFLYLGPFKDSAT VRIVVDDVDEPPVFSKLAYILQIREDARIN TTIGSVAAQDPDAARNPVKYSVDRHTD MDRIFNIDSGNGSIFTSKLLDRETLLWHNI TVIATEINNPKQSSRVPLYIKVLDVNDNA PEFAEFYETFVCEKAKADQLIQTLRAVD KDDPYSGHQFSFSLAPEAASSSNFTIQDN KDNTAGILTRKNGYNRHEMSTYLLPVVI SDNDYPVQSSTGTVTVRVCACDHHGNM QSCHAEALIHPTGLSTGAGSEFRHDSGLN DIFEAQKIEWHE
大鼠CDH6 FL	NM_012927.1	大鼠(褐鼠(*Rattus norvegicus*))全長CDH6 (SEQ ID NO:9)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIIKIHDINDNEPIFTKDVYTATVP EMADVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGENAEIEYSITDGEG HDMFDVITDQETQEGIITVKKLLDFEKKR VYTLKVEASNPHIEPRFLYLGPFKDSATV RIVVDDVDEPPVFSKLAYILQIREDAQINT TIGSVAAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLLWHNIT VIATEINNPKQSSRVPLYIKVLDVNDNAP EFAEFYETFVCEKAKADQLIQTLHAVDK DDPYSGHQFSFSLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCACDHHGNMQ SCHAEALIHPTGLSTGAGSEFRHDSGLND IFEAQKIEWHE

重組蛋白質表現及純化：

His6-SUMO-CDH6 aa54-260-APP-Avi

使用2xYT + 50 μg/ml康黴素(Kanamycin)及30 μg/ml氯黴素(氯黴素)，使用pET載體，在Rosetta® 2 De3 pLysS細胞(Millipore, Billerica, MA)中表現蛋白質。在30℃，用0.1 mM IPTG誘導細胞。將集結粒再懸浮於新鮮添加的400 ml 20 mM Tris-Cl (pH 8.0)、150 mM NaCl、3 mM CaCl2、20 mM咪唑、+ PI錠劑(每50 ml 1個) + 1 mg/ml溶菌酶中，均質化以破碎凝集塊且通過微流體化器3次。以20K×g離心30分鐘之後，使用上清液之可溶性溶離份在2 ml Ni-NTA (Qiagen超流動樹脂，Qiagen, Venlo, Netherlands)上純化。使溶胞物以2.0 ml/min通過管

柱，用10 CV (管柱體積) 20 mM Tris -Cl (pH 8.0)、150 mM NaCl、3 mM CaCl2、20 mM咪唑洗滌且使用20 mM Tris-Cl (pH 8.0)、500 mM NaCl、3 mM CaCl2、250 mM咪唑、使用4×3.0 ml溶離份溶離蛋白質。合併溶離份。向約15 ml蛋白質(約20 mg)中添加200個單位的SUMO蛋白酶(Invitrogen)且使用具有10 K截斷點之Snakeskin®摺疊管(Thermo Scientific, Rockford, IL)、在4℃、在5 L 20 mM Tris-Cl (pH 8.0)、150 mM NaCl、3 mM CaCl2中透析隔夜。收集所透析之物質且在2.0 ml Ni-NTA樹脂上再純化以移除未裂解的蛋白質及蛋白酶。自流過液及洗滌溶離份中收集所裂解的蛋白質。將得自逆相Ni-NTA的流過液及洗滌液濃縮至5 ml體積，添加NaCl直至500 mM最終濃度且注射至S200管柱上，緩衝液=20 mM Tris-Cl (pH 8.0)、150 mM NaCl、3 mM CaCl2。

hCDH6aa54-615 APPavi、*hCDH6aa54-615 Fc*、*cynoCDH6 FL*、*moCDH6 FL*、*大鼠CDH6 FL*

蛋白質在預先適應於懸浮培養液的HEK293 (ATCC CRL-1573)源細胞株中表現且在Novartis專有的無血清培養基中生長。在基於脂質體轉染的短暫6孔盤轉染分析中進行小規模表現檢驗。經由短暫轉染進行的大規模蛋白質製備係在Wave™生物反應器系統(GE Healthcare, Pittsburgh, PA)中，以10 L至20 L規模進行。DNA聚伸乙基亞胺(Polysciences, Warrington, PA)以1:3 (w:w)比率用作質體載劑。轉染後7至10天，收集細胞培養物上清液且藉由交叉流過濾及透濾加以濃縮，隨後純化。

純化時，使經澄清且過濾調節之得自短暫轉染的上清液以5 ml/min通過20 ml親和管柱。用20 CV PBS、1% TX100、0.3%三正丁基磷酸鹽緩衝液、20 CV PBS洗滌。使用100 mM檸檬酸鈉、150 mM NaCl pH3.0溶離，收集2 ml蛋白質溶離份。將合併的溶離份中和且接

著在4℃相對於5 L 50 mM Tris、150 mM NaCl pH 7.4、3 mM CaCl2透析隔夜。樣品接著在經透析緩衝液平衡的Superdex®S200 16/60管柱(GE Healthcare, Pittsburgh, PA)上進行尺寸排阻層析。

多種淘選策略之概述指示於表2中。

表2

淘選策略之概述

淘選代碼	噬菌體亞庫	目標及條件
1038.1	VH1A/B/5 λ+κ	
1038.2	VH3 λ+κ	對hCDH6aa54-615 APPavi進行SP，不使用$CaCl_2$
1038.3	VH2/6 λ+κ	
1038.4	VH6, κ	
1038.5	VH1A/B/5 λ+κ	對hCDH6aa54-615 APPavi進行SP，不使用$CaCl_2$
1038.6	VH3 λ+κ	
1038.7	VH2/6 λ+κ	
1038.8	VH6, κ	
1038.9	VH1A/B/5 λ+κ	使用1 mM $CaCl_2$，對His6-SUMO-CDH6 aa54-260-APP-Avi進行SP
1038.10	VH3 λ+κ	
1038.11	VH2/6 λ+κ	
1038.12	VH6, κ	
1038.13	VH1A/B/5 λ+κ	使用1 mM $CaCl_2$，對His6-SUMO-CDH6 aa54-260-APP-Avi進行SP
1038.14	VH3 λ+κ	使用工具抗體MAB2715進行結合競爭
1038.15	VH2/6 λ+κ	
1038.16	VH6, κ	
1038.17	VH1A/B/5 λ+κ	對生物素化hCDH6aa54-615 APPavi進行LP
1038.18	VH3 λ+κ	
1038.19	VH2/6 λ+κ	
1038.20	VH1A/B/5 λ+κ	對hCDH6aa54-615 APPavi進行LP
1038.21	VH3 λ+κ	使用生物素化工具抗體2B6進行下拉式淘選
1038.22	VH2/6 λ+κ	
1038.23	VH1A/B/5 λ+κ	對生物素化hCDH6aa54-615-Fc進行LP
1038.24	VH3 λ+κ	
1038.25	VH2/6 λ+κ	
1038.26	VH1A/B/5 λ+κ	對hCDH6aa54-615-Fc進行SP
1038.27	VH3 λ+κ	
1038.28	VH2/6 λ+κ	

蛋白質之生物素化

使用BirA酶，依循使Avi標記之蛋白質發生蛋白質生物素化的以下製造(Avidity、Aurora、CO)標準方案使Avi標記之蛋白質發生生物素化。生物素化之後，蛋白質於50 mM Tris、150 mM NaCl pH 7.4、3

mM CaCl2中、在Superdex®S200 16/60管柱上進行尺寸排阻層析。

未經Avi標記之蛋白質使用Slide-A-Lyzer Mini透析單元10000 MWCO (#69576 Thermo Scientific, Rockford, IL)、在室溫下、在攪拌下相對於5 L 1×PBS透析兩次歷時2小時，隨後進行生物素化。EZ連接的磺基-NHS-LC-生物素(#21327 Thermo Scientific, Rockford, IL)根據製造商方案進行復原。蛋白質與20倍莫耳濃度過量的生物素試劑一起在室溫下培育30分鐘。為了移除未反應的生物素試劑，使樣品再次在室溫下、在攪拌下相對於5 L 1×PBS透析兩次歷時2小時。藉助於Nanodrop®裝置(Thermo Scientific, Rockford, IL)測定蛋白質濃度。樣品在4℃儲存直至使用。

固相淘選

在固相淘選中，呈現Fab片段的噬菌體與藉由直接固著而已結合至表面載體的抗原一起培育。

抗原選擇方法之前，進行塗層檢查ELISA以測定最佳抗原塗佈濃度。為此目的，產生一系列2倍稀釋的hCDH6aa54-615 APPavi(參見表1)，其範圍為24 μg/mL至0.19 μg/mL。個別稀釋液經由直接固著而用於塗佈96孔Maxisorp™盤(#442404 Nunc, Rochester, NY)之各孔。塗佈之後，培養盤用300 μL PBS洗滌三次且隨後在室溫下用1×阻斷緩衝液(2.5%牛乳，2.5%BSA，0.05% Tween 20)阻斷2小時。

為了偵測所結合之抗原，添加抗APP抗體(內部產生)直至1 μM、0.18 μM或0.04 μM。使用1:5000稀釋的經AP標記之抗小鼠IgG -F(ab)2特異性抗體(參考號115-056-006，Jackson-Immunoresearch, West Grove, PA)進行二次偵測。觀測到信號飽和時的抗原濃度選作SP淘選的塗佈濃度。

淘選代碼1038.1-8

對於SP淘選1038.1-8 (參見表2)而言，經由直接固著將

hCDH6aa54-615 APPavi (參見表1，SEQ ID NO: 4)塗佈於96孔Maxisorp™盤(Nunc)上。每種噬菌體亞庫組合使用300 μL抗原溶液(10 μg/mL，於PBS中)塗佈兩個孔。在4℃，在1 mM CaCl2存在(淘選1038.1-4)或不存在(淘選1038.4-8)下塗佈隔夜。隨後用400 μL PBS洗滌孔兩次且在室溫下、在400 rpm下用400 μL阻斷緩衝液阻斷2小時。阻斷之後，用400 μL PBS洗滌細胞兩次。

結合噬菌體之前，阻斷亞庫且在室溫下用10 μg/mL之無關FLT2-APPavi耗乏1小時以消除非特異性的標記結合子。每個所塗孔轉移300 μL經阻斷及耗乏的噬菌體庫且在室溫及400 rpm下培育2小時。未特異性結合的噬菌體藉由下表3中所列的洗滌步驟移除。

表3

第一輪	第二輪	第三輪(僅淘選代碼1038.9-16)
3×PBST (快速)	1× PBST (快速)	10× PBST (快速)
2×PBST / 5min	4× PBST / 5min	5× PBST / 5min
3× PBS (快速)	1× PBS (快速)	10× PBS (快速)
2× PBS / 5min	4× PBS / 5min	5× PBS / 5min

特異性結合的噬菌體在室溫下用300 μL溶離緩衝液溶離10分鐘。所溶離的噬菌體在OD600=0.6至0.8之光學密度下用於再感染14 mL大腸桿菌TG1F+ (Stratagene/Agilent, Santa Clara, CA)。大腸桿菌TG1F+與噬菌體溶離液之混合物在37℃水浴中培育45分鐘用於噬菌體感染。將細菌集結粒再懸浮於2xYT培養基中，塗鋪於補充有34 μg/mL氯黴素的LB瓊脂盤上且在37℃培育隔夜。將盤上的菌落刮下且用於增濃純系之多株擴增及噬菌體製備。使用經純化之噬菌體開始下一輪淘選。根據第一輪方案進行第二輪淘選，但其中的洗滌條件更嚴格。由於第二輪輸出效價低(約104 cfu/mL)，因此省去第三輪淘選。

淘選代碼1038.9-16

對於SP淘選1038.9-16 (表2)而言，如針對陶選代碼1038.1-8所述，經由直接固著將His6-SUMO-CDH6 aa54-260-APP-Avi (參見表1)

塗佈於96孔Maxisorp™盤(Nunc)上。對於淘選1038.13-16而言，每孔添加300 μL 100 nM工具抗體MAB2715溶液且在室溫下培育1小時以避免選擇與MAB2715相同識別抗原決定基的結合子。除所塗抗原及第三輪淘選之外，如針對淘選代碼1038.1-8所述進行淘選。

淘選代碼1038.26-28

對於SP淘選1038.26-28 (參見表2)而言，如針對淘選代碼1038.1-8所述，經由直接固著將hCDH6aa54-615-Fc (參見表1，SEQ ID NO: 6)塗佈於96孔Maxisorp™盤(Nunc)上。除所塗抗原及洗滌嚴格度之外，如針對淘選代碼1038.1-8所述進行淘選。

液相淘選

在溶液淘選期間，將呈現Fab片段的噬菌體及生物素化抗原在預期可增加噬菌體接近抗原的溶液中培育。如上文所述進行抗原生物素化。

淘選代碼1038.17-22

在室溫下，在轉輪上，用等體積之2×Chemiblocker阻斷各噬菌體文庫亞庫2小時。為了避免選擇針對APPavi及生物素標記無關FLT3-APPAvi之抗體及及生物素化抗環孢素，在阻斷步驟中添加msIgG分別至7.5 μg/mL及18 μg/mL。為了移除結合至抗生蛋白鏈菌素珠粒的噬菌體顆粒，使用經阻斷之抗生蛋白鏈菌素珠粒(#112.06D Invitrogen, Carlsbad, CA)對經阻斷之噬菌體顆粒進行預吸附。經阻斷且經預吸附之噬菌體與生物素化hCDH6aa54-615 APPavi (參見表1，SEQ ID NO: 4)一起在室溫下、在轉輪上培育1小時。噬菌體-抗原複合物用經洗滌之珠粒捕捉(淘選代碼1038.17-19)或用經生物素化抗CDH6抗體2B6 (Genway, San Diego, CA)預塗之珠粒捕捉以富集針對非2B6抗原決定基之結合子(淘選代碼1038.20-22)。藉由若乾洗滌步驟移除非特異性噬菌體顆粒(參見下文)。特異性結合之噬菌體顆粒之溶離、感染及擴

增如針對淘選代碼1038.1-8所述進行。

表4

洗滌條件淘選代碼1038.17-25

第一輪	第二輪	第三輪(僅淘選代碼1038.9-16)
5×PBST (快速)	10×PBST (快速)	10× PBST (快速)
2× PBST / 5min	3× PBST / 5min	5× PBST / 5min
3× PBS (快速)	5× PBS (快速)	5× PBS (快速)

淘選代碼1038.23-25

如針對淘選代碼1038.1-8所述進行淘選，但使用生物素化hCDH6aa54-615-Fc (參見表1，SEQ ID NO: 6)作為抗原。

次選殖

轉化用於FAB-FH表現

為了促進可溶性Fab片段之快速表現，將所選HuCAL® PLATINUM噬菌體顆粒之Fab編碼插入物自pMORPH®30呈現載體次選殖入pMORPH®11_FH表現載體中。使用Nucleobond®Xtra Midi Plus套組，根據製造商手冊(#740.412.50 Machery Nagel, Bethlehem, PA)，使用含有經最後一輪淘選輸出噬菌體感染之大腸桿菌的甘油儲備液接種用於pMORPH®30 DNA純化的培養物。5 μg各pMORPH®30 DNA輸出庫經由EcoRI/XbaI/BmtI (所有限制酶均購自England Biolabs, Ipswich, MA)進行三重消化。所得EcoRI/XbaI Fab編碼1485 bp片段使用Wizard SV凝膠/PCR純化套組、根據製造商手冊(A9282, Promega, Madison, WI)進行凝膠純化且接入EcoRI/XbaI酶切pMORPH®11_FH載體主鏈中。

轉化用於IgG表現

為了表現全長IgG，依循RapCLONE®方案(Morphosys, Martinsried/Planegg, Germany)將VH及VL之可變域片段自Fab表現載體次選殖入pMORPH®4_hIgG1f載體中。RapCLONE®為兩步選殖方

法，用於將大量Fab表現載體批量轉化成IgG表現載體。在第一選殖步驟中，經由BsiWI/MfeI (對於κ庫)或HpaI/MfeI (對於λ庫)消化及隨後連接將真核表現卡匣引入pMORPH®11表現載體中。隨後進行第二選殖步驟，其中使用EcoRV/BlpI (κ庫與λ庫)消化含有表現卡匣的Fab庫且隨後選殖入pMORPH®4_IgG1f受體載體中以便在哺乳動物細胞中表現。

Fab片段之表現及純化

大腸桿菌TG1 F-之轉形

50 μL電穿孔勝任大腸桿菌TG1F-等分試樣在冰上解凍，與50 pg/μl pMORPH®11_FH質體DNA混合且轉移至預先冷卻之電穿孔比色管中。將細胞電穿孔(Bio-Rad Gene Pulser；配置：1.75 kV，200 Ω及25 μF (Bio-Rad, Hercules, CA)，轉移至950 μl預溫熱之SOB培養基中且在37℃、在220 rpm振盪培育1小時。將適當體積的轉形樣品塗鋪於補充有34 μg/mL氯黴素的LB瓊脂盤上且在37℃培育隔夜以獲得單一菌落。

主盤之產生

挑選氯黴素耐藥性單一純系置入預填有60 μl 2xYT培養基(補充有34 μg/ml氯黴素及1%葡萄糖)的無菌384孔微量滴定盤(Nunc)之各孔中且在37℃生長隔夜。次日晨，將20 μl含有60%甘油及1%葡萄糖的無菌2xYT培養基添加至主盤之各孔中。盤用鋁箔密封且在-8℃儲存。

2.3.3 產生含Fab之細菌溶胞物用於ELISA篩選

自主盤各孔轉移5 μl至預填有40 μl 2xYT培養基(每孔補充有34 μg/ml氯黴素及0.1%葡萄糖)之無菌384孔微量滴定盤中。盤在37℃、480 rpm及80%濕度下培育直至培養物稍微混濁。每孔添加10 μl補充有34 μg/ml氯黴素及5 mM IPTG之2xYT培養基用於誘導Fab片段表

現。盤用可透氣膠帶密封且在22℃、在500 rpm及80%濕度下培育隔夜。次日，向各孔中添加15 μl BEL溶胞緩衝液(2.5 mg/ml溶菌酶(#10837059001, Roche, Nutley, NJ)、4 mM EDTA、10 U/μl核酸酶(Benzonase)(#1.01654.0001 Merck, White House Station, NJ)且盤在500 rpm及80%濕度下培育1小時。所得Fab溶胞物藉由每孔添加15 μL 2×Chemiblocker、隨後在22℃、500 rpm及80%濕度下培育30分鐘來阻斷。

產生含Fab之細菌溶胞物用於FACS篩選

自壓緊盤之各孔轉移5 μl至預填有每孔100 μl 2xYT培養基(補充有34 μg/ml氯黴素)的無菌96孔圓底微量滴定盤中。盤在37℃、500 rpm及80%濕度下培育直至培養物稍微混濁。每孔添加10 μl補充有34 μg/ml氯黴素及5 mM IPTG之2xYT培養基用於誘導Fab片段表現。盤用可透氣膠帶密封且在22℃、在500 rpm及80%濕度下培育隔夜。次日，盤在1200 g離心10分鐘且丟棄上清液。細菌集結粒在-20℃冷凍隔夜以促進溶解步驟。解凍之集結粒再懸浮於200 μL BEL溶胞緩衝液中(參見上文)且在22℃及250 rpm下培育1小時。所得Fab溶胞物以1200 g離心10分鐘以移除細胞碎片。含有Fab的上清液用於篩選目的。

His6標記之Fab片段在大腸桿菌中之表現及純化

在補充有34 μg mL氯黴素及1%葡萄糖的2xYT中單選出含有pMORPH®11_Fab_FH DNA的大腸桿菌TG1F-轉形體。挑選個別純系且轉移至補充有34 μg/mL氯黴素及1%葡萄糖之3 mL 2xYT接種培養物中且在37℃、220 rpm培育4小時。接種培養物用於在補充有34 μg/mL氯黴素及1%葡萄糖之2xYT中接種50 mL主要培養物且在250 mL振盪燒瓶中在30℃培育直至OD600值達到0.6。藉由添加IPTG至0.75 mM最終濃度來誘導Fab表現且培養物在25℃及220 rpm下進一步培育隔夜。次日，收集細胞且細胞集結粒在-20℃冷凍隔夜。細胞集結粒藉由再

懸浮於溶胞緩衝液((25 mM TRIS/pH=8、500 mM NaCl、2 mM $MgCl_2$、10 U/μl核酸酶(#1.01654.0001 Merck)、0.1%溶菌酶(#10837059001, Roche)、不含EDTA之競爭性蛋白酶抑制劑1個錠劑/50 mL緩衝液(#11873580001 Roche))中且在搖盪台上、在室溫下培育1小時來破碎。溶胞物藉由15000 g離心30分鐘及經由200 nm孔徑過濾器過濾上清液來澄清。經His6標記之Fab片段經由固著型金屬離子親和層析(Ni-NTA Superflow®珠粒, #30430 Qiagen, Venlo, Netherlands)分離且使用咪唑溶離。使用PD-10管柱(# 17-0851-01 GE Healthcare, Pittsburgh, PA)相對於1×PBS進行緩衝液交換。樣品無菌過濾且藉由UV分光光度法測定蛋白質濃度。用變性、還原型15%SDS-PAGE分析樣品純度。藉由MS確認樣品身分。

IgG之表現及純化

IgG在篩選規模上之表現

96孔表現系統中使用真核HEK293c18細胞(ATCC CRL-10852)產生含有全長IgG之經調節細胞培養上清液，隨後用於特異性及/或功能分析。分析前一天，將真核HEK293 c18細胞再懸浮於轉染培養基(D-MEM，補充有2% L-麩醯胺酸(#25030-024 Gibco, Grand Island, NY)、10% FCS (#3302 PAN Biotech, Aidenbach, Germany)及1%青黴素/鏈黴素(#15140-122 Gibco, Grand Island, NY))中且接種於96孔F底盤中直至每孔50 μl約$4x10^4$個細胞之密度。藉由將每孔0.6 μl Lipofectamine® 2000 (#11668 Invitrogen, Carlsbad, CA)與25 μL Opti-MEM® I培養基(#31985-047 Invitrogen, Carlsbad, CA)混合來製備轉染母液混合物。母液混合物在室溫下培育15分鐘。向新盤各孔添加含有300 ng DNA的20 μL Opti-MEM® I培養基且輕緩地混合。隨後，將DNA與預培育的Lipofectamine® 2000合併，輕緩地混合且在室溫下培育20分鐘。接著轉移100 μl預培育Lipofectamine® 2000/DNA複合物至具有細胞之盤

之各孔中且輕緩地混合。盤在37℃及6% CO2下培育40小時用於短暫表現。轉移培養上清液至V型底96孔盤中且藉由離心澄清。所得含IgG上清液藉由抗Fd捕捉型ELISA加以測試以便參照已知標準評估IgG蛋白質濃度且在-80℃儲存供隨後使用。

藉由抗Fd ELISA檢查IgG表現

為了評估篩選規模所得之上清液中的IgG含量，Maxisorp® 96孔盤(#437111 Nunc)用每孔50 µl於PBS中1:1000稀釋的Fd片段特異性綿羊抗人類IgG (#PC075 The Binding Site, San Diego, CA)塗佈。塗佈之後，盤用TBST洗滌兩次且用含有5%脫脂乳粉的TBST阻斷1小時。同時，含有IgG的上清液在含有2.5%脫脂乳粉的TBST中1:50稀釋。ELISA盤用TBST洗滌三次之後，每孔轉移100 µL經稀釋之上清液且盤在室溫下培育1小時。隨後，用TBST洗滌盤五次且藉由與50 µl F(ab')2-特異性山羊抗人類IgG (#109-055-097 Dianova, Hamburg, Germany)(1:5000稀釋)一起在含有0.5%脫脂乳粉的TBST中培育1小時來偵測所捕捉的IgG。盤用TBST洗滌五次之後，根據製造商說明書添加AttoPhos螢光受質(#1484281 Roche, Nutley, NJ)且使用ELISA讀取器記錄535 nm螢光發射及430 nm激發。

IgG在微量規模上之表現及純化

使用40 kDa線性PEI ((PEI Max (#24765-2 Polysciences Warrington,PA))作為基因運載工具，在FreeStyle293®表現培養基(#12338 Invitrogen, Carlsbad, CA)中用pMORPH®4 IgG表現質體短暫轉染CAP-T®細胞(CEVEC Pharmaceuticals, Cologne, Germany)。

轉染之前一天，將細胞稀釋至每毫升約0.8E+06個細胞以確保指數級生長。在轉染當天，細胞在9 mL預溫熱的Freestyle® (Invitrogen, Carlsbad, CA)培養基中稀釋至每毫升約$0.5x10^7$個細胞且轉移至125 ml振盪瓶中。30 µg DNA在500 µl OptiMEM中稀釋。1200 µg PEI Max

(#24765-2 Polysciences Warrington, PA)在8.80 mL OptiMEM培養基中稀釋。逐滴添加DNA溶液至細胞中且輕緩地混合。隨後，向細胞中添加500 μL PEI Max溶液且輕緩地混合。

在37℃、6% CO2、85%濕度下、在100 rpm攪拌下培育細胞。4小時之後，添加10 mL補充有4 mM L-麩醯胺酸及5 μg/ml殺稻瘟菌素(#R21001 Invitrogen, Carlsbad, CA)的預溫熱PEM。同時添加400 μL丙戊酸(#P4543-25G Sigma Aldrich, St. Louis, MO)直至4 mM之最終濃度。在37℃、6% CO2、85%濕度下、在100 rpm攪拌下培育細胞6天。

在4℃以1200 g離心5分鐘之後，將上清液無菌過濾(0.2 μm孔徑)且使用液體操作站進行蛋白質A親和層析(MabSelect® SURE, GE Healthcare, Pittsburgh, PA)。相對於1×PBS進行緩衝液交換且對樣品進行無菌過濾(0.2 μm孔徑)。藉由UV分光光度法測定蛋白質濃度且在SDS-PAGE中、在變性、還原條件下分析IgG純度。

篩選含Fab的原始細菌溶胞物

ELISA篩選

使用ELISA篩選，自淘選輸出中鑑別出結合至靶抗原的單一Fab純系。使用含有Fab的粗製大腸桿菌溶胞物測試Fab片段。

對直接塗佈之抗原進行的ELISA篩選

Maxisorp® (#442404 Nunc, Rochester, NY) 384孔盤在4℃用3 μg/ml濃度之存於PBS中之huCDH6蛋白質塗佈隔夜。洗滌之後，盤用含有5%脫脂牛乳的1xPBST阻斷2小時。添加含Fab的大腸桿菌溶胞物且允許在室溫下結合1小時。

為了偵測所結合之Fab片段，用TBST洗滌盤5次且以1/2500稀釋度添加AP-抗人類IgG F(ab')2 (#109-055-097 Jackson Immunoresearch, West Grove, PA)。在室溫下歷時1小時之後，用TBST洗滌盤5次且根據製造商說明書添加AttoPhos受質。添加受質之後5分鐘，用ELISA讀

取器讀盤。

使用NeutrAvidin®盤對生物素化抗原進行的ELISA篩選

Maxisorp® (#442404 Nunc, Rochester, NY) 384孔盤在4℃用10 μg/ml濃度之存於PBS中的NeutrAvidin® (#31000 Thermo Scientific, Rockford, IL)塗佈隔夜。洗滌之後，用1×Chemiblocker阻斷盤2小時。將含Fab的大腸桿菌溶胞物分配至新384孔微量滴定盤中且添加2.5 μg/mL濃度之生物素化CDH6抗原。接著轉移Fab-抗原複合物至塗有NeutrAvidin®之盤中且允許捕捉在室溫下發生1小時且如上文所述偵測。

FACS篩選

FACS篩選時，自淘選輸出中鑑別出結合至細胞表面所表現之CDH6抗原的Fab片段。轉移1x10^5個細胞/孔至U型底96孔盤且與每孔40 μl含Fab之細菌溶胞物混合。盤在4℃振盪培育1小時。培育之後，每孔添加100 μl冰冷FACS緩衝液(3% FCS、0.02% NaN_3、2 mM EDTA於PBS中)，細胞在4℃以250 g離心5分鐘且用每孔180 μl冰冷FACS緩衝液洗滌兩次。每個洗滌步驟之後，將細胞離心且小心地再懸浮。最後洗滌步驟之後，將細胞再懸浮於50 μL 1/200稀釋之二次偵測抗體(PE結合之山羊抗人類IgG (#109-116-088, Jackson Immunoresearch, West Grove, PA)中。在4℃培育1小時之後，細胞再次用每孔180 μL冰冷FACS緩衝液洗滌兩次。最後，將細胞集結粒再懸浮於每孔120 μl具有0.4%多聚甲醛的FACS緩衝液中且在裝備有HTS讀盤器的FACSCalibur® (BD Biosciences, San Jose, CA)中分析。

純系測序

Fab純系測序

對經確認的細胞結合Fab匹配結果進行VL及VH測序。補充有34 μg/mL氯黴素及1%葡萄糖的1.2 mL 2xYT用源於壓緊盤的5 μL細菌甘

油儲備液接種且在96孔深孔微量滴定盤中、在37℃及500 rpm下生長隔夜。次日，收集細菌且使用96孔DNA純化套組(Nucleospin® 96質體純化套組#740625.24, Machery Nagel, Bethlehem, PA)、根據製造商方案純化pMORPH®11_FH質體。為了測序，分別使用VL引子M13rev (5' CAGGAAACAGCTATGAC 3' (SEQ ID NO: 10))及VH引子HuCAL_VH_for ((5' GATAAGCATGCGTAGGAGAAA 3 (SEQ ID NO: 11))。

IgG純系測序

獨特的細胞結合Fab純系以多株方式轉化成IgG1形式且隨後藉由VL及VH測序來檢索。補充有100 μg/mL Amp及1%葡萄糖的1.5 mL 2xYT培養基用單一純系接種且在96孔深孔微量滴定盤中、在37℃、450 rpm及80%濕度下生長隔夜。次日，收集細菌且使用96孔DNA純化套組、根據製造商方案(Nucleospin® 96質體純化套組#740625.24, Machery Nagel, Bethlehem, PA)純化編碼IgG之pMORPH®4質體。為了測序，分別使用VL及VH引子((T7 5' TAATACGACTCACTATAGGG 3' (SEQ ID NO:12)及CMV_HC_for (5' CTCTAGCGCCACCATGAAACA 3' (SEQ ID NO:13))。

活體外分析

使用Octet® QK進行的親和力評估

經由Bio-Layer干涉法技術、藉由測定動力學參數來進行親和力評估。所有Fab樣品均使用抗生蛋白鏈菌素Dip and Read生物感測器(#18-0009 ForteBio, Menlo Park, CA)量測。將盤置放於Octet® QK儀器(ForteBio, Menlo Park, CA)中且允許在腔室中平衡至27℃。藉由將感測器置放於含有nM生物素化CDH6蛋白質之孔中300秒來起始運作。隨後將感測器置放於含有250 nM Fab樣品的孔中。Fab結合及解離各自藉由量測層厚度(奈米，nm)隨時間發生之變化來記錄(所有均

在電腦控制下進行)。使用Octet®用戶軟體3.0版自動處理資料。

評估抗體細胞內化傾向

藉由顯微鏡、使用VTI ArrayScan® HC讀取器(ThermoFischer, Waltham, MA)評估細胞藉由標靶介導性內吞對IgG的內化作用，如下文所述。潛在分析方案為Spot Detector V4演算法(ThermoScientific Cellomics®, Thermo Scientific, Rockford, IL)。簡言之，此分析方案提供快速且通用的斑點分析，從而在免疫螢光染色之後鑑別出細胞內斑點目標，諸如含有IgG之溶酶體微脂粒。接著可相對於所分析細胞的數目來得到總斑點螢光強度的平均值。

OVCAR3細胞(ATCC HTB-161)在T150組織培養瓶中生長至約90%匯合。丟棄培養基且用10 mL PBS沖洗細胞。藉由與4 mL細胞解離緩衝液一起在37℃培育5分鐘來拆分細胞。經拆分的細胞充分地再懸浮於生長培養基中且轉移至50 mL管中。細胞在Vi-Cell®分析儀(Beckman Coulter, Brea, CA)上計數之後，懸浮液在生長培養基中調節至10^5個細胞/毫升。100 µL細胞懸浮液接種於具有透明底的96孔微量滴定盤之各孔中。盤在37℃、5% CO2下培育24小時以允許細胞黏附及擴增。

含有IgG的細胞培養上清液如所述產生且在PBS中以4倍稀釋度系列(涵蓋的稀釋度範圍為1:4至1:128)稀釋。含有細胞之微量滴定盤每孔分配100 µl各樣品稀釋液且在37℃培育2小時以允許IgG內化。隨後，藉由每孔添加100 µl 1×CellFix®試劑(#340181 BD Biosciences, San Jose, CA)來固定細胞。10分鐘之後，用PBS洗滌盤兩次且接著藉由每孔添加100 µl 0.1% Triton X-100來使細胞通透。10分鐘之後，盤再次用PBS洗滌兩次且在室溫下用100 µl 1×Odyssey阻斷緩衝液(#927-40000 LiCor, Lincoln, NE)阻斷2小時。為了偵測內化之IgG，每孔添加100 µl補充有1:10000稀釋Hoechst核染色試劑(#B2261 Sigma, St.

Louis, Mo)之1:000稀釋二次抗體Alexa Fluor® 488山羊抗人類IgG (#11001 Molecular Probes, Grand Island, NY)且在室溫下、在黑暗中培育1小時。接著用PBS洗滌細胞兩次而不最後抽吸。接著將盤裝載至Cellomics® VTI ArrayScan HC讀取器(ThermoFischer, Waltham, MA)中且分析。IgG內化程度係藉由每個細胞之平均斑點強度(MSAI)來評估。

使用抗人類FAB-DM1結合物進行的替代ADC分析

為了測試CDH6抗體在受體結合之後內化及遞送細胞毒性有效負載的能力，藉由將抗人類Fab-DM1試劑(AffiniPure® Fab片段山羊抗人類IgG H+L與SMCC-DM1結合)與經純化之IgG以1:2固定比率混合來進行替代ADC分析。針對癌細胞株OVCAR3 (卵巢漿液癌，在McCoys + 20% FCS中培養)測試細胞毒性潛力，因為此等細胞顯示CDH6之高度表現。

對培養中之細胞計數且在培養基中稀釋至$1x10^5$個細胞/毫升之濃度。每孔轉移1000個細胞至384孔盤(Corning Costar#3707, Corning, Tewksbury, MA)中。在1.4 ml Matrix管(Thermo, #3790, Rockford, IL)中，藉由將666 nM Fab-DM1與333 nM於細胞培養基中稀釋之一次人類IgG合併來製備一次抗體/Fab-DM1溶液且在37℃培育30分鐘。在384孔深孔盤(Brandtech Scientific Inc #701355, Essex, CT)中製備10點1:3連續稀釋液且每個分析盤轉移25 µl (一式三份)以分別產生66 nM及33 nM FAB-DM1/人類IgG之最高初始濃度。作為對照，製備僅具有細胞的孔(=100%存活率對照)及僅與Fab-DM1一起培育之細胞(以檢查二次試劑之非特異性殺死)。盤在37℃及5% CO2下培育120小時。使用CellTiter-Glo®試劑(#G7571 Promega, Madison, WI)，根據製造商說明書測定一次抗體/Fab-DM1複合物之細胞活性。存活率相對於僅具有細胞的對照歸一化。

抗體篩選概述

HuCAL® PLATINUM噬菌質體文庫用於選擇針對人類CDH6-ECD抗原的特定Fab片段。淘選使用重組人類APPAvi與Fc融合體以及截短的域APPAvi融合蛋白。HuCAL® PLATINUM抗體噬菌體顆粒以不同亞庫組合進行總共8種不同淘選策略，產生28種淘選輸出庫。概言之，八種策略中有六種高產且產生771個ELISA陽性篩選匹配結果。

對表現人類CDH6之CHO細胞以及OVCAR3細胞進行FACS篩選，產生271種經確認之細胞結合匹配結果。為了鞏固此等細胞結合匹配結果，進行VL及VH測序，從而鑑別出53種獨特的Fab抗體純系。

為了達成功能表征，將Fab抗體純系轉化成IgG形式，產生47種獨特IgG純系，其中44種在篩選規模上成功表現。對經純化之獨特IgG進行一系列表徵分析，包括藉由FACS分析人類/食蟹獼猴/大鼠/小鼠交叉反應性、藉由Octet進行親和力排序、細胞內化分析，以及使用抗人類IgG Fab-SMCC-DM1二次試劑進行替代ADC分析。基於此等分析，選擇人類IgG用於依比例製備，隨後與ADC連接子/有效負載直接結合且在活體外及活體內實驗中以ADC形式測試。

為進一步深度表徵所選擇之IgG的序列資訊顯示於表5中。

表5

針對依比例製備及深度表徵所選擇之IgG之序列資訊

NOV ID	類別	值
NOV0670	LCDR1 (Kabat) (SEQ ID NO:14)	SGSSSNIGSQYVY
	LCDR2 (Kabat) (SEQ ID NO:15)	YNSERPS
	LCDR3 (Kabat) (SEQ ID NO:16)	QTWDASSQSFV

	HCDR1 (Kabat) (SEQ ID NO:17)	SYAIS
	HCDR2 (Kabat) (SEQ ID NO:18)	GIIPIFGTANYAQKFQG
	HCDR3 (Kabat) (SEQ ID NO:19)	KFPGRGPFAY
	vH序列 (SEQ ID NO:20)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPG QGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSL RSEDTAVYYCARKFPGRGPFAYWGQGTLVTVSS
	vL序列 (SEQ ID NO:21)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSQYVYWYQQLPGTA PKLLIYYNSERPSGMPDRFSGSKSGTSASLAITGLQAEDEADYY CQTWDASSQSFVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:22)	CAGGTGCAATTGGTGCAGAGCGGTGCCGAAGTGAAAAAAC CGGGCAGCAGCGTGAAAGTTAGCTGCAAAGCATCCGGAGG GACGTTTTCTTCTTACGCTATCTCTTGGGTGCGCCAGGCCCC GGGCCAGGGCCTCGAGTGGATGGGCGGTATCATCCCGATCT TCGGCACTGCGAACTACGCCCAGAAATTTCAGGGCCGGGTG ACCATTACCGCCGATGAAAGCACCAGCACCGCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGCCGTGTATTATT GCGCGCGTAAATTCCCGGGTCGTGGTCCGTTCGCTTACTGGG GCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:23)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTCTCAGTACGTGTACTGGTACCAGCAGCTGCCG GGCACGGCGCCGAAACTGCTGATCTACTACAACTCTGAACG CCCGAGCGGCATGCCGGATCGCTTTAGCGGATCCAAAAGCG GCACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAA GACGAAGCGGATTATTACTGCCAGACTTGGGACGCTTCTTCT CAGTCTTTCGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
NOV0672	LCDR1 (Kabat) (SEQ ID NO:24)	TGTSSDVGAYNYVS
	LCDR2 (Kabat) (SEQ ID NO:25)	GVSKRPS
	LCDR3 (Kabat) (SEQ ID NO:26)	QSYDHLLHVV
	HCDR1 (SEQ ID NO:27)	TYGIH
	HCDR2 (Kabat) (SEQ ID	YIHYSGSSTYYADSVKG

	NO:28)	
	HCDR3 (Kabat) (SEQ ID NO:29)	HAYGYMDF
	vH序列 (SEQ ID NO:30)	QVQLLESGGGLVQPGGSLRLSCAASGFTFNTYGIHWVRQAPG KGLEWVSYIHYSGSSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCARHAYGYMDFWGQGTLVTVSS
	vL序列 (SEQ ID NO:31)	DIALTQPASVSGSPGQSITISCTGTSSDVGAYNYVSWYQQHPGK APKLMIYGVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADY YCQSYDHLLHVVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:32)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTAACACTTACGGTATCCATTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCTACATCCATTACTCTGGTT CTTCTACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACCA TCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAATG AACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGC GCGTCATGCTTACGGTTACATGGATTTCTGGGGCCAAGGCA CCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:33)	GATATCGCGCTGACCCAGCCGGCGAGCGTGAGCGGTAGCCC GGGCCAGAGCATTACCATTAGCTGCACCGGCACCAGCAGCG ATGTGGGCGCTTACAACTACGTGTCTTGGTACCAGCAGCAT CCGGGCAAGGCGCCGAAACTGATGATCTACGGTGTTTCTAA ACGTCCGAGCGGCGTGAGCAACCGTTTTAGCGGATCCAAAA GCGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCG GAAGACGAAGCGGATTATTACTGCCAGTCTTACGACCATCT GCTGCATGTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCT A
NOV0674	LCDR1 (Kabat) (SEQ ID NO:34)	SGSSSNIGYNYVS
	LCDR2 (Kabat) (SEQ ID NO:35)	RDNQRPS
	LCDR3 (SEQ ID NO:36)	AAWTSGSIGWV
	HCDR1 (Kabat) (SEQ ID NO:37)	SYAMT
	HCDR2 (Kabat) (SEQ ID NO:38)	GISGGGSNTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:39)	GGGQYFDY
	vH序列	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMTWVRQAPG

	(SEQ ID NO:40)	KGLEWVSGISGGGSNTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCARGGGQYFDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:41)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGYNYVSWYQQLPGTA PKLLIYRDNQRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYY CAAWTSGSIGWVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:42)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTACGCTATGACTTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCGGTATCTCTGGTGGTGGTT CTAACACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGGTGGTGGTCAGTACTTCGATTACTGGGGCCAAGGC ACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:43)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTACAACTACGTGTCTTGGTACCAGCAGCTGCCG GGCACGGCGCCGAAACTGCTGATCTACCGTGACAACCAGCG CCCGAGCGGCGTGCCGGATCGCTTTAGCGGATCCAAAAGCG GCACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAA GACGAAGCGGATTATTACTGCGCTGCTTGGACTTCTGGTTCT ATCGGTTGGGTGTTTGGCGGCGGCACGAAGTTAACCGTCCT A
NOV0682	LCDR1 (Kabat) (SEQ ID NO:44)	RASQTINSYLN
	LCDR2 (Kabat) (SEQ ID NO:45)	RASNLQS
	LCDR3 (SEQ ID NO:46)	QQGDSSWT
	HCDR1 (Kabat) (SEQ ID NO:47)	SYAIS
	HCDR2 (Kabat) (SEQ ID NO:48)	FIKSNADGYTTNYAAPVKG
	HCDR3 (Kabat) (SEQ ID NO:49)	IRYFRNWDY
	vH序列 (SEQ ID NO:50)	QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAISWVRQAPGK GLEWVGFIKSNADGYTTNYAAPVKGRFTISRDDSKNTLYLQM NSLKTEDTAVYYCARIRYFRNWDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:51)	DIQMTQSPSSLSASVGDRVTITCRASQTINSYLNWYQQKPGKA PKLLIYRASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGDSSWTFGQGTKVEIK
	vH DNA	CAGGTGCAATTGGTGGAAAGCGGCGGTGGCCTGGTGAAACC

	序列 (SEQ ID NO:52)	AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCCTCCGGATTCA CCTTTTCTTCTTACGCTATCTCTTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTGGGCTTCATCAAATCTAACGCT GACGGTTACACTACTAACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTCGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTATCCGTTACTTCCGTAACTGGGATTACTGGG GCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:53)	GATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCCAG CGTGGGCGATCGCGTGACCATTACCTGCAGAGCCAGCCAGA CTATTAACTCTTACCTGAACTGGTACCAGCAGAAACCGGGC AAAGCGCCGAAACTATTAATCTACCGTGCTTCTAACCTGCA AAGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGATCCGGCA CCGATTTCACCCTGACCATTAGCTCTCTGCAACCGGAAGACT TTGCGACCTATTATTGCCAGCAGGGTGACTCTTCTTGGACCT TTGGCCAGGGCACGAAAGTTGAAATTAAA
NOV0685	LCDR1 (Kabat) (SEQ ID NO:54)	SGSSSNIGSYYVS
	LCDR2 (Kabat) (SEQ ID NO:55)	YNTKRPS
	LCDR3 (Kabat) (SEQ ID NO:56)	QSWDKLGKGYV
	HCDR1 (Kabat) (SEQ ID NO:57)	GNSAAWN
	HCDR2 (Kabat) (SEQ ID NO:58)	IIYYRSKWYNDYAVSVKS
	HCDR3 (Kabat) (SEQ ID NO:59)	SSYSGGFDY
	vH序列 (SEQ ID NO:60)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSGNSAAWNWIRQSP SRGLEWLGIIYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLN SVTPEDTAVYYCARSSYSGGFDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:61)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSYYVSWYQQLPGTA PKLLIYYNTKRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYY CQSWDKLGKGYVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:62)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCGGTAACTCTGCTGCTTGGAACTGGATTCGTCAG AGCCCGAGCCGTGGCCTCGAGTGGCTGGGCATCATCTACTA CCGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAA GCCGCATTACCATTAACCCGGATACTTCGAAAAACCAGTTT AGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGT GTATTATTGCGCGCGTTCTTCTTACTCTGGTGGTTTCGATTAC

		TGGGGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:63)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTCTTACTACGTGTCTTGGTACCAGCAGCTGCCGG GCACGGCGCCGAAACTGCTGATCTACTACAACACTAAACGC CCGAGCGGCGTGCCGGATCGCTTTAGCGGATCCAAAAGCGG CACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAAG ACGAAGCGGATTATTACTGCCAGTCTTGGGACAAACTGGGT AAAGGTTACGTGTTTGGCGGCGGCACGAAGTTAACCGTCCT A
NOV0689	LCDR1 (Kabat) (SEQ ID NO:64)	SGSSSNIGSNFVS
	LCDR2 (Kabat) (SEQ ID NO:65)	DNSNRPS
	LCDR3 (Kabat) (SEQ ID NO:66)	SSYDSFDHSWV
	HCDR1 (Kabat) (SEQ ID NO:67)	SFAMN
	HCDR2 (Kabat) (SEQ ID NO:68)	VISSSGSNTNYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:69)	PSYFQAMDY
	vH序列 (SEQ ID NO:70)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSFAMNWVRQAPG KGLEWVSVISSSGSNTNYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCARPSYFQAMDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:71)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSNFVSWYQQLPGTAP KLLIYDNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYC SSYDSFDHSWVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:72)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTTCGCTATGAACTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCTCTTCTTCTGGTT CTAACACCAACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTCCGTCTTACTTCCAGGCTATGGATTACTGGGGCCAAG GCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:73)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTCTAACTTCGTGTCTTGGTACCAGCAGCTGCCGG GCACGGCGCCGAAACTGCTGATCTACGACAACTCTAACCGC CCGAGCGGCGTGCCGGATCGCTTTAGCGGATCCAAAAGCGG

		CACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAAG ACGAAGCGGATTATTACTGCTCTTCTTACGACTCTTTCGACC ATTCTTGGGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
NOV0690	LCDR1 (Kabat) (SEQ ID NO:74)	SGDAIGTKFAH
	LCDR2 (Kabat) (SEQ ID NO:75)	YDHERPS
	LCDR3 (Kabat) (SEQ ID NO:76)	YSRASSNLV
	HCDR1 (Kabat) (SEQ ID NO:77)	DHAID
	HCDR2 (Kabat) (SEQ ID NO:78)	VIAGDGSITYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:79)	DTGVYREYMDV
	vH序列 (SEQ ID NO:80)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSDHAIDWVRQAPGK GLEWVSVIAGDGSITYYADSVKGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCARDTGVYREYMDVWGQGTLVTVSS
	vL序列 (SEQ ID NO:81)	DIELTQPPSVSVSPGQTASITCSGDAIGTKFAHWYQQKPGQAPV LVIYYDHERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCY SRASSNLVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:82)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTGACCATGCTATCGACTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCGCTGGTGACGGTT CTATCACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGACACTGGTGTTTACCGTGAATACATGGATGTTTGG GGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:83)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATGCTATCG GTACTAAATTCGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACTACGACCATGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCTACTCTCGTGCTTCTTCTAACCTGGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTA
NOV0691	LCDR1 (Kabat) (SEQ ID	TGTSSDVGRYNFVS

	NO:84)	
	LCDR2 (Kabat) (SEQ ID NO:85)	RVSNRPS
	LCDR3 (Kabat) (SEQ ID NO:86)	QSWTTYSNVV
	HCDR1 (Kabat) (SEQ ID NO:87)	SYALN
	HCDR2 (Kabat) (SEQ ID NO:88)	RIKSKTYGGSTDYAAPVKG
	HCDR3 (Kabat) (SEQ ID NO:89)	DRGGYVGFDS
	vH序列 (SEQ ID NO:90)	QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYALNWVRQAPG KGLEWVGRIKSKTYGGSTDYAAPVKGRFTISRDDSKNTLYLQ MNSLKTEDTAVYYCARDRGGYVGFDSWGQGTLVTVSS
	vL序列 (SEQ ID NO:91)	DIALTQPASVSGSPGQSITISCTGTSSDVGRYNFVSWYQQHPGK APKLMIYRVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADY YCQSWTTYSNVVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:92)	CAGGTGCAATTGGTGGAAAGCGGCGGTGGCCTGGTGAAACC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCCTCCGGATTCA CCTTTTCTTCTTACGCTCTGAACTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTGGGCCGTATCAAATCTAAAACT TACGGTGGTTCTACTGACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTCGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTGACCGTGGTGGTTACGTTGGTTTCGATTCTT GGGGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:93)	GATATCGCGCTGACCCAGCCGGCGAGCGTGAGCGGTAGCCC GGGCCAGAGCATTACCATTAGCTGCACCGGCACCAGCAGCG ATGTGGGCCGTTACAACTTCGTGTCTTGGTACCAGCAGCATC CGGGCAAGGCGCCGAAACTGATGATCTACCGTGTTTCTAAC CGTCCGAGCGGCGTGAGCAACCGTTTTAGCGGATCCAAAAG CGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCGG AAGACGAAGCGGATTATTACTGCCAGTCTTGGACTACTTAC TCTAACGTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
NOV0692	LCDR1 (Kabat) (SEQ ID NO:94)	SGDSIGSKYAQ
	LCDR2 (Kabat) (SEQ ID NO:95)	YNSERPS

	LCDR3 (Kabat) (SEQ ID NO:96)	QSWDGQSTIRV
	HCDR1 (Kabat) (SEQ ID NO:97)	RYWMD
	HCDR2 (Kabat) (SEQ ID NO:98)	RIKSKANGGITDYAAPVKG
	HCDR3 (Kabat) (SEQ ID NO:99)	GMTFLGI
	vH序列 (SEQ ID NO:100)	QVQLVESGGGLVKPGGSLRLSCAASGFTFSRYWMDWVRQAP GKGLEWVGRIKSKANGGITDYAAPVKGRFTISRDDSKNTLYLQ MNSLKTEDTAVYYCARGMTFLGIWGQGTLVTVSS
	vL序列 (SEQ ID NO:101)	DIELTQPPSVSVSPGQTASITCSGDSIGSKYAQWYQQKPGQAPV LVIYYNSERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQS WDGQSTIRVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:102)	CAGGTGCAATTGGTGGAAAGCGGCGGTGGCCTGGTGAAACC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCCTCCGGATTCA CCTTTTCTCGTTACTGGATGGACTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTGGGCCGTATCAAATCTAAAGCT AACGGTGGTATCACTGACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTCGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTGGTATGACTTTCCTGGGTATCTGGGGCCAA GGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:103)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATTCTATCG GTTCTAAATACGCTCAGTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACTACAACTCTGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTTGGGACGGTCAGTCTACTATC CGTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
NOV0693	LCDR1 (Kabat) (SEQ ID NO:104)	RASQSISFYLA
	LCDR2 (Kabat) (SEQ ID NO:105)	GASTLQS
	LCDR3 (Kabat) (SEQ ID NO:106)	HQYSYWLRT
	HCDR1 (Kabat)	SYALH

	(SEQ ID NO:107)	
	HCDR2 (Kabat) (SEQ ID NO:108)	YIFYDSSSTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:109)	FLYSAYGVAN
	vH序列 (SEQ ID NO:110)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYALHWVRQAPG KGLEWVSYIFYDSSSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCARFLYSAYGVANWGQGTLVTVSS
	vL序列 (SEQ ID NO:111)	DIQMTQSPSSLSASVGDRVTITCRASQSISFYLAWYQQKPGKAP KLLIYGASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCH QYSYWLRTFGQGTKVEIK
	vH DNA 序列 (SEQ ID NO:112)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTACGCTCTGCATTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCTACATCTTCTACGACTCTT CTTCTACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACCA TCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAATG AACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGC GCGTTTCCTGTACTCTGCTTACGGTGTTGCTAACTGGGGCCA AGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:113)	GATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCCAG CGTGGGCGATCGCGTGACCATTACCTGCAGAGCCAGCCAGT CTATTTCTTTCTACCTGGCTTGGTACCAGCAGAAACCGGGCA AAGCGCCGAAACTATTAATCTACGGTGCTTCTACTCTGCAA AGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGATCCGGCAC CGATTTCACCCTGACCATTAGCTCTCTGCAACCGGAAGACTT TGCGACCTATTATTGCCATCAGTACTCTTACTGGCTGCGTAC CTTTGGCCAGGGCACGAAAGTTGAAATTAAA
NOV0695	LCDR1 (Kabat) (SEQ ID NO:114)	RASQGIFTYLN
	LCDR2 (Kabat) (SEQ ID NO:115)	AASTLQS
	LCDR3 (Kabat) (SEQ ID NO:116)	QQYYSTSLT
	HCDR1 (Kabat) (SEQ ID NO:117)	SNSAAWN
	HCDR2 (Kabat) (SEQ ID NO:118)	RIYYRSKWYNDYAVSVKS

	HCDR3(Kabat) (SEQ ID NO:119)	ERSYRDYFDY
	vH序列 (SEQ ID NO:120)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSP SRGLEWLGRIYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCARERSYRDYFDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:121)	DIQMTQSPSSLSASVGDRVTITCRASQGIFTYLNWYQQKPGKA PKLLISAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQYYSTSLTFGQGTKVEIK
	vH DNA 序列 (SEQ ID NO:122)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTAACTCTGCTGCTTGGAACTGGATTCGTCAGA GCCCGAGCCGTGGCCTCGAGTGGCTGGGCCGTATCTACTAC CGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAAG CCGCATTACCATTAACCCGGATACTTCGAAAAACCAGTTTA GCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGTG TATTATTGCGCGCGTGAACGTTCTTACCGTGACTACTTCGAT TACTGGGGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:123)	GATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCCAG CGTGGGCGATCGCGTGACCATTACCTGCAGAGCCAGCCAGG GTATTTTCACTTACCTGAACTGGTACCAGCAGAAACCGGGC AAAGCGCCGAAACTATTAATCTCTGCTGCTTCTACTCTGCAA AGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGATCCGGCAC CGATTTCACCCTGACCATTAGCTCTCTGCAACCGGAAGACTT TGCGACCTATTATTGCCAGCAGTACTACTCTACTTCTCTGAC CTTTGGCCAGGGCACGAAAGTTGAAATTAAA
NOV0699	LCDR1 (Kabat) (SEQ ID NO:124)	SGDNIRKYVVH
	LCDR2 (Kabat) (SEQ ID NO:125)	RDNNRPS
	LCDR3 (Kabat) (SEQ ID NO:126)	QSWDSFLAVV
	HCDR1 (Kabat) (SEQ ID NO:127)	SYAMH
	HCDR2 (Kabat) (SEQ ID NO:128)	FISSLGSYTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:129)	ETAGYGYAFDP
	vH序列 (SEQ ID	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVSFISSLGSYTYYADSVKGRFTISRDNSKNTLYLQMNS

	NO:130)	LRAEDTAVYYCARETAGYGYAFDPWGQGTLVTVSS
	vL序列 (SEQ ID NO:131)	DIELTQPPSVSVSPGQTASITCSGDNIRKYVVHWYQQKPGQAP VLVIYRDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYC QSWDSFLAVVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:132)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTACGCTATGCATTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCTTCATCTCTTCTCTGGGTT CTTACACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGAAACTGCTGGTTACGGTTACGCTTTCGATCCGTGGG GCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:133)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAACATCC GTAAATACGTTGTTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACCGTGACAACAACCGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTTGGGACTCTTTCCTGGCTGTT GTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
NOV0705	LCDR1 (Kabat) (SEQ ID NO:134)	SGSSSNIGLDYVN
	LCDR2 (Kabat) (SEQ ID NO:135)	RNKQRPS
	LCDR3 (Kabat) (SEQ ID NO:136)	QAWAGRTNYVV
	HCDR1 (Kabat) (SEQ ID NO:137)	NYWIG
	HCDR2 (Kabat) (SEQ ID NO:138)	FIDPGVSYTRYSPSFQG
	HCDR3 (Kabat) (SEQ ID NO:139)	VLAHSTEYNWPAF
	vH序列 (SEQ ID NO:140)	QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPG KGLEWMGFIDPGVSYTRYSPSFQGQVTISADKSISTAYLQWSSL KASDTAMYYCARVLAHSTEYNWPAFWGQGTLVTVSS
	vL序列 (SEQ ID NO:141)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGLDYVNWYQQLPGTA PKLLIYRNKQRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYY CQAWAGRTNYVVFGGGTKLTVL
	vH DNA 序列	CAGGTGCAATTGGTGCAGAGCGGTGCGGAAGTGAAAAAAC CGGGCGAAAGCCTGAAAATTAGCTGCAAAGGCTCCGGATAT

	(SEQ ID NO:142)	AGCTTCACTAACTACTGGATCGGTTGGGTGCGCCAGATGCC GGGCAAAGGTCTCGAGTGGATGGGCTTCATCGACCCGGGTG TTAGCTACACCCGTTATAGCCCGAGCTTTCAGGGCCAGGTG ACCATTAGCGCGGATAAAAGCATCAGCACCGCGTATCTGCA ATGGAGCAGCCTGAAAGCGAGCGATACCGCGATGTATTATT GCGCGCGTGTTCTGGCTCATTCTACTGAATACAACTGGCCGG CTTTCTGGGGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:143)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTCTGGACTACGTGAACTGGTACCAGCAGCTGCCG GGCACGGCGCCGAAACTGCTGATCTACCGTAACAAACAGCG CCCGAGCGGCGTGCCGGATCGCTTTAGCGGATCCAAAAGCG GCACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAA GACGAAGCGGATTATTACTGCCAGGCTTGGGCTGGTCGTAC TAACTACGTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCT A
NOV0709	LCDR1 (Kabat) (SEQ ID NO:144)	TGTSSDVGSYNYVS
	LCDR2 (Kabat) (SEQ ID NO:145)	YVSNRPS
	LCDR3 (Kabat) (SEQ ID NO:146)	ASYTHQGSWV
	HCDR1 (Kabat) (SEQ ID NO:147)	TYYMH
	HCDR2 (Kabat) (SEQ ID NO:148)	VISSDGSFTFYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:149)	HGYGAFDY
	vH序列 (SEQ ID NO:150)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSTYYMHWVRQAPG KGLEWVSVISSDGSFTFYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCARHGYGAFDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:151)	DIALTQPASVSGSPGQSITISCTGTSSDVGSYNYVSWYQQHPGK APKLMIYYVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADY YCASYTHQGSWVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:152)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTACTTACTACATGCATTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCTCTTCTGACGGTT CTTTCACCTTCTATGCGGATAGCGTGAAAGGCCGCTTTACCA TCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAATG AACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGC GCGTCATGGTTACGGTGCTTTCGATTACTGGGGCCAAGGCA

		CCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:153)	GATATCGCGCTGACCCAGCCGGCGAGCGTGAGCGGTAGCCC GGGCCAGAGCATTACCATTAGCTGCACCGGCACCAGCAGCG ATGTGGGCTCTTACAACTACGTGTCTTGGTACCAGCAGCATC CGGGCAAGGCGCCGAAACTGATGATCTACTACGTTTCTAAC CGTCCGAGCGGCGTGAGCAACCGTTTTAGCGGATCCAAAAG CGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCGG AAGACGAAGCGGATTATTACTGCGCTTCTTACACTCATCAG GGTTCTTGGGTGTTTGGCGGCGGCACGAAGTTAACCGTCCT A
NOV0710	LCDR1 (Kabat) (SEQ ID NO:154)	RASQSISLWLN
	LCDR2 (Kabat) (SEQ ID NO:155)	AASTLQS
	LCDR3 (Kabat) (SEQ ID NO:156)	QQYYTSPYT
	HCDR1 (Kabat) (SEQ ID NO:157)	SYAMS
	HCDR2 (Kabat) (SEQ ID NO:158)	VIRSSGSSTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:159)	GGGYFDY
	vH序列 (SEQ ID NO:160)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSVIRSSGSSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCARGGGYFDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:161)	DIQMTQSPSSLSASVGDRVTITCRASQSISLWLNWYQQKPGKA PKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQYYTSPYTFGQGTKVEIK
	vH DNA 序列 (SEQ ID NO:162)	CAGGTGCAGCTGCTGGAATCAGGCGGCGGACTGGTGCAACC TGGCGGATCCCTGAGGCTGAGCTGCGCTGCTAGTGGCTTCA CCTTCTCTAGCTACGCTATGAGCTGGGTCCGCCAGGCCCCTG GTAAAGGCCTCGAGTGGGTGTCAGTGATTAGATCTAGCGGC TCTAGCACCTACTACGCCGATAGCGTGAAGGGCCGGTTCAC TATCTCTAGGGATAACTCTAAGAACACCCTGTACCTGCAGA TGAACTCCCTGAGGGCCGAGGACACCGCCGTCTACTACTGC GCTAGAGGCGGAGGCTACTTCGACTACTGGGGTCAAGGCAC CCTGGTCACCGTGTCTAGC
	vL DNA 序列 (SEQ ID NO:163)	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGT CTATTAGCCTGTGGCTGAACTGGTATCAGCAGAAGCCCGGT AAAGCCCCTAAGCTGCTGATCTACGCCGCCTCTACCCTGCA GTCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCA

		CCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCGAGGACT TCGCTACCTACTACTGTCAGCAGTACTACACTAGCCCCTACA CCTTCGGTCAGGGCACTAAGGTCGAGATTAAG
NOV0712	LCDR1 (Kabat) (SEQ ID NO:164)	RASQSISSYLN
	LCDR2 (Kabat) (SEQ ID NO:165)	AVSTLQS
	LCDR3 (Kabat) (SEQ ID NO:166)	QQSGTFPPTT
	HCDR1 (Kabat) (SEQ ID NO:167)	SHGMH
	HCDR2 (Kabat) (SEQ ID NO:168)	VISGSGSNTGYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:169)	QWGSYAFDS
	vH序列 (SEQ ID NO:170)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSHGMHWVRQAPG KGLEWVSVISGSGSNTGYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCARQWGSYAFDSWGQGTLVTVSS
	vL序列 (SEQ ID NO:171)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAVSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ QSGTFPPTTFGQGTKVEIK
	vH DNA 序列 (SEQ ID NO:172)	CAGGTGCAGCTGCTGGAATCAGGCGGCGGACTGGTGCAGCC TGGCGGATCCCTGAGGCTGAGCTGCGCTGCTAGTGGCTTCA CCTTTAGCTCTCACGGAATGCACTGGGTCCGCCAGGCCCCTG GTAAAGGCCTCGAGTGGGTGTCAGTGATTAGCGGTAGCGGC TCTAACACCGGCTACGCCGATAGCGTGAAGGGCCGGTTCAC TATCTCTAGGGATAACTCTAAGAACACCCTGTACCTGCAGA TGAACTCCCTGAGGGCCGAGGACACCGCCGTCTACTACTGC GCTAGACAGTGGGGCTCCTACGCCTTCGATAGCTGGGGTCA AGGCACCCTGGTCACCGTGTCTAGC
	vL DNA 序列 (SEQ ID NO:173)	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGT CTATCTCTAGCTACCTGAACTGGTATCAGCAGAAGCCCGGT AAAGCCCCTAAGCTGCTGATCTACGCCGTGTCTACCCTGCA GTCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCA CCGACTTCACCCTGACTATTAGTAGCCTGCAGCCCGAGGAC TTCGCTACCTACTACTGTCAGCAGTCAGGCACCTTCCCCCCT ACTACCTTCGGTCAGGGCACTAAGGTCGAGATTAAG
NOV0713	LCDR1 (Kabat)	SGDNLRSYYVH

	(SEQ ID NO:174)	
	LCDR2 (Kabat) (SEQ ID NO:175)	GNNKRPS
	LCDR3 (Kabat) (SEQ ID NO:176)	GVYTLSSVV
	HCDR1 (Kabat) (SEQ ID NO:177)	SNSAAWN
	HCDR2 (Kabat) (SEQ ID NO:178)	RIYYRSKWYNDYAVSVKS
	HCDR3 (Kabat) (SEQ ID NO:179)	GLVGRYGQPYHFDV
	vH序列 (SEQ ID NO:180)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSP SRGLEWLGRIYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCARGLVGRYGQPYHFDVWGQGTLVTVSS
	vL序列 (SEQ ID NO:181)	DIELTQPPSVSVSPGQTASITCSGDNLRSYYVHWYQQKPGQAP VLVIYGNNKRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYC GVYTLSSVVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:182)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTAACTCTGCTGCTTGGAACTGGATTCGTCAGA GCCCGAGCCGTGGCCTCGAGTGGCTGGGCCGTATCTACTAC CGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAAG CCGCATTACCATTAACCCGGATACTTCGAAAAACCAGTTTA GCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGTG TATTATTGCGCGCGTGGTCTGGTTGGTCGTTACGGTCAGCCG TACCATTTCGATGTTTGGGGCCAAGGCACCCTGGTGACTGTT AGCTCA
	vL DNA 序列 (SEQ ID NO:183)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAACCTGC GTTCTTACTACGTTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGGTAACAACAAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCGGTGTTTACACTCTGTCTTCTGTTGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTA
NOV0718	LCDR1 (Kabat) (SEQ ID NO:184)	SGDKIPTYTVH
	LCDR2 (Kabat) (SEQ ID	DDNKRPS

	NO:185)	
	LCDR3 (Kabat) (SEQ ID NO:186)	QSTASGTVV
	HCDR1 (Kabat) (SEQ ID NO:187)	SYALH
	HCDR2 (Kabat) (SEQ ID NO:188)	RIKSKTNGGTTDYAAPVKG
	HCDR3 (Kabat) (SEQ ID NO:189)	VDATYSYSGYYYPMDY
	vH序列 (SEQ ID NO:190)	QVQLVESGGGLVKPGGSLRLSCAASGFTFNSYALHWVRQAPG KGLEWVGRIKSKTNGGTTDYAAPVKGRFTISRDDSKNTLYLQ MNSLKTEDTAVYYCARVDATYSYSGYYYPMDYWGQGTLVT VSS
	vL序列 (SEQ ID NO:191)	DIELTQPPSVSVSPGQTASITCSGDKIPTYTVHWYQQKPGQAPV LVIYDDNKRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQ STASGTVVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:192)	CAGGTGCAATTGGTGGAAAGCGGCGGTGGCCTGGTGAAACC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCCTCCGGATTCA CCTTTAACTCTTACGCTCTGCATTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTGGGCCGTATCAAATCTAAAACT AACGGTGGTACTACTGACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTCGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTGTTGACGCTACTTACTCTTACTCTGGTTACT ACTACCCGATGGATTACTGGGGCCAAGGCACCCTGGTGACT GTTAGCTCA
	vL DNA 序列 (SEQ ID NO:193)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAAAATCC CGACTTACACTGTTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGACGACAACAAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTACTGCTTCTGGTACTGTTGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTA
NOV0719	LCDR1 (Kabat) (SEQ ID NO:194)	RASQSIVSYLN
	LCDR2 (Kabat) (SEQ ID NO:195)	DASSLQS
	LCDR3 (Kabat) (SEQ ID NO:196)	QQSGSHSIT

	HCDR1 (Kabat) (SEQ ID NO:197)	SHWVH
	HCDR2 (Kabat) (SEQ ID NO:198)	VISYMGSSTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:199)	GSYDMAFDV
	vH序列 (SEQ ID NO:200)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSHWVHWVRQAPG KGLEWVSVISYMGSSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCARGSYDMAFDVWGQGTLVTVSS
	vL序列 (SEQ ID NO:201)	DIQMTQSPSSLSASVGDRVTITCRASQSIVSYLNWYQQKPGKAP KLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ QSGSHSITFGQGTKVEIK
	vH DNA 序列 (SEQ ID NO:202)	CAGGTGCAGCTGCTGGAATCAGGCGGCGGACTGGTGCAGCC TGGCGGTAGCCTGAGACTGAGCTGCGCTGCTAGTGGCTTCA CCTTTAGCTCTCACTGGGTGCACTGGGTCAGACAGGCCCCTG GTAAAGGCCTGGAGTGGGTGTCAGTGATTAGCTATATGGGC TCTAGCACCTACTACGCCGATAGCGTGAAGGGCCGGTTCAC TATCTCTAGGGATAACTCTAAGAACACCCTGTACCTGCAGA TGAATAGCCTGAGAGCCGAGGACACCGCCGTCTACTACTGC GCTAGAGGCTCCTACGATATGGCCTTCGACGTGTGGGGTCA GGGCACCCTGGTCACCGTGTCTAGC
	vL DNA 序列 (SEQ ID NO:203)	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGT CTATCGTCAGCTACCTGAACTGGTATCAGCAGAAGCCCGGT AAAGCCCCTAAGCTGCTGATCTACGACGCCTCTAGCCTGCA GTCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCA CCGACTTCACCCTGACTATTAGTAGCCTGCAGCCCGAGGAC TTCGCTACCTACTACTGTCAGCAGTCAGGCTCTCACTCTATC ACCTTCGGTCAGGGCACTAAGGTCGAGATTAAG
NOV0720	LCDR1 (Kabat) (SEQ ID NO:204)	SGDNIGSMTAH
	LCDR2 (Kabat) (SEQ ID NO:205)	DKNERPS
	LCDR3 (Kabat) (SEQ ID NO:206)	QSWDDSYNSVV
	HCDR1 (Kabat) (SEQ ID NO:207)	SNSAGWN
	HCDR2 (Kabat)	RIYYRSKWYNDYAVSVKS

	(SEQ ID NO:208)	
	HCDR3 (Kabat) (SEQ ID NO:209)	EKYTVSFYDFFDY
	vH序列 (SEQ ID NO:210)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAGWNWIRQSP SRGLEWLGRIYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCAREKYTVSFYDFFDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:211)	DIELTQPPSVSVSPGQTASITCSGDNIGSMTAHWYQQKPGQAPV LVIYDKNERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQ SWDDSYNSVVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:212)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTAACTCTGCTGGTTGGAACTGGATTCGTCAG AGCCCGAGCCGTGGCCTCGAGTGGCTGGGCCGTATCTACTA CCGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAA GCCGCATTACCATTAACCCGGATACTTCGAAAAACCAGTTT AGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGT GTATTATTGCGCGCGTGAAAAATACACTGTTTCTTTCTACGA CTTCTTCGATTACTGGGGCCAAGGCACCCTGGTGACTGTTAG CTCA
	vL DNA 序列 (SEQ ID NO:213)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAACATCG GTTCTATGACTGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGACAAAAACGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTTGGGACGACTCTTACAACTCT GTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA

實例2：藉由定點突變誘發進行工程改造抗體

使用QuikChange®定點突變誘發套組(Agilent Technologies, Santa Clara, CA)對抗CDH6抗體亞群進行定點突變誘發以便移除潛在的轉譯後修飾及生殖系化位點。改變NOV690序列：$D_{53}S$及VL (3-J-germ)，產生抗體NOV1126。改變NOV695序列：$N_{31}Q$及$S_{49}Y$，產生抗體NOV1127。改變NOV0720序列：$N_{31}Q$、$N_{95}Q$及VL (3-J-germ)，產生抗體NOV1132。經工程改造之抗體之序列資訊描述於表6中。

表6

經工程改造之抗體之序列資訊

NOV1126	LCDR1 (Kabat) (SEQ ID NO:214)	SGDAIGTKFAH
	LCDR2	YDHERPS

	(Kabat) (SEQ ID NO:215)	
	LCDR3 (Kabat) (SEQ ID NO:216)	YSRASSNLV
	HCDR1 (Kabat) (SEQ ID NO:217)	DHAID
	HCDR2 (Kabat) (SEQ ID NO:218)	VIAGSGSITYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:219)	DTGVYREYMDV
	vH序列 (SEQ ID NO:220)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDHAIDWVRQAPGK GLEWVSVIAGSGSITYYADSVKGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCARDTGVYREYMDVWGQGTLVTVSS
	vL序列 (SEQ ID NO:221)	SYELTQPLSVSVALGQTARITCSGDAIGTKFAHWYQQKPGQAP VLVIYYDHERPSGIPERFSGSNSGNTATLTISRAQAGDEADYYC YSRASSNLVFGGGTKLTVL
	vH DNA 序列 (SEQ ID NO:222)	GAAGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTGACCATGCTATCGACTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCGCTGGTAGCGGTT CTATCACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGACACTGGTGTTTACCGTGAATACATGGATGTTTGG GGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA 序列 (SEQ ID NO:223)	AGCTATGAACTGACCCAGCCGCTGAGCGTGAGCGTGGCGCT GGGCCAGACCGCGCGCATTACCTGTAGCGGCGATGCTATCG GTACTAAATTCGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACTACGACCATGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCCGCGCGCAGGCGGGCGACGAA GCGGATTATTACTGCTACTCTCGTGCTTCTTCTAACCTGGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTA
NOV1127	LCDR1 (Kabat) (SEQ ID NO:224)	RASQGIFTYLN
	LCDR2 (Kabat) (SEQ ID NO:225)	AASTLQS
	LCDR3 (Kabat) (SEQ ID	QQYYSTSLT

	NO:226)	
	HCDR1 (Kabat) (SEQ ID NO:227)	SQSAAWN
	HCDR2 (Kabat) (SEQ ID NO:228)	RIYYRSKWYNDYAVSVKS
	HCDR3 (Kabat) (SEQ ID NO:229)	ERSYRDYFDY
	vH序列 (SEQ ID NO:230)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSQSAAWNWIRQSP SRGLEWLGRIYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCARERSYRDYFDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:231)	DIQMTQSPSSLSASVGDRVTITCRASQGIFTYLNWYQQKPGKA PKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQYYSTSLTFGQGTKVEIK
	vH DNA 序列 (SEQ ID NO:232)	CAGGTGCAGCTGCAGCAGTCAGGCCCTGGCCTGGTCAAGCC TAGTCAGACCCTGAGCCTGACCTGCGCTATTAGCGGCGATA GTGTGTCTAGTCAGTCAGCCGCCTGGAACTGGATTAGACAG TCACCCTCTAGGGGCCTGGAGTGGCTGGGTAGAATCTACTA TAGGTCTAAGTGGTATAACGACTACGCCGTCAGCGTGAAGT CTAGGATCACTATTAACCCCGACACCTCTAAGAATCAGTTTA GCCTGCAGCTGAATAGCGTGACCCCCGAGGACACCGCCGTC TACTACTGCGCTAGAGAGCGGTCCTATAGAGACTACTTCGA CTACTGGGGTCAGGGCACCCTGGTCACCGTGTCTAGC
	vL DNA 序列 (SEQ ID NO:233)	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGG GAATCTTCACCTACCTGAACTGGTATCAGCAGAAGCCCGGT AAAGCCCCTAAGCTGCTGATCTACGCCGCCTCTACCCTGCA GTCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCA CCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCGAGGACT TCGCTACCTACTACTGTCAGCAGTACTACTCTACTAGCCTGA CCTTCGGTCAGGGCACTAAGGTCGAGATTAAG
NOV1132	LCDR1 (Kabat) (SEQ ID NO:234)	SGDNIGSMTAH
	LCDR2 (Kabat) (SEQ ID NO:235)	DKNERPS
	LCDR3 (Kabat) (SEQ ID NO:236)	QSWDDSYTSVV
	HCDR1 (Kabat) (SEQ ID NO:237)	SQSAGWN
	HCDR2	RIYYRSKWYNDYAVSVKS

	(Kabat) (SEQ ID NO:238)	
	HCDR3 (Kabat) (SEQ ID NO:239)	EKYTVSFYDFFDY
	vH序列 (SEQ ID NO:240)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSQSAGWNWIRQSP SRGLEWLGRIYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCAREKYTVSFYDFFDYWGQGTLVTVSS
	vL序列 (SEQ ID NO:241)	SYELTQPLSVSVALGQTARITCSGDNIGSMTAHWYQQKPGQAP VLVIYDKNERPSGIPERFSGSNSGNTATLTISRAQAGDEADYYC QSWDDSYTSVVFGGGTKLTVL
	vH DNA序列 (SEQ ID NO:242)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTCAGTCTGCTGGTTGGAACTGGATTCGTCAG AGCCCGAGCCGTGGCCTCGAGTGGCTGGGCCGTATCTACTA CCGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAA GCCGCATTACCATTAACCCGGATACTTCGAAAAACCAGTTT AGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGT GTATTATTGCGCGCGTGAAAAATACACTGTTTCTTTCTACGA CTTCTTCGATTACTGGGGCCAAGGCACCCTGGTGACTGTTAG CTCA
	vL DNA序列 (SEQ ID NO:243)	AGCTATGAACTGACCCAGCCGCTGAGCGTGAGCGTGGCGCT GGGCCAGACCGCGCGCATTACCTGTAGCGGCGATAACATCG GTTCTATGACTGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGACAAAAACGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCCGCGCGCAGGCGGGCGACGAA GCGGATTATTACTGCCAGTCTTGGGACGACTCTTACACCTCT GTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA

實例3：測定抗CDH6 IgG對以表現源於人類、食蟹獼猴、大鼠及小鼠之CDH6為特徵之細胞的結合

為了測定抗CDH6對以表現來自不同物種之CDH6為特徵之細胞的結合，對內源性表現CDH6的OVCAR3細胞以及經工程改造以表現源於人類、食蟹獼猴、大鼠及小鼠之CDH6的CHO細胞進行FACS (螢光活化細胞分選術)分析。

OVCAR3 (卵巢漿液癌，在RPMI + 20% FCS中培養)獲自ATCC (#HTB-161)。以CDH6表現為特徵之CHO細胞株的產生描述於上述實例1中。

藉由根據製造商說明書用Accutase®細胞解離試劑(#A1110501 Gibco, Grand Island, NY)處理培養中之細胞、隨後用FACS緩衝液

(PBS/1% BSA, Gibco)洗滌細胞來製備細胞懸浮液。將細胞以1x10E6個細胞/毫升再懸浮於FACS緩衝液中且等分試樣置於圓形底96孔盤(Corning #CLS3360，100微升/孔)。製備一次抗體之8點1:5連續稀釋液以產生10 μg/ml之最高最終初始濃度且每孔添加100 μl至細胞懸浮液中。作為陰性對照抗體，使用人類同型對照IgG (R&D systems #1-001-A Minneapolis, MN)。細胞與一次抗體溶液一起在冰上培育30分鐘，隨後用200 μl冷FACS緩衝液洗滌三次。將細胞再懸浮於100 μl PE結合之抗人類人類Fc (以1/500稀釋度使用)(Jackson Immuno Research #109-116-098 West Grove, PA)且細胞在冰上培育30分鐘。用200 μl冷FACS緩衝液洗滌三次之後，在BD FACS Canto II® (BD Biosciences, San Jose, CA)上分析細胞。使用FlowJo®軟體測定每個樣品之信號幾何平均值且藉由對信號幾何平均值相對於濃度作圖且使用Tibco Spotfire® (Tibco, Boston, MA)進行非線性回歸曲線擬合來測定EC50。所有20種所分析抗CDH6抗體對OVCAR3細胞(圖1)及表現CDH6之CHO細胞展示劑量依賴性、標靶特異性結合。對於不表現CDH6的野生型CHO細胞未觀測到反應性。EC50值概括於表7中。

表7

CDH6 IgG對OVCAR3細胞及CHO細胞的細胞結合親和力(EC50)，該等細胞對於CDH6表現而言呈陰性(CHO-TREX)或經工程改造以表現人類、食蟹獼猴、大鼠或小鼠CDH6。

抗體	OVCAR3	CHO-cyCDH6	CHO-huCDH6	CHO-moCDH6	CHO-大鼠CDH6	CHO-TREX
hIgG	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
NOV0670	4.092	0.281	0.205	0.312	0.521	n.a.
NOV0672	7.524	0.294	0.339	0.525	0.53	n.a.
NOV0674	13.398	0.32	0.494	0.527	0.537	n.a.
NOV0682	17.028	0.624	0.556	0.758	0.558	n.a.
NOV0685	5.214	0.178	0.179	0.23	0.321	n.a.
NOV0689	0.396	0.116	0.257	0.177	0.12	n.a.
NOV0690	0.924	0.777	0.136	3.041	16.595	n.a.
NOV0691	1.056	0.042	0.493	0.104	0.102	n.a.

NOV0692	1.056	0.08	0.107	0.221	0.155	n.a.
NOV0693	4.686	0.528	0.556	0.66	0.55	n.a.
NOV0695	2.64	0.306	0.267	0.427	0.659	n.a.
NOV0699	1.188	1.254	0.972	1.554	1.43	n.a.
NOV0705	0.858	0.005	0.511	0.018	0.646	n.a.
NOV0709	1.518	0.53	n.a.	0.669	0.531	n.a.
NOV0710	0.858	0.15	0.151	0.22	0.152	n.a.
NOV0712	1.122	0.202	0.21	0.537	0.523	n.a.
NOV0713	11.22	4.779	3.115	7.034	8.369	n.a.
NOV0718	0.66	0.313	0.187	0.52	0.322	n.a.
NOV0719	1.914	0.171	0.248	0.527	0.222	n.a.
NOV0720	0.66	0.543	0.428	0.338	0.493	n.a.

實例4：藉由Biacore量測法測定對來自人類、食蟹獼猴、大鼠及小鼠之重組CDH6的結合親和力及交叉反應性

使用SPR技術、在Biacore® T100儀器(GE Healthcare, Pittsburgh, PA)上且使用CM5感測晶片測定抗體對源於人類、食蟹獼猴、大鼠及小鼠之重組CDH6蛋白質的親和力。

簡言之，在所有實驗中，使用補充有0.5%牛白蛋白溶離份V (7.5%溶液)(Gibco 15260-037)的HBS-P (0.01 M HEPES pH 7.4、0.15 M NaCl、0.005%界面活性劑P20)作為操作緩衝液。藉由反應單位(RU)量測固著程度及分析物相互作用。進行試驗性實驗以測試及證實固著抗人類Fc抗體(Jackson ImmunoResearch 109-006-098 West Grove, PA)及捕捉測試抗體之可能性。

進行動力學量測實驗，其中抗體經由所固著之抗人類Fc抗體捕捉至感測晶片表面且測定CDH6蛋白質在游離溶液中結合的能力。簡言之，30 μg/ml抗人類Fc抗體(pH 5)在12微升/分鐘之流速下經由胺偶合反應而固著於所有四個流動池之CM5感測晶片上以達成7500 RU。接著將5-10 μg/ml測試抗體以10 μl/min注射至流動池2、3及4歷時12秒。隨後，對0.78-50 nM CDH6受體細胞外域(ECD)進行2倍連續稀釋且在80 μl/min流速下注射至參考池(流動池1)及測試流動池2、3、4上歷時100秒。所測試之ECD列於下表中。隨後對結合進行解離10分

OnCusp
Ex. 1002

鐘。每個注射循環之後，晶片表面用60 μl/min之10 mM甘胺酸pH2.0再生30秒。所有實驗均在25℃進行且使用簡單的1:1相互作用模型、使用Biacore® T100評價軟體2.0.3版對反應資料進行全面擬合。結果表明此組中所分析之大部分CDH6抗體對人類、食蟹獼猴、大鼠及小鼠具有交叉反應性(表8)。

表8

藉由Biacore量測所得之抗CDH6 IgG對來自人類、食蟹獼猴、大鼠及小鼠之重組CDH6的結合親和力

抗體	KD [M] 人類CDH6	KD [M] 食蟹獼猴CDH6	KD [M] 大鼠CDH6	KD [M] 小鼠CDH6
NOV0670	9.329E-09	7.378E-09	7.232E-09	1.903E-08
NOV0672	2.463E-09	4.589E-09	3.291E-09	4.283E-09
NOV0674	1.954E-09	6.995E-09	2.829E-09	4.77E-09
NOV0682	6.188E-09	1.273E-08	5.554E-09	1.776E-07
NOV0685	4.551E-09	4.115E-09	4.636E-09	5.321E-09
NOV0689	5.648E-09	6.402E-09	6.083E-09	8.854E-09
NOV0690	6.969E-09	n/a	n/a	1.111E-09
NOV0691	8.343E-09	9.797E-09	4.332E-09	n/a
NOV0692	5.082E-09	5.554E-09	2.502E-09	2.494E-09
NOV0693	1.184E-09	1.966E-09	1.078E-09	1.843E-09
NOV0695	3.023E-12	n/a	n/a	1.67E-11
NOV0705	2.479E-09	n/a	2.334E-09	4.926E-11
NOV0709	8.174E-10	1.983E-09	6.977E-10	2.139E-09
NOV0710	2.065E-09	3.84E-09	2.385E-09	4.009E-09
NOV0712	2.904E-09	3.784E-09	5.719E-09	4.835E-09
NOV0713	1.419E-08	9.049E-09	7.147E-09	2.006E-08
NOV0718	5.455E-09	6.903E-09	6.608E-09	5.941E-09
NOV0719	1.899E-09	4.944E-09	8.789E-09	5.172E-09
NOV0720	2.47E-09	3.335E-09	1.406E-09	2.268E-09

實例5：藉由Biacore進行的抗原決定基分組

使用表面電漿子共振(SPR)技術，在Biacore® A-100儀器(GE Healthcare, Pittsburgh, PA)上使用CM5感測晶片測定CDH6抗體之抗原決定基定位。簡言之，在所有實驗中使用HBS-EP緩衝液(10 mM HEPES pH 7.4、150 mM NaCl、3.4 mM EDTA、補充有0.25% BSA及10 mM鈣之0.005%界面活性劑P20)作為操作緩衝液。藉由反應單位(RU)量測固著程度及分析物相互作用。進行試驗性實驗以測試及證實

固著抗人類Fc抗體(Jackson ImmunoResearch, 目錄號109-006-098 West Grove, PA)及捕捉測試抗體之可能性。

對於抗原決定基定位而言，抗人類Fc抗體以10,000 RU固著於所有四個流動池之斑點1、2及4、5上。斑點5用作參考。一次測試CDH6抗體中之每一者接著經由所固著之抗人類Fc、以大於300 RU之反應程度捕捉於生物感測晶片上，隨後以高於20 RU之結合量注射CDH6蛋白質於斑點1及5。斑點2及4用作額外的參考表面。各流動池之所有五個斑點均經由兩次注射1 mg/ml之人類IgG來阻斷，以阻斷抗人類Fc之任何游離結合位點。接著注射二次測試抗體中之每一者至斑點1、2或4、5上以評估一次測試抗體與CDH6蛋白質之複合物的結合程度。人類IgG同型對照物用作一次及二次測試陰性對照抗體。抗體在所有四個流動池中並行測試直至所有可能的抗體組合均已評價。每個一次及二次抗體結合循環之後的所有流動池表面再生均經由注射10 mM甘胺酸pH2.0來進行。

結果係使用Biacore® 4000評價軟體中之抗原決定基定位模組評價且以矩陣(一次抗體成列且二次抗體成行)呈現(圖2)。二次測試抗體對一次測試抗體與CDH6蛋白質之複合物的另外結合係由陽性反應值指示。標記陰性對且與人類IgG同型對照進行比較。接著利用矩陣對抗體識別的抗原決定基、根據其如何與其他抗體可形成對來進行定位。抗體NOV0710與NOV0712彼此間競爭，表明其識別的抗原上之抗原決定基重疊。抗體NOV1127當其用作一次及二次結合抗體時顯示陽性結合，表明其可結合至CDH6上之多個位點或初始結合改變構形且打開額外的結合位點。基於此分析，NOV0719、NOV0692、NOV1126及NOV1132均似乎結合不同的抗原決定基。

實例6：藉由氫-氘交換/質譜進行的抗原決定基定位

使用氫-氘交換(HDx)與質譜(MS)之組合(Woods等人, J. Cell

Biochem. 2001 S37: 89-98))，對抗體NOV1127、NOV0719、NOV0710及NOV0712針對全長hCDH6 (aa54-615)之全長細胞外域(ECD)的結合位點進行定位，全長hCDH6包括鈣黏素域(EC) 1至5 (表9)。另外，亦使用抗體NOV0710及NOV0712 (表10)對由EC 1至3組成的截短ECD進行HDx。在HDx中，蛋白質之可交換醯胺氫經氘置換。此方法對蛋白質結構/動力學及溶劑可接近性敏感，且因此能夠報導出在配位體結合時經歷氘吸收減少之位置。此等實驗之目標在於鑑別潛在抗原決定基及瞭解hCDH6當與本發明人之治療抗體結合時的動力學。重要的是注意到，氘吸收之變化對直接結合與異位事件均敏感；為了準確地確定抗原決定基，HDx必須與正交技術(例如X射線結晶學)組合。

使用類似於文獻中所述之方法(Chalmers等人, Anal Chem. 2006: 78(4):1005-14)進行自動化HDx/MS實驗。實驗在Waters HDx-MS®平台上進行，該平台包括LEAP自動取樣器、nanoACQUITY UPLC系統及Synapt G2質譜儀(Waters Corp, Milford MA)。以氘標記全長hCDH6(54-615)之蛋白質主鏈所用的氘緩衝液為50 mM D-Tris、150 mM NaCl pH 7.4 + 3 mM CaCl2；溶液中的總氘百分比為89.5%。在缺乏hCDH6抗體的hCDH6(54-615)氘標記實驗中，使用45 µl氘緩衝液在冷卻管中稀釋體積為5 µl的600 pmol hCDH6(54-615)且在旋轉器上、在4℃培育25分鐘。標記反應物接著在冰上用75 µl經冷卻之淬滅緩衝液淬滅3分鐘，隨後注射至LC-MS系統上用於自動化胃蛋白酶消化及肽分析。在存在所結合之hCDH6抗體的hCDH6(54-615)氘標記實驗中，首先使600 pmol hCDH6抗體固著於Thermo Protein G Plus珠粒上且使用辛二酸二丁二醯亞胺酯(DSS)發生交聯。為進行標記實驗，將抗體珠粒(含有600 pmol抗體)與600 pmol hCDH6(54-615)一起在4℃培育30分鐘。30分鐘後，用200 µl Tris緩衝液(50 mM Tris、150 mM NaCl pH 7.4 + 3 mM CaCl2)洗滌珠粒。接著添加200 µl經冷卻之氘緩

衝液(80.6%氘)且複合物在4℃培育25分鐘。25分鐘之後，標記反應物在冰上用125 μl經冷卻之淬滅緩衝液淬滅2.5分鐘。樣品在離心機中離心30秒之後，將所淬滅之溶液注射至LC-MS系統上進行自動化胃蛋白酶消化及肽分析。亦對僅含有EC 3至5的hCDH6(267-615)構築體進行類似實驗。在此等實驗中，緩衝液為25 mM HEPES pH=7.4、150 mM NaCl、3 mM CaCl2及含有94.2%氘之氘型緩衝液。

所有量測均使用最少三次分析、一式三份來進行。所有氘交換實驗均使用0.5 M TCEP及3 M尿素(pH=2.5)淬滅。淬滅之後，所交換之抗原使用Poroszyme®固著胃蛋白酶管柱(2.1×30 mm)、在12℃進行線上胃蛋白酶消化，隨後捕獲於WatersVanguard®HSS T3 (Waters Corp. Milford MA)捕獲管柱上。自捕獲管柱中溶離出肽且在Waters CSH C18 1×100 mm管柱(維持於1℃)上、在40 μl/min流速下、使用2%至35% B之二元8分鐘梯度(移動相A為99.9%水及0.1%甲酸；移動相B為99.9%乙腈及0.1%甲酸)進行分離。

對於hCDH6(54-615)蛋白質而言，藉由氘交換實驗監測73%序列；此等肽之完整清單呈現於表9中。圖3提供hCDH6(54-615)蛋白質之交換特徵之概述。氘吸收較大的區域(諸如EC3)暴露於溶劑較多或展現較弱氘吸收的區域(諸如區域EC4及EC5)具有較弱氫鍵網路。總體而言，觀測到EC1至EC3域中的氘交換大於EC4或EC5域。舉例而言，EC2肽181-199 VTATDADDPTYGNSAKVVY (SEQ ID NO: 244)意謂氘吸收為3.61 Da；相比之下，EC5肽506-525 IQTLHAVDKDDPYSGHQFSF (SEQ ID NO: 245)意謂氘吸收僅為1.18 Da。有限的氘吸收可使得保護區域(抗體結合時，經歷-0.5 Da或小於-0.5 Da之位移的區域)的確定由於動態範圍的限制而具有更大挑戰性。

對於EC1 (54-159)而言，所有四種抗體結合時展現氘吸收降低的唯一肽為61-70 FLLEEYTGSD (SEQ ID NO: 246)。在EC1中，抗體

NOV1127及NOV0719證明氘吸收之變化大於或等於0.5 Da的結構出現顯著的不穩定。NOV0710及NOV0712之結合未明顯改變抗原之EC1域中之氘交換行為。

對於所有抗體而言，EC2 (160-268)中之區域195-202 AKVVYSIL (SEQ ID NO: 247)的氘吸收出現邊界性降低。更有趣的是，區域203-221 QGQPYFSVESETGIIKTAL (SEQ ID NO: 248)對於NOV0719而言出現實質性不穩定(亦即經歷氘吸收之增加)且對於NOV0712而言稍微較輕。NOV1127及NOV0710均未使其中氘併入變化為+0.5 Da或大於+0.5 Da的此區域失去穩定。最後，NOV0719結合至hCDH6抗原時，僅區域225-237 DRENREQYQVVIQ (SEQ ID NO: 249)失去穩定。

NOV0719使EC3 (269-383)中的區域275-302 FKTPESSPPGTPIGRIKASDADVGENAE (SEQ ID NO: 250)失去穩定。區域303-315 IEYSITDGEGLDM (SEQ ID NO: 251)對於所有抗體而言均展現氘吸收降低，但相對於其他兩種抗體，NOV0710及NOV0712使該區域的氘吸收出現更明顯的降低。區域316-330 FDVITDQETQEGIIT (SEQ ID NO: 252)對於所有抗體而言均展現氘吸收降低，但對於NOV0719而言，出現的降低最小。相比之下，NOV0719使區域331-336 VKKLLD (SEQ ID NO: 253)失去穩定，且NOV0712的去穩定作用較輕。對於除NOV0719之外的所有抗體，區域337-358 FEKKKVYTLKVEASNPYVEPRF (SEQ ID NO: 254)均展現氘吸收降低；相比之下，NOV0719為使區域337-345 FEKKKVYTL (SEQ ID NO: 255)失去穩定的唯一抗體。最後，觀測到NOV0719亦使區域370-376 VRIVVED (SEQ ID NO:256)失去穩定。

對於EC4 (384-486)及EC5 (487-608)而言，抗原中的氘交換(圖3)總體上相對較低，使得偵測氘吸收降低具挑戰性。對於NOV0710而言，EC4中的區域407-427 AQDPDAARNPVKYSVDRHTDM (SEQ ID

NO: 257)展現氘吸收發生邊界性降低。EC4中不存在與四種抗體中的任一者結合時氘吸收發生降低的其他區域。總體而言，此等觀察結果強烈表明EC4不涉及抗原決定基。相比之下，459-488 IATEINNPKQSSRVPLYIKVLDVNDNAPEF (SEQ ID NO: 258)對於NOV0719、NOV1127、NOV0712及NOV0710而言展現不同程度的去穩定(以去穩定之降低次序列舉)。

當hCDH6與NOV0710或NOV0712複合時，EC5中僅區域564-586 YLLPVVISDNDYPVQSSTGTVTV (SEQ ID NO: 259)展現氘吸收發生邊界性降低。應注意，當hCDH6與四種所研究抗體中的任一者相互作用時，五個細胞外域中僅EC5未展現任何去穩定區域。

亦對僅由hCDH6 EC3至EC5 (267-615)組成的hCDH6構築體進行HDx實驗。在此等實驗中，研究抗體NOV0710及NOV0712。此構築體為結晶學實驗中所用的相同構築體。此等實驗中之序列覆蓋率為86%。表10提供所有肽之全面清單。

在EC3中，NOV0710與NOV0712在使用此構築體的情況下，觀測到區域295-315 ADVGENAE IEYSITDGEGLDM (SEQ ID NO: 260)中的氘吸收發生降低；此行為非常類似於全長抗原，其中區域303-315 IEYSITDGEGLDM (SEQ ID NO: 251)對於所有抗體均展現氘吸收降低，而且對於NOV0712及NOV0710展現的氘吸收降低更多。有趣的是，EC3中存在展現兩種構築體之間差異行為的區域。舉例而言，在hCDH6(54-615)中，NOV0719引起多個區域失去穩定，而其他抗體則不然。相比之下，NOV0710與NOV0712均使hCDH6(267-615)蛋白質中明顯失去穩定的區域亦非常類似於所觀測到之NOV0719使全長hCDH6(54-615)蛋白質中失去穩定的區域。

在EC4中，觀測到類似的去穩定傾向。在hCDH6(54-615)中，NOV0719使得此域之C末端一側出現最顯著的不穩定且NOV0710及

NOV0712具有極小作用。相比之下，當使用hCDH6(267-615)構築體時，NOV0710與NOV0712均引起EC4之C末端一側明顯失去穩定。去穩定行為差異之起因尚未充分瞭解。重要的是注意，在EC4域中，構築體對於NOV0710或NOV0712而言均未出現氘吸收實質性降低，表明此區域不涉及結合NOV0710或NOV0712。

在EC5中，本發明人觀測到hCDH6(54-615)與hCDH6(267-615)構築體之間存在最一致的氘交換行為。對於NOV0712或NOV0710而言，構築體均未展現顯著的去穩定。此外，hCD6 (54-615)之氘吸收(不小於-0.5 Da)出現的稍微且通常不顯著的降低在hCDH6 (267-615)中變得更明顯。在hCDH6 (267-615)之EC5中，結合NOV0710或NOV0712時氘吸收展現最顯著降低的區域包括區域492-505 YETFVCEKAKADQL (SEQ ID NO: 261)、551-563 TRKNGYNRHEMST (SEQ ID NO: 262)及572-586 DNDYPVQSSTGTVTV (SEQ ID NO: 263)。對於NOV0710與NOV0712而言，572-586 DNDYPVQSSTGTVTV (SEQ ID NO: 263)之實質性保護與得自X射線結晶學之抗原決定基資料非常符合。胺基酸N573、D574及Y575展現較大的可接近表面區域且在與任一抗體形成複合物時，所有三者均被實質性包埋。V577亦埋入兩種結構中，表明更符合。結晶學資料未指示492-505 YETFVCEKAKADQL (SEQ ID NO: 264)被包埋，因此此保護似乎具有異位性質，但551-563 TRKNGYNRHEMST (SEQ ID NO: 262)之保護在其中R552實質上被包埋的NOV0712複合物中似乎特別顯著。

最後，重要的是注意到，EC5域中存在當與兩種抗體中之任一者形成複合物時展現氘吸收顯著(-0.5 Da或小於-0.5 Da)降低的其他區域。對於NOV0710而言，此等區域包括510-525 HAVDKDDPYSGHQFSF (SEQ ID NO: 265)、542-550 NKDNTAGIL (SEQ ID NO: 266)及591-604 CDHHGNMQSCHAEA (SEQ ID NO: 267)。對於NOV0712而言，

此等區域包括512-522 VDKDDPYSGHQ (SEQ ID NO: 268)、542-550 NKDNTAGIL (SEQ ID NO: 266)及591-604 CDHHGNMQSCHAEA (SEQ ID NO: 267)。

總體而言，HDx資料表明所鑑別之CDH6結合抗體結合CDH6使得CDH6蛋白質之若干區域變得更容易發生氘交換，可能反映CDH6抗體之結合所誘發的構形變化。該等經鑑別在CDH6抗體存在下防止發生氘交換的區域符合NOV0710及NOV0712之x射線結晶學資料且形成此等抗體之抗原決定基之一部分。

表9

NOV1127、NOV0719、NOV0710及NOV0712對含有鈣黏素1至5域之hCDH6(54-615)的作用

肽名稱	序列	氘併入(道爾頓)之變化			
		NOV 1127	**NOV 0719**	**NOV 0710**	**NOV 0712**
61-70	FLLEEYTGSD (SEQ ID NO:246)	-1.1	-1.2	-1.1	-1.3
63-70	LEEYTGSD (SEQ ID NO:269)	-0.1	-0.3	-0.4	-0.2
71-77	YQYVGKL (SEQ ID NO:270)	0.2	0.2	-0.1	0.1
71-88	YQYVGKLHSDQDRGDGSL (SEQ ID NO:271)	0.2	0.2	-0.1	0.1
71-100	YQYVGKLHSDQDRGDGSLKYILSGDGAGDL (SEQ ID NO:272)	1.0	0.9	-0.1	0.2
90-100	YILSGDGAGDL (SEQ ID NO:273)	0	0	0	0.1
101-112	FIINENTGDIQA (SEQ ID NO:274)	0.4	0.4	0.1	0.3
101-124	FIINENTGDIQATKRLDREEKPVY (SEQ ID NO:275)	0.4	0.6	-0.3	0
101-126	FIINENTGDIQATKRLDREEKPVYIL (SEQ ID NO:276)	0.6	0.7	-0.2	0
101-128	FIINENTGDIQATKRLDREEKPVYILRA (SEQ ID NO:277)	1.1	1.1	-0.2	0.2
102-124	IINENTGDIQATKRLDREEKPVY (SEQ ID NO:278)	0.4	0.5	-0.3	0.1
106-124	NTGDIQATKRLDREEKPVY (SEQ ID NO:279)	0.1	0.3	-0.4	0
106-126	NTGDIQATKRLDREEKPVYIL (SEQ ID NO:280)	0.6	0.6	-0.2	0
113-124	TKRLDREEKPVY (SEQ ID NO:281)	0.1	0.1	-0.2	-0.1
125-144	ILRAQAINRRTGRPVEPESE (SEQ ID NO:282)	0.3	0.4	-0.2	0.1
125-145	ILRAQAINRRTGRPVEPESEF (SEQ ID NO:283)	0.7	0.9	0	0.3
127-144	RAQAINRRTGRPVEPESE (SEQ ID NO:284)	0.3	0.4	-0.3	-0.1
127-145	RAQAINRRTGRPVEPESEF (SEQ ID NO:285)	0.3	0.4	0	0.2
129-144	QAINRRTGRPVEPESE (SEQ ID NO:286)	0.1	0.2	-0.3	-0.2
129-145	QAINRRTGRPVEPESEF (SEQ ID NO:287)	0.2	0.3	-0.1	0.1

145-159	FIIKIHDINDNEPIF (SEQ ID NO:288)	0.9	0.9	0.4	0.5
145-162	FIIKIHDINDNEPIFTKE (SEQ ID NO:289)	0.7	0.7	0	0.2
146-159	IIKIHDINDNEPIF (SEQ ID NO:290)	0.5	0.6	0.2	0.3
146-160	IIKIHDINDNEPIFT (SEQ ID NO:291)	0.4	0.1	0.1	0.2
146-162	IIKIHDINDNEPIFTK (SEQ ID NO:292)	0.3	0.3	0	0.1
160-176	TKEVYTATVPEMSDVGT (SEQ ID NO:293)	-0.4	0.5	-0.3	-0.2
160-177	TKEVYTATVPEMSDVGTF (SEQ ID NO:294)	-0.5	0.3	-0.6	-0.4
163-171	VYTATVPEMSDVGTF (SEQ ID NO:295)	-0.1	0.6	0.2	0.2
177-184	FVVQVTAT (SEQ ID NO:296)	0.4	0.8	0.2	0.6
178-184	VVQVTAT (SEQ ID NO:297)	0.3	0.5	0.2	0.3
178-194	VVQVTATDADDPTYGNS (SEQ ID NO:298)	-0.1	0	-0.2	-0.1
178-199	VVQVTATDADDPTYGNSAKVVY (SEQ ID NO:299)	-0.6	-0.1	-0.8	-0.5
181-199	VTATDADDPTYGNSAKVVY (SEQ ID NO:244)	-0.7	-0.3	-0.9	-0.6
185-199	DADDPTYGNSAKVVY (SEQ ID NO:300)	-0.3	-0.5	-0.4	-0.4
200-208	SILQGQPYF (SEQ ID NO:301)	-0.3	-0.1	-0.3	-0.3
203-211	QGQPYFSVE (SEQ ID NO:302)	-0.1	0.5	0	0.1
203-221	QGQPYFSVESETGIIKTAL (SEQ ID NO:248)	0.1	2.6	0.4	1.1
209-211	SVESETGIIKTAL (SEQ ID NO:303)	-0.1	2.1	0.3	0.8
212-221	SETGIIKTAL (SEQ ID NO:304)	0	1.9	0.4	0.8
214-222	TGIIKTALL (SEQ ID NO:305)	0.1	0.8	-0.1	0
222-232	LNMDRENREQY (SEQ ID NO:306)	-0.1	0	-0.1	-0.1
222-233	LNMDRENREQYQ (SEQ ID NO:307)	-0.2	0.1	-0.2	-0.1
225-233	DRENREQYQ (SEQ ID NO:308)	-0.4	-0.3	-0.4	-0.4
225-237	DRENREQYQVVIQ (SEQ ID NO:249)	-0.4	1.1	-0.1	0.2
275-294	FKTPESSPPGTPIGRIKASD (SEQ ID NO:309)	0.1	1.0	-0.1	0.2
275-300	FKTPESSPPGTPIGRIKASDADVGEN (SEQ ID NO:310)	0.1	1.3	0	0.3
275-302	FKTPESSPPGTPIGRIKASDADVGENAE (SEQ ID NO:250)	0.1	1.4	0	0.3
303-315	IEYSITDGEGLDM (SEQ ID NO:251)	-0.9	-1.1	-1.3	-1.3
305-315	YSITDGEGLDM (SEQ ID NO:311)	-0.6	-0.7	-0.8	-0.8
306-315	SITDGEGLDM (SEQ ID NO:312)	-0.2	-0.1	-0.2	-0.1
316-326	FDVITDQETQE (SEQ ID NO:313)	-1.0	-0.6	-0.9	-0.8
316-330	FDVITDQETQEGIIT (SEQ ID NO:252)	-1.2	-0.7	-1.4	-1.5
316-336	FDVITDQETQEGIITVKKLLD (SEQ ID NO:314)	-0.6	2.2	-0.8	-0.2
316-337	FDVITDQETQEGIITVKKLLDF (SEQ ID NO:315)	-0.6	2.3	-0.8	-0.2
316-345	FDVITDQETQEGIITVKKLLDFEKKKVYTL (SEQ ID NO:316)	-0.2	3.3	-1.1	-0.5
317-336	DVITDQETQEGIITVKKLLD (SEQ ID NO:317)	-0.2	2.2	-0.1	0.6
317-337	DVITDQETQEGIITVKKLLDF (SEQ ID NO:318)	-0.2	2.3	-0.1	0.6
318-337	VITDQETQEGIITVKKLLDF (SEQ ID NO:319)	-0.2	2.3	-0.3	0.3
327-336	GIITVKKLLD (SEQ ID NO:320)	0.1	0.9	-0.1	0.1
327-337	GIITVKKLLDF (SEQ ID NO:321)	0.3	1.1	-0.1	0.1
331-358	VKKLLDFEKKKVYTLKVEASNPYVEPRF (SEQ ID NO:322)	-0.4	1.3	-1.0	-0.7
337-358	FEKKKVYTLKVEASNPYVEPRF (SEQ ID NO:254)	-0.9	0.5	-1.1	-0.9

338-345	EKKKVYTL (SEQ ID NO:323)	-0.1	-0.6	-0.2	-0.2
346-358	KVEASNPYVEPRF (SEQ ID NO:324)	-0.7	-0.4	-0.5	-0.4
370-376	VRIVVED (SEQ ID NO:256)	0.3	1.6	0	0.2
370-386	VRIVVEDVDEPPVFSKL (SEQ ID NO:325)	0.3	1.6	0.1	0.4
376-383	DVDEPPVF (SEQ ID NO:326)	0.2	0.3	0.1	0.1
376-386	DVDEPPVFSKL (SEQ ID NO:327)	-0.1	0	-0.2	-0.2
377-383	VDEPPVF (SEQ ID NO:328)	0.3	0.6	0	0.1
377-386	VDEPPVFSKL (SEQ ID NO:329)	-0.2	-0.1	-0.4	-0.3
407-427	AQDPDAARNPVKYSVDRHTDM (SEQ ID NO:257)	-0.3	-0.3	-0.6	-0.4
413-427	ARNPVKYSVDRHTDM (SEQ ID NO:330)	-0.2	-0.2	-0.4	-0.4
420-427	SVDRHTDM (SEQ ID NO:331)	-0.1	-0.2	-0.1	-0.1
428-441	DRIFNIDSGNGSIF (SEQ ID NO:332)	1.0	0.1	-0.3	-0.3
442-451	TSKLLDRETL (SEQ ID NO:333)	0	-0.2	-0.1	-0.1
446-452	LDRETLL (SEQ ID NO:334)	-0.2	-0.2	-0.2	-0.2
459-475	IATEINNPKQSSRVPLY (SEQ ID NO:335)	0.6	1.0	0.2	0.4
461-474	TEINNPKQSSRVPL (SEQ ID NO:336)	0.3	0.6	0.1	0.2
461-475	TEINNPKQSSRVPLY (SEQ ID NO:337)	0.6	0.9	0.2	0.4
462-474	EINNPKQSSRVPL (SEQ ID NO:338)	0.2	0.3	-0.1	0.1
462-475	EINNPKQSSRVPLY (SEQ ID NO:339)	0.6	0.9	0.3	0.5
462-488	EINNPKQSSRVPLYIKVLDVNDNAPEF (SEQ ID NO:340)	1.4	2.2	0.7	1.0
463-475	INNPKQSSRVPLY (SEQ ID NO:341)	0.6	0.8	0.2	0.4
475-488	YIKVLDVNDNAPEF (SEQ ID NO:342)	0.5	0.8	0.3	0.4
476-488	IKVLDVNDNAPEF (SEQ ID NO:343)	0.5	0.7	0.2	0.4
496-505	VCEKAKADQL (SEQ ID NO:344)	-0.4	-0.4	-0.6	-0.6
506-522	IQTLHAVDKDDPYSGHQ (SEQ ID NO:345)	0.1	0	-0.1	0
506-525	IQTLHAVDKDDPYSGHQFSF (SEQ ID NO:245)	0.2	0.2	-0.1	-0.1
510-522	HAVDKDDPYSGHQ (SEQ ID NO:346)	-0.2	-0.4	-0.3	-0.3
510-524	HAVDKDDPYSGHQFS (SEQ ID NO:347)	-0.3	-0.5	-0.3	-0.3
510-525	HAVDKDDPYSGHQFSF (SEQ ID NO:265)	-0.2	-0.2	-0.3	-0.3
512-522	VDKDDPYSGHQ (SEQ ID NO:268)	-0.2	-0.4	-0.3	-0.4
512-525	VDKDDPYSGHQFSF (SEQ ID NO:348)	-0.1	-0.1	-0.3	-0.3
551-563	TRKNGYNRHEMST (SEQ ID NO:262)	-0.2	-0.1	-0.4	-0.4
587-602	RVCACDHHGNMQSCHA (SEQ ID NO:349)	-0.1	-0.3	-0.3	-0.4
591-602	CDHHGNMQSCHA (SEQ ID NO:350)	-0.2	-0.6	-0.4	-0.6

表10

NOV0710及NOV0712對含有鈣黏素3至5域之hCDH6 (267-615)的作用

肽名稱	序列	氘併入(道爾頓)之變化	
		NOV0710	**NOV0712**
274-283	QFKTPESSPP (SEQ ID NO:351)	-0.4	-0.3
275-294	FKTPESSPPGTPIGRIKASD (SEQ ID NO:352)	0.3	0.3
275-294	FKTPESSPPGTPIGRIKASDA (SEQ ID NO:353)	0.3	0.4
282-294	PPGTPIGRIKASD (SEQ ID NO:354)	0.2	0.1
295-302	ADVGENAE (SEQ ID NO:355)	-0.9	-0.9
303-312	IEYSITDGEG (SEQ ID NO:356)	-0.7	-0.6

303-315	IEYSITDGEGLDM (SEQ ID NO:251)	-1.1	-1.1
306-312	SITDGEG (SEQ ID NO:357)	-0.6	-0.5
308-315	TDGEGLDM (SEQ ID NO:358)	-0.7	-0.8
316-323	FDVITDQE (SEQ ID NO:359)	0.1	0.1
316-326	FDVITDQETQE (SEQ ID NO:360)	-0.2	-0.3
316-336	FDVITDQETQEGIITVKKLLD (SEQ ID NO:361)	2.2	2.0
316-337	FDVITDQETQEGIITVKKLLDF (SEQ ID NO:362)	2.5	2.2
317-330	DVITDQETQEGIIT (SEQ ID NO:363)	-0.8	-0.8
317-336	DVITDQETQEGIITVKKLLD (SEQ ID NO:364)	2.0	1.8
318-336	VITDQETQEGIITVKKLLD (SEQ ID NO:365)	2.0	1.8
320-326	TDQETQE (SEQ ID NO:366)	-0.6	-0.6
321-336	DQETQEGIITVKKLLD (SEQ ID NO:367)	2.3	2.1
321-337	DQETQEGIITVKKLLDF (SEQ ID NO:368)	2.5	2.3
323-336	ETQEGIITVKKLLD (SEQ ID NO:369)	2.1	1.9
324-336	TQEGIITVKKLLD (SEQ ID NO:370)	1.8	1.8
327-336	GIITVKKLLD (SEQ ID NO:371)	1.3	1.2
327-337	GIITVKKLLDF (SEQ ID NO:372)	1.5	1.4
328-337	IITVKKLLDF (SEQ ID NO:373)	1.4	1.3
329-336	ITVKKLLD (SEQ ID NO:374)	1.1	1.0
329-337	ITVKKLLDF (SEQ ID NO:375)	1.3	1.2
330-336	TVKKLLD (SEQ ID NO:376)	1.1	0.9
330-337	TVKKLLDF (SEQ ID NO:377)	1.3	1.0
331-337	VKKLLDF (SEQ ID NO:378)	0.5	0.5
337-344	FEKKKVYT (SEQ ID NO:379)	-0.2	-0.1
337-345	FEKKKVYTL (SEQ ID NO:255)	0.5	0.6
338-345	EKKKVYTL (SEQ ID NO:380)	0.3	0.3
346-358	KVEASNPYVEPRF (SEQ ID NO:381)	-0.7	-0.4
348-358	EASNPYVEPRF (SEQ ID NO:382)	-0.9	-0.6
359-369	LYLGPFKDSAT (SEQ ID NO:383)	-0.5	-0.3
359-370	LYLGPFKDSATV (SEQ ID NO:384)	-0.2	-0.1
361-369	LGPFKDSAT (SEQ ID NO:385)	-0.4	-0.2
370-383	VRIVVEDVDEPPVF (SEQ ID NO:386)	1.8	1.7
370-386	VRIVVEDVDEPPVFSKL (SEQ ID NO:387)	2.0	1.9
373-383	VVEDVDEPPVF (SEQ ID NO:388)	0.5	0.5
376-383	DVDEPPVF (SEQ ID NO:389)	0.4	0.4
376-386	DVDEPPVFSKL (SEQ ID NO:390)	-0.1	0.0
376-388	DVDEPPVFSKLAY (SEQ ID NO:391)	-0.3	-0.1
377-383	VDEPPVF (SEQ ID NO:392)	0.4	0.4
377-386	VDEPPVFSKL (SEQ ID NO:393)	-0.2	-0.1
407-419	AQDPDAARNPVKY (SEQ ID NO:394)	-0.1	0.1
407-427	AQDPDAARNPVKYSVDRHTDM (SEQ ID NO:257)	-0.2	-0.1
413-427	ARNPVKYSVDRHTDM (SEQ ID NO:395)	0.1	0
421-427	VDRHTDM (SEQ ID NO:396)	-0.2	-0.3

428-441	DRIFNIDSGNGSIF (SEQ ID NO:397)	0.1	0.2
442-451	TSKLLDRETL (SEQ ID NO:398)	0	0
446-452	LDRETLL (SEQ ID NO:399)	-0.3	-0.1
459-474	IATEINNPKQSSRVPL (SEQ ID NO:400)	1.0	1.1
459-475	IATEINNPKQSSRVPLY (SEQ ID NO:401)	1.2	1.4
461-475	TEINNPKQSSRVPLY (SEQ ID NO:402)	1.0	1.0
461-478	TEINNPKQSSRVPLYIKV (SEQ ID NO:403)	2.5	2.6
462-474	EINNPKQSSRVPL (SEQ ID NO:404)	0.7	0.8
462-475	EINNPKQSSRVPLY (SEQ ID NO:405)	1.1	1.2
463-475	INNPKQSSRVPLY (SEQ ID NO:406)	1.2	1.2
464-474	NNPKQSSRVPL (SEQ ID NO:407)	1.7	1.7
464-476	NNPKQSSRVPLYI (SEQ ID NO:408)	1.2	1.2
475-488	YIKVLDVNDNAPEF (SEQ ID NO:409)	1.1	1.3
476-483	IKVLDVND (SEQ ID NO:410)	1.1	1.1
476-488	IKVLDVNDNAPEF (SEQ ID NO:411)	0.8	1.0
477-488	KVLDVNDNAPEF (SEQ ID NO:412)	0.4	0.4
479-488	LDVNDNAPEF (SEQ ID NO:413)	-0.1	0.1
492-505	YETFVCEKAKADQL (SEQ ID NO:264)	-1.1	-1.1
495-505	FVCEKAKADQL (SEQ ID NO:414)	-0.7	-0.6
496-505	VCEKAKADQL (SEQ ID NO:415)	-0.8	-0.7
499-505	KAKADQL (SEQ ID NO:416)	-0.7	-0.7
506-513	IQTLHAVD (SEQ ID NO:417)	0.3	0.4
506-522	IQTLHAVDKDDPYSGHQ (SEQ ID NO:418)	0	0.1
506-524	IQTLHAVDKDDPYSGHQFS (SEQ ID NO:419)	0.1	0.1
506-525	IQTLHAVDKDDPYSGHQFSF (SEQ ID NO:420)	-0.1	0
510-522	HAVDKDDPYSGHQ (SEQ ID NO:421)	-0.4	-0.3
510-524	HAVDKDDPYSGHQFS (SEQ ID NO:422)	-0.3	-0.2
510-525	HAVDKDDPYSGHQFSF (SEQ ID NO:265)	-0.5	-0.4
512-522	VDKDDPYSGHQ (SEQ ID NO:268)	-0.6	-0.6
512-525	VDKDDPYSGHQFSF (SEQ ID NO:423)	-0.5	-0.4
542-550	NKDNTAGIL (SEQ ID NO:266)	-0.5	-0.6
549-563	ILTRKNGYNRHEMST (SEQ ID NO:424)	-0.5	-0.4
551-563	TRKNGYNRHEMST (SEQ ID NO:262)	-0.6	-0.5
552-563	RKNGYNRHEMST (SEQ ID NO:425)	-0.7	-0.8
564-571	YLLPVVIS (SEQ ID NO:426)	-0.1	0.1
564-575	YLLPVVISDNDY (SEQ ID NO:427)	-0.5	-0.4
564-578	YLLPVVISDNDYPVQ (SEQ ID NO:428)	-1.0	-1.0
567-586	PVVISDNDYPVQSSTGTVTV (SEQ ID NO:429)	-1.5	-0.8
587-600	RVCACDHHGNMQSC (SEQ ID NO:430)	-0.5	-0.5
587-602	RVCACDHHGNMQSCHA (SEQ ID NO:431)	-0.3	-0.3

591-600	CDHHGNMQSC (SEQ ID NO:432)	-0.7	-0.7
591-602	CDHHGNMQSCHA (SEQ ID NO:433)	-0.4	-0.4
591-604	CDHHGNMQSCHAEA (SEQ ID NO:267)	-0.6	-0.8
592-602	DHHGNMQSCHA (SEQ ID NO:434)	-0.6	-0.6
605-618	LIHPTGLSTGAGSE (SEQ ID NO:435)	-0.5	-0.4
619-625	FRHDSGL (SEQ ID NO:436)	-0.3	-0.2
619-627	FRHDSGLND (SEQ ID NO:437)	-0.4	-0.4
630-637	EAQKIEWH (SEQ ID NO:438)	-0.6	-0.5
630-638	EAQKIEWHE (SEQ ID NO:439)	-0.8	-0.7

實例7：藉由x射線結晶學進行的抗原決定基定位

測定與NOV0712或NOV0710之Fab片段(SEQ ID NO: 444-447，表12及13)結合之人類CDH6片段(胞外域5，或EC5，SEQ ID NO: 443，表11)的晶體結構。如下詳述，CDH6 EC5與NOV0712或NOV0710 Fab共表現於哺乳動物細胞中以產生經純化之複合物。接著利用蛋白質結晶學產生與NOV0712或NOV0710 Fab結合之CDH6 EC5的原子解析度資料且定義抗原決定基。

產生用於抗原決定基定位的蛋白質

根據結晶學所產生之CDH6 EC5、NOV0712 Fab及NOV0710 Fab的序列顯示於上述表9中。CDH6 EC5構築體包含在人類CDH6之上下文中顯示有下劃線的殘基490至608 (UniProt標識符P55285，SEQ ID NO: 442，表11)，及下文表11中如SEQ ID NO: 443所示者。來自小鼠IgGκ輕鏈的N末端信號序列用於CDH6 EC5之分泌性表現且在表現期間裂解，得到CDH6 EC5之完整N末端。CDH6 EC5之C末端與源於β澱粉狀蛋白之純化標記(APP標記，胺基酸：EFRHDS (SEQ ID NO: 440))融合，純化標記之後為PreScission®蛋白酶(GE Healthcare, Piscataway, NJ)識別位點(胺基酸：LEVLFQGP (SEQ ID NO: 441))以在純化之後促進標記裂解及移除。對於NOV0712及NOV0710 Fab而言，顯示重鏈及輕鏈之序列(SEQ ID NO: 444-447)。

表11

結構生物學研究中所用的蛋白質

構築體	單字母碼之胺基酸序列	SEQ ID NO
人類CDH6 (P55285)	MRTYRYFLLLFWVGQPYPTLSTPLSKRTSGFPAKKRALELSGNS KNELNRSKRSWMWNQFFLLEEYTGSDYQYVGKLHSDQDRGDG SLKYILSGDGAGDLFIINENTGDIQATKRLDREEKPVYILRAQAIN RRTGRPVEPESEFIIKIHDINDNEPIFTKEVYTATVPEMSDVGTFV VQVTATDADDPTYGNSAKVVYSILQGQPYFSVESETGIIKTALLN MDRENREQYQVVIQAKDMGGQMGGLSGTTTVNITLTDVNDNP PRFPQSTYQFKTPESSPPGTPIGRIKASDADVGENAEIEYSITDGEG LDMFDVITDQETQEGIITVKKLLDFEKKKVYTLKVEASNPYVEP RFLYLGPFKDSATVRIVVEDVDEPPVFSKLAYILQIREDAQINTTI GSVTAQDPDAARNPVKYSVDRHTDMDRIFNIDSGNGSIFTSKLL DRETLLWHNITVIATEINNPKQSSRVPLYIKVLDVNDNAPEFAEF YETFVCEKAKADQLIQTLHAVDKDDPYSGHQFSFSLAPEAASGS NFTIQDNKDNTAGILTRKNGYNRHEMSTYLLPVVISDNDYPVQS STGTVTVRVCACDHHGNMQSCHAEALIHPTGLSTGALVAILLCI VILLVTVVLFAALRRQRKKEPLIISKEDIRDNIVSYNDEGGGEEDT QAFDIGTLRNPEAIEDNKLRRDIVPEALFLPRRTPTARDNTDVRD FINQRLKENDTDPTAPPYDSLATYAYEGTGSVADSLSSLESVTTD ADQDYDYLSDWGPRFKKLADMYGGVDSDKDS	(SEQ ID NO:442)
CDH6 EC5表現構築體	EFYETFVCEKAKADQLIQTLHAVDKDDPYSGHQFSFSLAPEAAS GSNFTIQDNKDNTAGILTRKNGYNRHEMSTYLLPVVISDNDYPV QSSTGTVTVRVCACDHHGNMQSCHAEALIHP	(SEQ ID NO:443)
NOV0712 Fab重鏈	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSHGMHWVRQAPGK GLEWVSVISGSGSNTGYADSVKGRFTISRDNSKNTLYLQMNSLR AEDTAVYYCARQWGSYAFDSWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTH	(SEQ ID NO:444)
NOV0712 Fab輕鏈	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPK LLIYAVSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQS GTFPPTTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ ID NO:445)
NOV0710 Fab重鏈	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK GLEWVSVIRSSGSSTYYADSVKGRFTISRDNSKNTLYLQMNSLR AEDTAVYYCARGGGYFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC DKTH	(SEQ ID NO:446)
NOV0710 Fab輕鏈	DIQMTQSPSSLSASVGDRVTITCRASQSISLWLNWYQQKPGKAP KLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQ YYTSPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ ID NO:447)

CDH6 EC5與NOV0712或NOV0710 Fab共表現於Expi293®細胞中以產生複合物用於結晶學分析。詳言之，將0.5 mg編碼CDH6 EC5的質體與0.5 mg NOV0712或NOV0710 Fab質體混合，在50 ml OptiMEM I培養基(Life Technologies, Grand Island, NY)中稀釋且與2.5 mg PEI

(Polysciences, Warrington, PA)一起在50 ml相同培養基中培育30分鐘。接著將混合物添加至1 L含有Expi293®細胞之Expi293®表現培養基(Life Technologies Grand Island, NY)中，該等Expi293®細胞在37℃、8% CO2下以1百萬個細胞/毫升懸浮生長於該表現培養基中。72小時之後，藉由離心收集含有CDH6 EC5-Fab複合物的培養基且補充CaCl2至3 mM。接著向培養基中添加10 ml與抗APP標記IgG (內部產生)結合的Sepharose® 4B珠粒(GE Healthcare Pittsburgh, PA)且在4℃持續攪拌隔夜。次日，將珠粒裝填至重力管柱中且用25 mM Hepes pH 7.4 + 150 mM NaCl (HBS)及3 mM CaCl2洗滌。標靶複合物用3個管柱體積(CV)之100 mM 甘胺酸pH 2.5、150 mM NaCl、3 mM CaCl2溶離至1/10 (v/v)之1 M Tris pH 8.5中。複合物與1/100 (w/w) GST標記PreScission®蛋白酶(GE Healthcare, Pittsburgh, PA)一起在4℃培育隔夜以使APP標記裂解。次日，藉由使混合物通過1 ml GSTrap® HP管柱(GE Healthcare, Pittsburgh, PA)而移除PreScission®蛋白酶。流過物接著與1/10 (w/w) PNGaseF(內部純化)一起在37℃培育隔夜以移除N連接型糖基化。去糖基化之後，濃縮混合物且裝載至經HBS + 3 mM CaCl2平衡之HiLoad 16/600 Superdex® 200 pg (GE Healthcare, Pittsburgh, PA)上。藉由SDS-PAGE及LCMS分析含有經純化之CDH6-Fab複合物的峰值溶離份，合併且濃縮結晶。

結晶及結構測定

CDH6 EC5/NOV0712及CDH6 EC5/NOV0710複合物分別濃縮至9.3 mg/ml及14.7 mg/ml，以20,000 g離心5分鐘且篩選用於結晶。供收集資料用的晶體在20℃藉由懸滴氣相擴散來生長。CDH6 EC5/NOV0712複合物晶體如下生長：將1.2 μl複合物與1 μl含有20% (v/v) PEG3350及0.2 M檸檬酸二氫銨的儲集溶液混合且使液滴相對於450 μl相同儲集溶液加50 μl水平衡。CDH6 EC5/NOV0710複合物晶體

如下生長：將0.8 μl複合物與1 μl含有0.7 M檸檬酸三鈉及0.1 M Tris•HCl pH 8.5的儲備溶液混合，且使液滴相對於425 μl相同儲集溶液加75 μl水平衡。資料收集之前，將晶體轉移至75%儲集溶液加25%甘油中且在液氮中急驟冷卻。

在先進光子源中心(Advanced Photon Source, Argonne National Laboratory, USA)收集光束線17-ID的繞射資料。使用Autoproc (Global Phasing, LTD)處理及按比例調整資料。在空間群P212121中，CDH6 EC5/NOV0712資料經處理為2.3 Å，其中晶胞尺寸a=78.83 Å、b=88.86 Å、c=186.73 Å、α=90°、β=90°、γ=90°。在空間群P43212中，CDH6 EC5/NOV0710複合物資料經處理為3.5 Å，其中晶胞尺寸a=101.48 Å、b=101.48 Å、c=240.96 Å、α=90°、β=90°、γ=90°。複合物結構係使用Phaser (McCoy等人, (2007) J. Appl. Cryst. 40:658-674)、以內部Fab結構作為搜尋模型、藉由分子置換來求解。使用CCP4程式套件(Winn等人, (2011) Acta. Cryst. D67:235-242)中的Buccaneer (K. Cowtan (2006) Acta Cryst. D62:1002-1011)從頭建構CDH6 EC5結構。最終模型用COOT (Emsley及Cowtan (2004) Acta Cryst. D60:2126-2132)建構且用Buster (Global Phasing, LTD, Cambridge,UK)改進。對於CDH6 EC5/NOV0712複合物而言，$R_{功}$及$R_{自由值}$分別為21.2%及25.2%；且鍵長及鍵角之均方根(r.m.s)偏差值分別為0.010 Å及1.24°。對於CDH6 EC5/NOV0710複合物而言，$R_{功}$及$R_{自由}$值分別為18.2%及24.6%；且鍵長及鍵角之r.m.s偏差值分別為0.010 Å及1.28°。

與NOV0712或NOV0710 Fab接觸之CDH6 EC5殘基、相互作用類型及包埋表面積皆藉由PISA (Krissinel等人, (2007) J Mol Biol. 372:774-97)鑑別且列於表12及表13中。對於不對稱單元(晶體中的最小獨特單元)中含有超過一個複合物複本的結構而言，僅列舉所有複本中共同的彼等抗體接觸殘基作為抗原決定基殘基。

NOV0712及NOV0710之針對CDH6之抗原決定基

總體結構

此時未報導CDH6 EC5之晶體結構。CDH6 EC5之總體摺疊類似於CDH2 (N-鈣黏素)EC5，其均由一個三股β片相對於另一個四股β片堆疊而構成。兩個結構覆疊，產生2.4 Å之較小均方根距離(RMSD)且使得N末端與C末端之取向類似。因此，可基於EC5域之疊合將CDH6 EC5/Fab複合物結構覆疊於CDH2之全長ECD結構上，以便估算取向及NOV0712及NOV0710 Fab。如圖4中所示，NOV0712及NOV0710結合CDH6 EC5之同側，且共有顯著重疊的抗原決定基。相較於NOV0710，NOV0712結合稍微偏離EC4-EC5連接子。

NOV0712抗原決定基

使用CDH6 EC5/NOV0712複合物之晶體結構鑑別CDH6上之NOV0712抗原決定基。NOV0712 Fab針對CDH6 EC5的相互作用表面係由若干個連續及不連續(亦即非鄰接)序列形成：亦即殘基503、520-527、529、532-534、538-543、550、552、569及571-577，如表12中所詳述。此等殘基形成由NOV0712 Fab識別的三維構形抗原決定基(圖5上圖)。藉由結晶學定義的此抗原決定基與藉由氫氘交換質譜(HDx-MS)定義的抗原決定基非常一致，其中殘基572-586實質上由NOV0712保護。有趣的是，CDH6 EC5 (殘基571-579)之潛在Ca2+結合環大部分(10個殘基中有8個)與NOV0712接觸，尤其Tyr575及Asn573，其幾乎被抗體完全包埋(表12及圖5下圖)。相較於CDH2結構，CDH6 EC5之此Ca2+結合環為由NOV0712結合誘導的「翻出」構形(例如CDH6中之Asp572相較於其在CDH2中的對應殘基Asp525翻出)。

表12

CDH6上之NOV0712抗原決定基。晶體結構中與NOV0712接觸的

所有CDH6殘基均藉由PISA鑑別，根據其被NOV0712包埋的表面積列舉及分選。在適用情況下，亦列舉相互作用的類型。

殘基名稱	殘基數目	可接近表面積(ASA, Å^2)	重鏈所包埋之表面積(BSA) (Å^2)	輕鏈之BSA (Å^2)	NOV0712之總BSA (Å^2)	BSA / ASA (%)	相互作用的類型
TYR	575	205.77	131.73	47.11	178.84	86.91	H-SC[1], H-MC[2], 疏水性
ASN	573	106.72	103.67	0	103.67	97.14	H-SC, H-MC
LYS	543	147.48	65.84	37.33	103.17	69.96	鹽橋
ARG	552	148.25	0	78.9	78.9	53.22	H-SC
ASP	574	104.57	68.99	0	68.99	65.97	H-SC, H-MC
GLN	540	99.91	0	68.29	68.29	68.35	H-SC
PRO	529	122.44	0	65.25	65.25	53.29	
ALA	532	67.01	0	64.9	64.9	96.85	H-MC
SER	533	103.84	0	59.58	59.58	57.38	H-SC
VAL	577	97.82	53.24	0	53.24	54.43	H-MC
SER	526	52.04	0	47.12	47.12	90.55	
ASP	541	45.28	8.86	36.42	45.28	100.00	H-MC
GLN	522	100.04	45.14	0	45.14	45.12	
SER	524	43.52	26.98	16.54	43.52	100.00	
GLY	520	64.48	32.88	0	32.88	50.99	H-MC
ASP	503	113.22	0	32.06	32.06	28.32	
ILE	539	31.09	0	29.09	29.09	93.57	H-MC
HIS	521	104.3	23.91	0	23.91	22.92	
THR	538	39.69	0	23	23	57.95	
LEU	527	24.51	0	20.01	20.01	81.64	H-MC
PRO	576	111.16	17.57	0	17.57	15.81	
ASN	542	72.05	0	17.39	17.39	24.14	
PHE	525	15.47	0.95	14.52	15.47	100.00	
SER	571	16.16	6.96	7.1	14.06	87.00	
VAL	569	23.13	0	8.54	8.54	36.92	
LEU	550	23.71	0	7.9	7.9	33.32	
GLY	534	71.3	0	5.13	5.13	7.19	
PHE	523	9.81	4.5	0	4.5	45.87	
ASP	572	23.71	2.26	0	2.26	9.53	

[1]側鏈原子之氫鍵；[2]主鏈原子之氫鍵

NOV0710之抗原決定基

使用CDH6 EC5/NOV0710複合物之晶體結構鑑別CDH6上之NOV0710抗原決定基。NOV0712 Fab針對CDH6 EC5的相互作用表面由若干個連續及不連續(亦即非鄰接)序列形成：亦即殘基520-527、

529、541、543、569及571-579，如表13中所詳述。此等殘基形成由NOV0710 Fab識別的三維構形抗原決定基(圖6上圖)。藉由結晶學定義的此抗原決定基與藉由氫氘交換質譜(HDx-MS)定義的抗原決定基非常一致，其中殘基572-586實質上由NOV0710保護。有趣的是，類似於CDH6 EC5/NOV0712複合物結構，CDH6 EC5 (殘基571-579)之潛在Ca2+結合環中的所有殘基均與NOV0710接觸；其中，Tyr575、Asn573及Asp574幾乎被抗體完全包埋(表13及圖6下圖)。相較於CDH2結構，CDH6 EC5之此Ca2+結合環為由NOV0710結合誘導的「翻出」構形(例如CDH6中之Asp572相較於其在CDH2中的對應殘基Asp525翻出)。

表13

CDH6上之NOV0710抗原決定基。晶體結構中與NOV0710接觸的所有CDH6殘基均藉由PISA鑑別，根據其被NOV0710包埋的表面積列舉及分選。在適用情況下，亦列舉相互作用的類型。

殘基名稱	殘基數目	可接近表面積(ASA) (Å^2)	重鏈所包埋之表面積 (BSA)(Å^2)	輕鏈之BSA (Å^2)	NOV0710之總BSA (Å^2)	BSA / ASA (%)	相互作用的類型
TYR	575	201.38	147.28	54.1	201.38	100.00	H-MC[1], 疏水性
ASN	573	128.75	116.17	4.34	120.51	93.60	H-SC[2], H-MC
ASP	574	95.9	87.31	0	87.31	91.04	鹽橋
LYS	543	145.5	0	78.92	78.92	54.24	H-SC
VAL	577	93.73	21.59	52.36	73.95	78.90	
PRO	529	133.4	0	72.75	72.75	54.54	
SER	526	58.42	0	46.58	46.58	79.73	
SER	524	40.31	17.45	22.86	40.31	100.00	H-SC
GLN	522	108.66	29.79	0	29.79	27.42	
SER	571	28.68	0.34	24.21	24.55	85.60	
PRO	576	83.21	24.36	0	24.36	29.28	H-MC
ASP	541	33.17	0	22.2	22.2	66.93	H-SC
GLY	520	74.53	17.18	0	17.18	23.05	
VAL	569	26.11	0	16.9	16.9	64.73	
SER	579	82.89	0	13.6	13.6	16.41	
GLN	578	116.86	13.18	0	13.18	11.28	

HIS	521	84.59	10.25	0	10.25	12.12	
LEU	527	41.01	0	10.07	10.07	24.55	
ASP	572	18.64	6.51	0	6.51	34.92	鹽橋
PHE	525	9.03	0	5.15	5.15	57.03	
PHE	523	15.28	0.31	0	0.31	2.03	

[1]側鏈原子之氫鍵；[2]主鏈原子之氫鍵

實例8：抗體藥結合物之製備

藉由一步法製備DM4結合物

將濃度為約10.0 mg/mL之抗CDH6抗體(例如NOV7012)與DM4 (相對於抗體量為6.8倍莫耳過量)混合且接著與磺基-SPDB (相對於抗體量為約5.2倍過量)混合。反應在20℃、在含有10% DMA的20 mM EPPS [4-(2-羥基乙基)-1-哌嗪丙烷磺酸]緩衝液(pH 8.1)中進行約16小時。藉由添加1 M乙酸將pH調節至5.0來淬滅反應。pH調節之後，反應混合物經由多層(0.45/0.22 μm) PVDF過濾器過濾且經純化且使用切向流過濾、在10 mM丁二酸鹽緩衝液(pH 4.5)中透濾。用於切向流過濾之儀器參數之實例列舉於下表14中。

表14

用於切向流過濾的儀器參數

TFF參數	TFF設定點
本體濃度(Cb - g/L)	20
TMP (psi)	12-18
饋料流速(LMH)	324
膜負荷(g/m2)	50-150
透濾體積	16
透濾緩衝液	20 mM丁二酸鹽，pH 4.5
溫度(℃)	室溫(20 - 25)

獲自上述方法的結合物藉由以下分析：細胞毒性劑負載(類美登素與抗體比率，MAR)之UV光譜學；用於測定結合物單體之SEC-HPLC；及用於游離類美登素百分比的逆相HPLC或疏水性遮蔽相(Hisep)-HPLC。

使用SPDB或磺基-SPDB連接子及DM4細胞毒性劑製備ADC

在25℃，將抗CDH6抗體(例如抗體NOV0712)與DM4 (6.8倍及10.2倍莫耳過量)合併於含有約10% DMA的50 mM EPPS緩衝液(pH 8.1)中。向此混合物中添加N-丁二醯亞胺基4-(2-吡啶基二硫基)丁酸酯(SPDB，分別為4.0倍及6.0倍莫耳過量)，使得最終抗體濃度為4 mg/mL且最終DMA含量為10%。允許反應在25℃、在50 EPPS緩衝液(pH 8.1)中進行約16小時。使用經平衡之SEPHADEX™ G25管柱且使用10 mM丁二酸鹽、250 mM甘胺酸、0.5%蔗糖、0.01% Tween 20 (pH 5.5)溶離來純化結合反應混合物。使用類似程序產生抗CDH6-磺基-SPDB-DM4結合物。

任一種上述方法適用於抗體與SPDB-DM4或磺基-SPDB-DM4之結合。下表15提供CDH6 ADC之實例。

表15

DM4結合之抗體之特性

Ab	MAR	單體%	產率(%)	游離DM (%)
NOV0709	3.8	97	84	1.6
NOV0691	3.6	96	97	1.5
NOV0690	3.2	97	74	4.0
NOV0689	3.3	99	96	2.0
NOV0670	3.1	98	100	1.5
NOV0720	3.3	99	78	2.0
NOV0712	3.2	99	78	3.1
NOV0674	3.2	99	78	2.6
NOV0719	3.8	98	79	1.9

藉由原位方法製備SMCC-DM1結合物

亦可使用原位方法、根據以下程序使抗CDH6抗體與SMCC-DM1結合。使用磺基丁二醯亞胺基4-(N-順丁烯二醯亞胺基甲基)環己烷-1-甲酸酯(磺基-SMCC)連接子使CDH6抗體與DM1結合。製備DM1及磺基-SMCC異雙官能連接子於DMA中之儲備溶液。在25℃，在含有40% v/v之50 mM丁二酸鹽緩衝水溶液、2 mM EDTA pH 5.0的DMA中，將磺基-SMCC與DM1硫醇混合在一起反應10分鐘，其中DM1與連接子之

莫耳當量比為1.3:1且DM1最終濃度為1.95 mM。接著使抗體與原位產生之上述SMCC-DM1之等分試樣反應，使得最終結合條件包括含有2.5 mg/mL Ab之50 mM EPPS (pH 8.0)、10% DMA (v/v)及約6.5之SMCC:Ab莫耳比。在25℃歷時約18小時之後，使用經10 mM丁二酸鹽、250 mM甘胺酸、0.5%蔗糖、0.01% Tween 20 (pH 5.5)平衡的SEPHADEX® G25管柱純化結合反應混合物。

實例9：靶向CDH6之ADC之活體外細胞活性

測定抗CDH6抗體之所選SMCC-DM1結合物針對一組細胞株的活體外細胞活性，該組細胞株包含OVCAR3 (卵巢漿液癌，在RPMI + 20% FCS中培養)、JHOS4 (1:1 F12:DMEM+10%FBS)、KNS42 (EMEM+10%FBS)、NCIH661 (RPMI+10%FBS)、SNU8 (RPMI+10%FBS)及OVCAR8 (RPMI+10%FBS)。OVCAR3及細胞株獲自ATCC (#HTB-161及#HTB-183, ATCC Manassas,VA)。JHOS4獲自RIKEN (#RCB1678, RIKEN Cell Bank, RIKEN, Tsukuba, Japan)。KNS42獲自健康科學研究資源庫(Health Science Research Resources Bank，HSRRB)(#IFO50356, HSRRB, Osaka, Japan)。SNU8獲自韓國細胞株庫(Korean Cell Line Bank，KCLB)(#00008, KCLB, Seoul, Korea)。OVCAR8獲自NCI/DCTD腫瘤/細胞株貯存中心(NCI, Frederick, MA)。

對培養中之細胞計數且在培養基中稀釋至1x10^{5}個細胞/毫升之濃度。每孔轉移1000個細胞至384孔盤(Corning Costar#3707, Corning, Tewksbury, MA)。在1.4 ml Matrix管(Thermo, #3790, Rockford, IL)中製備ADC儲備溶液。在384孔深孔盤(Brandtech Scientific Inc #701355, Essex, CT)中製備10點1:3連續稀釋液且每個分析盤轉移25 µl (一式三份)，產生33 nM之最高初始ADC濃度。作為對照，製備僅具有細胞的孔(=100%存活率對照)及具有與SMCC-DM1結合之非靶向抗體一起培

育之細胞的孔(以檢查非標靶驅動活性)。盤在37℃及5% CO2下培育120小時。使用CellTiter-Glo®試劑(Promega #G7571, Madison, WI)，根據製造商說明書測定一次抗體/Fab-DM1複合物之細胞活性。存活率相對於僅具有細胞的對照歸一化。靶向CDH6之ADC亞群在對缺乏CDH6表現之細胞(OVCAR8)具非活性的濃度(1.22 nM)下能夠抑制CDH6陽性細胞增殖，表明CDH6-ADC具有標靶依賴性活體外細胞活性(表16)。

表16

抗CDH6 SMCC-DM1結合物之活體外細胞活性。表顯示1.22 nM ADC之抑制百分比。

抗體	OVCAR3	JHOS4	KNS42	NCIH661	SNU8	OVCAR8
NOV0670	-29.97	-27.88	-18.63	5.14	-15.57	-23.77
NOV0672	-16.25	-22.96	-12.26	-6.14	-10.94	-16.16
NOV0674	-10.29	-11.94	-6.82	3.9	-1.42	-8.97
NOV0682	61.75	33.92	23.75	16.44	10.83	-2.17
NOV0685	-20.65	-14.67	-14.65	2.08	-0.1	-11.51
NOV0689	7.21	3.63	-3.11	-0.53	10.27	-7.29
NOV0690	84.8	50.97	56.81	14.55	18.39	-15.8
NOV0691	-1.5	-14.37	-9.23	-10.47	-2.56	-10.48
NOV0692	88.01	62.3	57.32	14.77	15.66	-10.83
NOV0693	85.73	58.08	15.17	25.87	35.56	-7.07
NOV0695	89	66.94	66.31	18.69	21.56	-7.04
NOV0699	n/a	n/a	n/a	n/a	n/a	n/a
NOV0705	68.57	40.35	-13.35	-3.15	6.4	-22.58
NOV0709	46.88	4.5	-4.2	5.91	-7.7	-8.34
NOV0710	90.84	69.01	56.98	38.7	42.4	6.53
NOV0712	87.62	67.56	56.82	32.46	31.35	1.68
NOV0713	-3.55	-6.22	-17.26	-9.74	7.79	-0.08
NOV0718	-3.8	-5.03	3.5	2.51	3.35	6.64
NOV0719	76.05	27.25	40.97	-9.87	3.18	-2
NOV0720	80.72	43.52	56.97	1.94	3.56	-3.9

實例10：呈SMCC-DM1及SPDB-DM4結合物形式之抗CDH6 ADC針對卵巢癌細胞株的活體外細胞活性

評價呈SMCC-DM1及SPDB-DM4結合物形式之抗CDH6 ADC針對一組卵巢癌細胞株的活體外細胞活性(圖7及表17)。為了評估抗CDH6 ADC之標靶依賴性活性及特異活性，產生OVCAR3及OVCAR8細胞株

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的同基因型細胞株。OVCAR3內源性高量表現CDH6。為了產生CDH6表現受抑制的同基因型細胞株，用遞送靶向CDH6之shRNA的豆狀病毒載體(Mission shRNA細菌甘油儲備液, #TRCN0000054117, Sigma, St. Louis, MO)、根據製造商說明書轉導OVCAR3。OVCAR8細胞並非內源性地表現CDH6。為了產生以CDH6表現為特徵之同基因型細胞株，用驅動人類CDH6 cDNA表現之慢病毒構築體轉導OVCAR8細胞。特定言之，自Genecopoeia (#Z2028, Genecopoeia, Rockville, MA)購得CDH6之cDNA且使用Gateway®選殖術、根據製造商說明書(Invitrogen, Carlsbad, CA)選殖入pLenti6.3中。

FACS分析證實CDH6在OVCAR3_shRNACDH6細胞株中受到抑制且CDH6外源性表現於OVCAR8_工程化_CDH6+細胞中(圖8)。特定言之，根據製造商說明書、藉由Accutase®細胞解離試劑(Gibco, #A1110501 Grand Island, NY)處理培養中的細胞，隨後用FACS緩衝液(RPMI/1% BSA, Gibco, Grand Island, NY)洗滌細胞來製備細胞懸浮液。細胞以1x10E6個細胞/毫升再懸浮於FACS緩衝液中且以每孔100 µl等分至圓形底96孔盤(Corning #CLS3360 Tewksbury, MA)中。一次抗體(抗CDH6-PE (R&D Systems, #FAB2715P Minneapolis, MN)及對照小鼠IgG1 PE結合物(R&D Systems, #IC002P Minneapolis, MN)在FACS緩衝液中以5 µg/ml稀釋。用200 µl冷FACS緩衝液洗滌三次之後，在BD FACS Canto II® (BD Biosciences, San Jose, CA)上分析細胞。使用FlowJo®軟體測定每個樣品的幾何平均值。

呈SMCC-DM1與SPDB-DM4形式之靶向CDH6之ADC展現標靶及劑量依賴性細胞活性，如表現CDH6之細胞株增殖受到抑制(相較於非表現同基因型細胞株對及同型對照ADC)所指示(圖7及表17)。細胞活性分析如實例9中所揭示來進行及分析。

表17

呈SMCC-DM1及SPDB-DM4結合物形式之抗CDH6 ADC針對卵巢癌細胞株的活體外細胞活性

化合物	連接子/有效負載	OVCAR3		OVCAR3 shRNA_CDH6		OVCAR8		OVCAR8 (工程改造之 CDH6+)	
		IP [nM]	Amax (%)	IP [nM]	Amax (%)	IP [nM]	Amax (%)	IP [nM]	Amax (%)
me-DM1	游離有效負載	0.002	90	0.002	89	0.104	85	0.087	84
hIgG	SMCC-DM1	29.993	91	18.468	92	33	n/a	33	n/a
hIgG	SPDB-DM4	3.966	91	2.168	91	17.786	79	32.728	83
NOV0710	SMCC-DM1	1.034	101	18.52	93	33	5	0.102	94
NOV0710	SPDB-DM4	0.01	88	7.543	91	33	n/a	0.018	85
NOV0712	SMCC-DM1	0.065	88	11.249	94	33	n/a	0.015	95
NOV0712	SPDB-DM4	0.008	88	3.785	90	33	n/a	0.012	84

實例11：呈SMCC-DM1結合物形式之抗CDH6抗體在異種移植小鼠卵巢癌模型中的活體內功效

評價所選抗CDH6 ADC在OVCAR-3卵巢異種移植模型中的抗腫瘤活性。將包含含有10×10^6個OVCAR-3細胞之50% Matrigel™的磷酸鹽緩衝溶液(PBS)皮下植入雌性NOD-scid-γ小鼠右側腹。含有細胞之懸浮液的總注射體積為200 µl。植入後29天，募集平均腫瘤體積為165 mm^3的小鼠進行研究。隨機歸入七組(n=4/組)之一之後，向小鼠投與單一靜脈內劑量之PBS (10 ml/kg)、非標靶同型對照hIgG1-SMCC-DM1 (10 mg/kg)，或五種抗CDH6-SMCC-DM1之一(10 mg/kg)。量測腫瘤體積及體重，每週兩次。單一劑量之10 mg/kg之後，相較於對照組，各種抗CDH6-SMCC-DM1 ADC誘發針對腫瘤生長的抑制性作用(圖9)。

評價第二次選擇之抗CDH6 ADC在OVCAR-3卵巢異種移植模型

中的抗腫瘤活性。將包含含有10×10^6個OVCAR-3細胞之50% Matrigel™ (BD Biosciences, San Jose, CA)的PBS皮下植入雌性NOD-scid-γ小鼠的右側腹。含有細胞之懸浮液的總注射體積為200 μl。植入後35天，募集平均腫瘤體積為166 mm^3的小鼠進行研究。隨機歸入七組(n=4/組)之一後，向小鼠投與單一靜脈內劑量之PBS (10 ml/kg)、非標靶同型對照hIgG1-SMCC-DM1 (10 mg/kg)，或五種抗CDH6-SMCC-DM1之一(10 mg/kg)加在先前OVCAR3篩分中已給予之NOV0712-SMCC-DM1。量測腫瘤體積及體重，每週兩次。小鼠皆未顯示體重降低，表明ADC耐受性良好(資料未顯示)。在五種抗CDH6-SMCC-DM1中，僅NOV0690誘發的反應類似於NOV0712-SMCC-DM1 (圖10)。

實例12：呈SPDB-DM4結合物形式之抗CDH6抗體在異種移植小鼠卵巢癌模型中的活體內功效

評價所選抗CDH6 ADC在OVCAR-3卵巢異種移植模型中的抗腫瘤活性。將包含含有10×10^6個OVCAR-3細胞之50% Matrigel™ (BD Biosciences, San Jose, CA)的PBS皮下植入雌性NOD-scid-γ小鼠的右側腹。含有細胞之懸浮液的總注射體積為200 μl。植入後21天，募集平均腫瘤體積為174 mm^3的小鼠進行研究。隨機歸入九組(n=5/組)之一後，向小鼠投與單一靜脈內劑量之PBS (10 ml/kg)、非標靶同型對照hIgG1-SPDB-DM4 (5 mg/kg)、非標靶同型對照hIgG1-SMCC-DM1 (5 mg/kg)、NOV0712-SMCC-DM1 (5 mg/kg)，或七種抗CDH6-SPDB-DM4之一 (5 mg/kg)。量測腫瘤體積及體重，每週1-2次。小鼠皆未顯示體重降低，表明ADC在此劑量下的耐受性良好(資料未顯示)。在所有抗CDH6-SPDB-DM4劑中，NOV0712-SPDB-DM4引起最大的抗腫瘤作用，給藥後70天消退。在此研究中，NOV0710-SPDB-DM4為活性次最強的抗CDH6-SPDB-DM4 (圖11)。

實例13：呈SMCC-DM1或SPDB-DM4結合物形式之抗CDH6抗體在異

種移植小鼠卵巢癌模型中的活體內功效

評價所選抗CDH6 ADC NOV0712以不同連接子-有效負載形式在OVCAR-3卵巢異種移植模型中的抗腫瘤活性。將包含含有10×10^6個OVCAR-3細胞之50% Matrigel™ (BD Biosciences, San Jose, CA)的PBS皮下植入雌性NOD-scid-γ小鼠的右側腹。含有細胞之懸浮液的總注射體積為200 µl。植入後21天，募集平均腫瘤體積為174 mm^3的小鼠進行研究。隨機歸入五組(n=5/組)之一後，向小鼠投與單一靜脈內劑量之PBS (10 ml/kg)、非標靶同型對照hIgG1-SPDB-DM4 (5 mg/kg)、非標靶同型對照hIgG1-SMCC-DM1 (5 mg/kg)、NOV0712-SMCC-DM1 (5 mg/kg)，或NOV0712-SPDB-DM4 (5 mg/kg)。量測腫瘤體積及體重，每週1-2次。小鼠皆未顯示體重降低(資料未顯示)。NOV0712之L/P形式均引起抗腫瘤作用，但SPDB-DM4形式強得多，給藥後引起逾70天的持久消退(圖12)。藥物動力學樣品分析顯示兩種藥劑具有類似的PK概況(資料未顯示)。

實例14：抗CDH6 ADC以不同連接子/有效負載形式在患者源原發腫瘤異種移植小鼠卵巢癌模型中的活體內功效

評價抗CDH6 ADC NOV0712之不同連接子有效負載形式對異種移植至小鼠中之表現CDH6之原發(患者源)卵巢瘤的抗腫瘤活性。將約27 mm^3尺寸之腫瘤片段皮下植入無胸腺裸小鼠右側腹。植入後48天，募集平均腫瘤體積為178 mm^3的小鼠進行研究。隨機歸入八組(n=5/組)之一後，每2週(Q14D)向小鼠投與靜脈內劑量之PBS (10 ml/kg)、非標靶同型對照hIgG1連接子有效負載形式(-SMCC-DM1、-SPDB-DM4、-磺基-SPDB-DM4)、NOV0712連接子有效負載形式(-SMCC-DM1、-SPDB-DM4、-磺基-SPDB-DM4)或裸抗體形式之NOV0712。所有群組給予5 mg/kg。量測腫瘤體積及體重，每週1-2次。小鼠皆未顯示體重降低(資料未顯示)。裸抗體形式之NOV0712對

腫瘤生長不產生抑制作用。NOV0712-SMCC-DM1治療在此模型中不引起消退。NOV0712之各種可裂解形式引起消退。NOV0712-磺基-SPDB-DM4 5 mg/kg Q14D為最強治療組，第一次給藥後，其持久消退持續逾150天(圖13)。

實例15：抗CDH6 ADC以不同連接子/有效負載形式在異種移植小鼠卵巢癌模型中的活體內功效

評價所選抗CDH6 ADC在OVCAR-3卵巢異種移植模型中的抗腫瘤活性。將包含含有10×10^6個OVCAR-3細胞之50% Matrigel™ (BD Biosciences, San Jose, CA)的PBS皮下植入雌性NOD-scid-γ小鼠的右側腹。含有細胞之懸浮液的總注射體積為200 µl。植入後20天，募集平均腫瘤體積為172 mm^3的小鼠進行研究。隨機歸入八組(n=5/組)之一後，向小鼠投與單一靜脈內劑量之PBS (10 ml kg)、非標靶同型對照hIgG1-SPDB-DM4 (5 mg/kg)、非標靶同型對照hIgG1-磺基-SPDB-DM4 (5 mg/kg)、NOV0712-SPDB-DM4 (1.25、2.5及5 mg/kg)，或NOV0712-磺基-SPDB-DM4 (1.25、2.5及5 mg/kg)。量測腫瘤體積及體重，整個研究期間每週1-2次。小鼠皆未顯示體重降低，表明ADC耐受性良好(資料未顯示)。NOV0712-磺基-SPDB-DM4在2.5 mg/kg與5 mg/kg劑量水準下比NOV0712-SPDB更有效。單一2.5 mg/kg劑量之NOV0712-磺基-SPDB-DM4引起消退，而等效劑量之NOV0712的SPDB-DM4形式則不然。單一5 mg/kg劑量之各種形式引起消退，但磺基-SPDB-DM4劑量的作用持續時間超過-SPDB-DM4劑量。總體而言，此等資料顯示在評估組中，磺基-SPDB-DM4形式為使用ADC靶向CDH6的最強活性形式(圖14)。

實例16：抗CDH6 ADC以不同連接子/有效負載形式在患者源原發腫瘤異種移植小鼠卵巢癌模型中的活體內功效

評價抗CDH6 ADC NOV0712之不同連接子有效負載形式對異種

移植至小鼠中之表現CDH6之原發(患者源)卵巢瘤的抗腫瘤活性。將約27 mm^3尺寸之腫瘤片段皮下植入無胸腺裸小鼠右側腹。由於原發性腫瘤之生長動力學潛伏期可變，因此小鼠以循環方式進入研究。當腫瘤達到147 mm^3與244 mm^3之間的適當體積(募集時的平均尺寸為180 mm^3)時，將腫瘤分組。前5個小鼠歸入第1組至第5組，接下來的5個小鼠歸入第5組至第1組等，直至5組(n=5/組)填滿。募集後，每2週(Q14D)向各小鼠投與靜脈內劑量之PBS (10 ml/kg)、非標靶同型對照hIgG1-SMCC-DM1 (5 mg/kg)、NOV0712-SMCC-DM1 (5 mg/kg)、非標靶同型對照hIgG1-磺基-SPDB-DM4 (2.5 mg/kg)或NOV0712-磺基-SPDB-DM4 (2.5 mg/kg)。量測腫瘤體積及體重，每週兩次。小鼠皆未顯示體重降低，表明ADC耐受性良好(資料未顯示)。NOV0712-SMCC-DM1 5 mg/kg Q14D能夠減緩此模型之腫瘤生長。NOV0712-磺基-SPDB-DM4 2.5 mg/kg Q14D能夠促使此模型中之腫瘤停滯42天(圖15)。

實例17：抗CDH6 ADC之組合療法

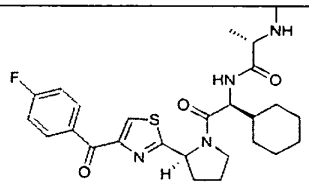
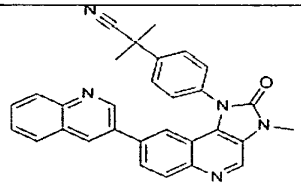
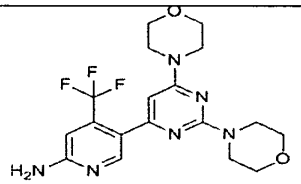
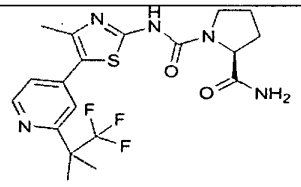
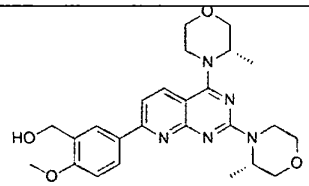
抗CDH6 ADC可與小分子抑制劑組合。使用Chalice軟體(Zalicus, Cambridge MA)或ComboExplorer應用程式(Novartis, Basel CH)，對組合與其單一藥劑針對廣泛使用之藥物與劑量本身相加型洛維模型(Loewe model)的反應進行比較(Lehar等人, Nat. Biotechnol. (2009) 27: 659-666；Zimmermann等人, Drug Discov. Today (2007) 12: 34-42)。過度抑制與相加作用的比較情況可繪製為完整劑量矩陣表以使發生協同作用的藥物濃度直觀化。表18顯示若干種抗CDH6 ADC/化合物組合。

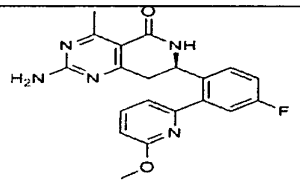
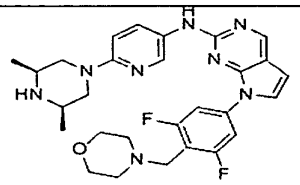
細胞存活率可藉由使用CellTiter Glo®發光分析(Promega, Madison WI)量測細胞ATP含量來量測。藥物添加前一天，將含有250-500個細胞的20 μl生長培養基塗鋪於384孔盤(Greiner, Monroe, NC)中。細胞接著與不同濃度之抗CDH6 ADC (表18)一起培育120小時，

該等抗CDH6 ADC呈單一藥劑、單一藥劑化合物或抗CDH6 ADC/化合物組合形式，隨後向各孔中添加CellTiter Glo®試劑且用Envision®讀盤器(Perkin Elmer, Waltham MA)記錄發光。發光值用於計算細胞存活之抑制(相對於經DMSO處理之細胞(0%抑制))。

表18

抗CDH6 ADC組合

化合物之標靶	**抗CDH6 ADC與** 以下之組合：	結構
RTK*i*	Glivec®	伊馬替尼
RTK*i*	Sutent®	舒尼替尼
IAP*i*	NVP-LCL161	
PI3K家族	NVP-BEZ235	
泛PI3K*i*	NVP-BKM120	
PI3K	NVP-BYL719	
mTOR*i* *(催化酶)*	NVP-CCG168	
mTOR*i* *(異型)*	Afinitor®	依維莫司

HSP90*i*	NVP-HSP990	
JAK2	NVP-BVB808	

概言之，本文所揭示之抗CDH6 ADC當與其他分子組合使用而產生更多治療選項時可具有協同作用。

應瞭解，本文所述之實例及態樣僅出於說明之目的，且熟習此項技術者將根據其提出各種潤飾或變化且此等潤飾或變化包括於本申請案之精神及範圍以及所附申請專利範圍之範疇內。

【符號說明】

無

【序列表】

<110> 瑞士商諾華公司

<120> 抗CDH6抗體藥結合物

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<151> 2014-08-12

<160> 447

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gcggcggcgg cggcggcgga ggcaggagca gcctgggcgg gtcgcagggt ctccgcgggc 180

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cgcacagact cgacggtgcc atcagcatga gaacttaccg ctacttcttg ctgctctttt 360

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Glu Tyr Thr Gly Ser Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp
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340 345 350

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Gly Gly Leu Ser Gly Thr Thr Thr Val Asn Ile Thr Leu Thr Asp Val
195 200 205

Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr Tyr Gln Phe Lys Thr
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Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile Lys Ala Ser
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195 200 205

Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr Tyr Gln Phe Lys Thr
210 215 220

Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile Lys Ala Ser

225 230 235 240

Asp Ala Asp Val Gly Glu Asn Ala Glu Ile Glu Tyr Ser Ile Thr Asp
245 250 255

Gly Glu Gly Leu Asp Met Phe Asp Val Ile Thr Asp Gln Glu Thr Gln
260 265 270

Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp Phe Glu Lys Lys Lys
275 280 285

Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro Tyr Val Glu Pro Arg
290 295 300

Phe Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala Thr Val Arg Ile Val
305 310 315 320

Val Glu Asp Val Asp Glu Pro Pro Val Phe Ser Lys Leu Ala Tyr Ile
325 330 335

Leu Gln Ile Arg Glu Asp Ala Gln Ile Asn Thr Thr Ile Gly Ser Val
340 345 350

Thr Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro Val Lys Tyr Ser Val
355 360 365

Asp Arg His Thr Asp Met Asp Arg Ile Phe Asn Ile Asp Ser Gly Asn
370 375 380

Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp Arg Glu Thr Leu Leu Trp
385 390 395 400

His Asn Ile Thr Val Ile Ala Thr Glu Ile Asn Asn Pro Lys Gln Ser
405 410 415

Ser Arg Val Pro Leu Tyr Ile Lys Val Leu Asp Val Asn Asp Asn Ala
420 425 430

Pro Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val Cys Glu Lys Ala Lys
435 440 445

Ala Asp Gln Leu Ile Gln Thr Leu His Ala Val Asp Lys Asp Asp Pro
450 455 460

Tyr Ser Gly His Gln Phe Ser Phe Ser Leu Ala Pro Glu Ala Ala Ser
465 470 475 480

Gly Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp Asn Thr Ala Gly Ile
485 490 495

Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu Met Ser Thr Tyr Leu
500 505 510

Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro Val Gln Ser Ser Thr
515 520 525

Gly Thr Val Thr Val Arg Val Cys Ala Cys Asp His His Gly Asn Met
530 535 540

Gln Ser Cys His Ala Glu Ala Leu Ile His Pro Thr Gly Leu Ser Thr
545 550 555 560

Gly Ala Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
565 570 575

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
580 585 590

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
595 600 605

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
610 615 620

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
625 630 635 640

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
645 650 655

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
660 665 670

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
675 680 685

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
690 695 700

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
705 710 715 720

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
725 730 735

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
740 745 750

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
755 760 765

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
770 775 780

Leu Ser Leu Ser Pro Gly Lys
785 790

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<211> 585
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<213> 食蟹猴

<400> 7

Ser Trp Met Trp Asn Gln Phe Phe Leu Leu Glu Glu Tyr Thr Gly Ser
1 5 10 15

Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp Gln Asp Arg Gly Asp
20 25 30

Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly Ala Gly Asp Leu Phe
35 40 45

Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu Asp
50 55 60

Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala Gln Ala Ile Asn Arg
65 70 75 80

Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu Phe Ile Ile Lys Ile
85 90 95

His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr Lys Glu Val Tyr Thr
100 105 110

Ala Thr Val Pro Glu Met Ser Asp Val Gly Thr Phe Val Val Gln Val
115 120 125

Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly Asn Ser Ala Lys Val
130 135 140

Val Tyr Ser Ile Leu Gln Gly Gln Pro Tyr Phe Ser Val Glu Ser Glu
145 150 155 160

Thr Gly Ile Ile Lys Thr Ala Leu Leu Asn Met Asp Arg Glu Asn Arg
165 170 175

Glu Gln Tyr Gln Val Val Ile Gln Ala Lys Asp Met Gly Gly Gln Met
180 185 190

Gly Gly Leu Ser Gly Thr Thr Thr Val Asn Ile Thr Leu Thr Asp Val
195 200 205

Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr Tyr Gln Phe Lys Thr
210 215 220

Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile Lys Ala Ser
225 230 235 240

Asp Ala Asp Val Gly Glu Asn Ala Glu Ile Glu Tyr Ser Ile Thr Asp
245 250 255

Gly Glu Gly Leu Asp Met Phe Asp Val Ile Thr Asp Gln Glu Thr Gln
260 265 270

Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp Phe Glu Lys Lys Lys
275 280 285

Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro His Val Glu Pro Arg
290 295 300

Phe Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala Thr Val Arg Ile Val
305 310 315 320

Val Glu Asp Val Asp Glu Pro Pro Val Phe Ser Lys Leu Ala Tyr Ile
325 330 335

Leu Gln Ile Arg Glu Asp Ala Gln Ile Asn Thr Thr Ile Gly Ser Val
340 345 350

Thr Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro Val Lys Tyr Ser Val
355 360 365

Asp Arg His Thr Asp Met Asp Arg Ile Phe Asn Ile Asp Ser Gly Asn
370 375 380

Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp Arg Glu Thr Leu Leu Trp
385 390 395 400

His Asn Ile Thr Val Ile Ala Thr Glu Ile Asn Asn Pro Lys Gln Ser
405 410 415

Ser Arg Val Pro Leu Tyr Ile Lys Val Leu Asp Val Asn Asp Asn Ala
420 425 430

Pro Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val Cys Glu Lys Ala Lys
435 440 445

Ala Asp Gln Leu Ile Gln Thr Leu Arg Ala Val Asp Lys Asp Asp Pro
450 455 460

Tyr Ser Gly His Gln Phe Ser Phe Ser Leu Ala Pro Glu Ala Ala Ser
465 470 475 480

Gly Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp Asn Thr Ala Gly Ile
485 490 495

Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu Met Ser Thr Tyr Leu

500 505 510

Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro Val Gln Ser Ser Thr
515 520 525

Gly Thr Val Thr Val Arg Val Cys Ala Cys Asp His His Gly Asn Met
530 535 540

Gln Ser Cys His Ala Glu Ala Leu Ile His Pro Thr Gly Leu Ser Thr
545 550 555 560

Gly Ala Gly Ser Glu Phe Arg His Asp Ser Gly Leu Asn Asp Ile Phe
565 570 575

Glu Ala Gln Lys Ile Glu Trp His Glu
580 585

<210> 8
<211> 585
<212> PRT
<213> 小鼠

<400> 8

Ser Trp Met Trp Asn Gln Phe Phe Leu Leu Glu Glu Tyr Thr Gly Ser
1 5 10 15

Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp Gln Asp Arg Gly Asp
20 25 30

Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly Ala Gly Asp Leu Phe
35 40 45

Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu Asp
50 55 60

Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala Gln Ala Val Asn Arg
65 70 75 80

Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu Phe Ile Ile Lys Ile
85 90 95

His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr Lys Asp Val Tyr Thr

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                100                 105                 110

Ala Thr Val Pro Glu Met Ala Asp Val Gly Thr Phe Val Val Gln Val
        115                 120                 125

Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly Asn Ser Ala Lys Val
    130                 135                 140

Val Tyr Ser Ile Leu Gln Gly Gln Pro Tyr Phe Ser Val Glu Ser Glu
145                 150                 155                 160

Thr Gly Ile Ile Lys Thr Ala Leu Leu Asn Met Asp Arg Glu Asn Arg
                165                 170                 175

Glu Gln Tyr Gln Val Val Ile Gln Ala Lys Asp Met Gly Gly Gln Met
            180                 185                 190

Gly Gly Leu Ser Gly Thr Thr Thr Val Asn Ile Thr Leu Thr Asp Val
        195                 200                 205

Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr Tyr Gln Phe Lys Thr
    210                 215                 220

Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile Lys Ala Ser
225                 230                 235                 240

Asp Ala Asp Val Gly Glu Asn Ala Glu Ile Glu Tyr Ser Ile Thr Asp
                245                 250                 255

Gly Glu Gly His Glu Met Phe Asp Val Ile Thr Asp Gln Glu Thr Gln
            260                 265                 270

Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp Phe Glu Lys Lys Lys
        275                 280                 285

Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro His Val Glu Pro Arg
    290                 295                 300

Phe Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala Thr Val Arg Ile Val
305                 310                 315                 320
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Val Asp Asp Val Asp Glu Pro Pro Val Phe Ser Lys Leu Ala Tyr Ile
325 330 335

Leu Gln Ile Arg Glu Asp Ala Arg Ile Asn Thr Thr Ile Gly Ser Val
340 345 350

Ala Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro Val Lys Tyr Ser Val
355 360 365

Asp Arg His Thr Asp Met Asp Arg Ile Phe Asn Ile Asp Ser Gly Asn
370 375 380

Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp Arg Glu Thr Leu Leu Trp
385 390 395 400

His Asn Ile Thr Val Ile Ala Thr Glu Ile Asn Asn Pro Lys Gln Ser
405 410 415

Ser Arg Val Pro Leu Tyr Ile Lys Val Leu Asp Val Asn Asp Asn Ala
420 425 430

Pro Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val Cys Glu Lys Ala Lys
435 440 445

Ala Asp Gln Leu Ile Gln Thr Leu Arg Ala Val Asp Lys Asp Asp Pro
450 455 460

Tyr Ser Gly His Gln Phe Ser Phe Ser Leu Ala Pro Glu Ala Ala Ser
465 470 475 480

Ser Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp Asn Thr Ala Gly Ile
485 490 495

Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu Met Ser Thr Tyr Leu
500 505 510

Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro Val Gln Ser Ser Thr
515 520 525

Gly Thr Val Thr Val Arg Val Cys Ala Cys Asp His His Gly Asn Met
530 535 540

Gln Ser Cys His Ala Glu Ala Leu Ile His Pro Thr Gly Leu Ser Thr
545 550 555 560

Gly Ala Gly Ser Glu Phe Arg His Asp Ser Gly Leu Asn Asp Ile Phe
565 570 575

Glu Ala Gln Lys Ile Glu Trp His Glu
580 585

<210> 9
<211> 585
<212> PRT
<213> 褐鼠

<400> 9

Ser Trp Met Trp Asn Gln Phe Phe Leu Leu Glu Glu Tyr Thr Gly Ser
1 5 10 15

Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp Gln Asp Arg Gly Asp
20 25 30

Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly Ala Gly Asp Leu Phe
35 40 45

Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu Asp
50 55 60

Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala Gln Ala Ile Asn Arg
65 70 75 80

Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu Phe Ile Ile Lys Ile
85 90 95

His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr Lys Asp Val Tyr Thr
100 105 110

Ala Thr Val Pro Glu Met Ala Asp Val Gly Thr Phe Val Val Gln Val
115 120 125

Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly Asn Ser Ala Lys Val
130 135 140

Val Tyr Ser Ile Leu Gln Gly Gln Pro Tyr Phe Ser Val Glu Ser Glu
145 150 155 160

Thr Gly Ile Ile Lys Thr Ala Leu Leu Asn Met Asp Arg Glu Asn Arg
165 170 175

Glu Gln Tyr Gln Val Val Ile Gln Ala Lys Asp Met Gly Gly Gln Met
180 185 190

Gly Gly Leu Ser Gly Thr Thr Thr Val Asn Ile Thr Leu Thr Asp Val
195 200 205

Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr Tyr Gln Phe Lys Thr
210 215 220

Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile Lys Ala Ser
225 230 235 240

Asp Ala Asp Val Gly Glu Asn Ala Glu Ile Glu Tyr Ser Ile Thr Asp
245 250 255

Gly Glu Gly His Asp Met Phe Asp Val Ile Thr Asp Gln Glu Thr Gln
260 265 270

Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp Phe Glu Lys Lys Arg
275 280 285

Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro His Ile Glu Pro Arg
290 295 300

Phe Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala Thr Val Arg Ile Val
305 310 315 320

Val Asp Asp Val Asp Glu Pro Pro Val Phe Ser Lys Leu Ala Tyr Ile
325 330 335

Leu Gln Ile Arg Glu Asp Ala Gln Ile Asn Thr Thr Ile Gly Ser Val
340 345 350

Ala Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro Val Lys Tyr Ser Val
355 360 365

Asp Arg His Thr Asp Met Asp Arg Ile Phe Asn Ile Asp Ser Gly Asn
370 375 380

Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp Arg Glu Thr Leu Leu Trp
385 390 395 400

His Asn Ile Thr Val Ile Ala Thr Glu Ile Asn Asn Pro Lys Gln Ser
405 410 415

Ser Arg Val Pro Leu Tyr Ile Lys Val Leu Asp Val Asn Asp Asn Ala
420 425 430

Pro Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val Cys Glu Lys Ala Lys
435 440 445

Ala Asp Gln Leu Ile Gln Thr Leu His Ala Val Asp Lys Asp Asp Pro
450 455 460

Tyr Ser Gly His Gln Phe Ser Phe Ser Leu Ala Pro Glu Ala Ala Ser
465 470 475 480

Gly Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp Asn Thr Ala Gly Ile
485 490 495

Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu Met Ser Thr Tyr Leu
500 505 510

Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro Val Gln Ser Ser Thr
515 520 525

Gly Thr Val Thr Val Arg Val Cys Ala Cys Asp His His Gly Asn Met
530 535 540

Gln Ser Cys His Ala Glu Ala Leu Ile His Pro Thr Gly Leu Ser Thr
545 550 555 560

Gly Ala Gly Ser Glu Phe Arg His Asp Ser Gly Leu Asn Asp Ile Phe
565 570 575

Glu Ala Gln Lys Ile Glu Trp His Glu

580 585

<210> 10
<211> 17
<212> DNA
<213> 人工序列

<220>
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<400> 10
caggaaacag ctatgac 17

<210> 11
<211> 21
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 11
gataagcatg cgtaggagaa a 21

<210> 12
<211> 20
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 12
taatacgact cactataggg 20

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<211> 21
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 13
ctctagcgcc accatgaaac a 21

<210> 14
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 14

Ser Gly Ser Ser Ser Asn Ile Gly Ser Gln Tyr Val Tyr
1 5 10

<210> 15
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 15

Tyr Asn Ser Glu Arg Pro Ser
1 5

<210> 16
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 16

Gln Thr Trp Asp Ala Ser Ser Gln Ser Phe Val
1 5 10

<210> 17
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 17

Ser Tyr Ala Ile Ser
1 5

<210> 18
<211> 17
<212> PRT

<213> 人工序列

<220>
<223> 合成肽

<400> 18

Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 19
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 19

Lys Phe Pro Gly Arg Gly Pro Phe Ala Tyr
1 5 10

<210> 20
<211> 119
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 20

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Lys Phe Pro Gly Arg Gly Pro Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 21
<211> 110
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 21

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Gln
20 25 30

Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asn Ser Glu Arg Pro Ser Gly Met Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Ala Ser Ser
85 90 95

Gln Ser Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 22

<211> 357
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 22
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agctgcaaag catccggagg gacgttttct tcttacgcta tctcttgggt gcgccaggcc 120

ccgggccagg gcctcgagtg gatgggcggt atcatcccga tcttcggcac tgcgaactac 180

gcccagaaat ttcagggccg ggtgaccatt accgccgatg aaagcaccag caccgcctat 240

atggaactga gcagcctgcg cagcgaagat acggccgtgt attattgcgc gcgtaaattc 300

ccgggtcgtg gtccgttcgc ttactggggc caaggcaccc tggtgactgt tagctca 357

<210> 23
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<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 23
gatatcgtgc tgacccagcc gccgagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagcagcag caacattggt tctcagtacg tgtactggta ccagcagctg 120

ccgggcacgg cgccgaaact gctgatctac tacaactctg aacgcccgag cggcatgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagacg aagcggatta ttactgccag acttgggacg cttcttctca gtctttcgtg 300

tttggcggcg gcacgaagtt aaccgtccta 330

<210> 24
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 24

Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Tyr Val Ser
1 5 10

<210> 25
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 25

Gly Val Ser Lys Arg Pro Ser
1 5

<210> 26
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 26

Gln Ser Tyr Asp His Leu Leu His Val Val
1 5 10

<210> 27
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 27

Thr Tyr Gly Ile His
1 5

<210> 28
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 28

Tyr Ile His Tyr Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys

1 5 10 15

Gly

<210> 29
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 29

His Ala Tyr Gly Tyr Met Asp Phe
1 5

<210> 30
<211> 117
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 30

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile His Tyr Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg His Ala Tyr Gly Tyr Met Asp Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 31
<211> 110
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 31

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Gly Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp His Leu
85 90 95

Leu His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 32
<211> 351
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 32

caggtgcaat tgctggaaag cggcggtggc ctggtgcagc cgggtggcag cctgcgtctg 60

agctgcgcgg cgtccggatt cacctttaac acttacggta tccattgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtttcctac atccattact ctggttcttc tacctactat 180

gcggatagcg tgaaaggccg ctttaccatc agccgcgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcatgct 300

tacggttaca tggatttctg gggccaaggc accctggtga ctgttagctc a 351

<210> 33
<211> 330
<212> DNA
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<400> 33
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agctgcaccg gcaccagcag cgatgtgggc gcttacaact acgtgtcttg gtaccagcag 120

catccgggca aggcgccgaa actgatgatc tacggtgttt ctaaacgtcc gagcggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattactgc cagtcttacg accatctgct gcatgttgtg 300

tttggcggcg gcacgaagtt aaccgtccta 330

<210> 34
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 34

Ser Gly Ser Ser Ser Asn Ile Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 35
<211> 7
<212> PRT
<213> 人工序列

<220>

<223> 合成肽

<400> 35

Arg Asp Asn Gln Arg Pro Ser
1 5

<210> 36
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 36

Ala Ala Trp Thr Ser Gly Ser Ile Gly Trp Val
1 5 10

<210> 37
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 37

Ser Tyr Ala Met Thr
1 5

<210> 38
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 38

Gly Ile Ser Gly Gly Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 39

<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 39

Gly Gly Gly Gln Tyr Phe Asp Tyr
1 5

<210> 40
<211> 117
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 40

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Gly Gly Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Gly Gln Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 41
<211> 110
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 41

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Tyr Asn
20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Thr Ser Gly Ser
85 90 95

Ile Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 42
<211> 351
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 42
caggtgcaat tgctggaaag cggcggtggc ctggtgcagc cgggtggcag cctgcgtctg 60

agctgcgcgg cgtccggatt caccttttct tcttacgcta tgacttgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtttccggt atctctggtg gtggttctaa cacctactat 180

gcggatagcg tgaaaggccg ctttaccatc agccgcgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtggtggt 300

ggtcagtact tcgattactg gggccaaggc accctggtga ctgttagctc a 351

<210> 43
<211> 330
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 43
gatatcgtgc tgacccagcc gccgagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagcagcag caacattggt tacaactacg tgtcttggta ccagcagctg 120

ccgggcacgg cgccgaaact gctgatctac cgtgacaacc agcgcccgag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagacg aagcggatta ttactgcgct gcttggactt ctggttctat cggttgggtg 300

tttggcggcg gcacgaagtt aaccgtccta 330

<210> 44
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 44

Arg Ala Ser Gln Thr Ile Asn Ser Tyr Leu Asn
1 5 10

<210> 45
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 45

Arg Ala Ser Asn Leu Gln Ser
1 5

<210> 46
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 46

Gln Gln Gly Asp Ser Ser Trp Thr
1 5

<210> 47
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 47

Ser Tyr Ala Ile Ser
1 5

<210> 48
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 48

Phe Ile Lys Ser Asn Ala Asp Gly Tyr Thr Thr Asn Tyr Ala Ala Pro
1 5 10 15

Val Lys Gly

<210> 49
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 49

Ile Arg Tyr Phe Arg Asn Trp Asp Tyr
1 5

<210> 50
<211> 120
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 50

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Phe Ile Lys Ser Asn Ala Asp Gly Tyr Thr Thr Asn Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Ile Arg Tyr Phe Arg Asn Trp Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 51
<211> 106
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 51

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Arg Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Ser Trp Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 52
<211> 360
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 52
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agctgcgccg cctccggatt caccttttct tcttacgcta tctcttgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtgggcttc atcaaatcta acgctgacgg ttacactact 180

aactatgccg ccccagtgaa aggccgcttt accattagcc gcgatgattc gaaaaacacc 240

ctgtatctgc aaatgaacag cctgaaaacc gaagatacgg ccgtgtatta ttgcgcgcgt 300

atccgttact tccgtaactg ggattactgg ggccaaggca ccctggtgac tgttagctca 360

<210> 53
<211> 318
<212> DNA

<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 53
gatatccaga tgacccagag cccgagcagc ctgagcgcca gcgtgggcga tcgcgtgacc 60

attacctgca gagccagcca gactattaac tcttacctga actggtacca gcagaaaccg 120

ggcaaagcgc cgaaactatt aatctaccgt gcttctaacc tgcaaagcgg cgtgccgagc 180

cgctttagcg gcagcggatc cggcaccgat ttcaccctga ccattagctc tctgcaaccg 240

gaagactttg cgacctatta ttgccagcag ggtgactctt cttggacctt tggccagggc 300

acgaaagttg aaattaaa 318

<210> 54
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 54

Ser Gly Ser Ser Ser Asn Ile Gly Ser Tyr Tyr Val Ser
1 5 10

<210> 55
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 55

Tyr Asn Thr Lys Arg Pro Ser
1 5

<210> 56
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 56

Gln Ser Trp Asp Lys Leu Gly Lys Gly Tyr Val
1 5 10

<210> 57
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 57

Gly Asn Ser Ala Ala Trp Asn
1 5

<210> 58
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 58

Ile Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 59
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 59

Ser Ser Tyr Ser Gly Gly Phe Asp Tyr
1 5

<210> 60
<211> 121
<212> PRT

<213> 人工序列

<220>
<223> 合成肽

<400> 60

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Gly Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Ile Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Ser Ser Tyr Ser Gly Gly Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 61
<211> 110
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 61

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Tyr
20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asn Thr Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Lys Leu Gly
85 90 95

Lys Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 62
<211> 363
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 62
caggtgcaat tgcagcagag cggtccgggc ctggtgaaac cgagccagac cctgagcctg 60

acctgcgcga tttccggaga tagcgtgagc ggtaactctg ctgcttggaa ctggattcgt 120

cagagcccga gccgtggcct cgagtggctg ggcatcatct actaccgtag caaatggtac 180

aacgactatg ccgtgagcgt gaaaagccgc attaccatta acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgttcttctt actctggtgg tttcgattac tggggccaag gcaccctggt gactgttagc 360

tca 363

<210> 63
<211> 330
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 63

gatatcgtgc tgacccagcc gccgagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagcagcag caacattggt tcttactacg tgtcttggta ccagcagctg 120

ccgggcacgg cgccgaaact gctgatctac tacaacacta aacgcccgag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagacg aagcggatta ttactgccag tcttgggaca aactgggtaa aggttacgtg 300

tttggcggcg gcacgaagtt aaccgtccta 330

<210> 64
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 64

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Phe Val Ser
1 5 10

<210> 65
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 65

Asp Asn Ser Asn Arg Pro Ser
1 5

<210> 66
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 66

Ser Ser Tyr Asp Ser Phe Asp His Ser Trp Val
1 5 10

<210> 67
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 67

Ser Phe Ala Met Asn
1 5

<210> 68
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 68

Val Ile Ser Ser Ser Gly Ser Asn Thr Asn Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 69
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 69

Pro Ser Tyr Phe Gln Ala Met Asp Tyr
1 5

<210> 70
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 70

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Ser Ser Ser Gly Ser Asn Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Pro Ser Tyr Phe Gln Ala Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 71
<211> 110
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 71

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Phe Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Asp Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Ser Phe Asp
85 90 95

His Ser Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 72
<211> 354
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 72
caggtgcaat tgctggaaag cggcggtggc ctggtgcagc cgggtggcag cctgcgtctg 60

agctgcgcgg cgtccggatt caccttttct tctttcgcta tgaactgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtttccgtt atctcttctt ctggttctaa caccaactat 180

gcggatagcg tgaaaggccg ctttaccatc agccgcgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtccgtct 300

tacttccagg ctatggatta ctggggccaa ggcaccctgg tgactgttag ctca 354

<210> 73
<211> 330
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 73
gatatcgtgc tgacccagcc gccgagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagcagcag caacattggt tctaacttcg tgtcttggta ccagcagctg 120

ccgggcacgg cgccgaaact gctgatctac gacaactcta accgcccgag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagacg aagcggatta ttactgctct tcttacgact ctttcgacca ttcttgggtg 300

tttggcggcg gcacgaagtt aaccgtccta 330

<210> 74
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 74

Ser Gly Asp Ala Ile Gly Thr Lys Phe Ala His
1 5 10

<210> 75
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 75

Tyr Asp His Glu Arg Pro Ser
1 5

<210> 76
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 76

Tyr Ser Arg Ala Ser Ser Asn Leu Val
1 5

<210> 77
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 77

Asp His Ala Ile Asp
1 5

<210> 78
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 78

Val Ile Ala Gly Asp Gly Ser Ile Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 79
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 79

Asp Thr Gly Val Tyr Arg Glu Tyr Met Asp Val
1 5 10

<210> 80
<211> 120
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 80

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp His
20 25 30

Ala Ile Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Ala Gly Asp Gly Ser Ile Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Gly Val Tyr Arg Glu Tyr Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 81
<211> 106
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 81

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Ala Ile Gly Thr Lys Phe Ala
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp His Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Arg Ala Ser Ser Asn Leu Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 82
<211> 360
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 82
caggtgcaat tgctggaaag cggcggtggc ctggtgcagc cgggtggcag cctgcgtctg 60

agctgcgcgg cgtccggatt caccttttct gaccatgcta tcgactgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtttccgtt atcgctggtg acggttctat cacctactat 180

gcggatagcg tgaaaggccg ctttaccatc agccgcgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgacact 300

ggtgtttacc gtgaatacat ggatgtttgg ggccaaggca ccctggtgac tgttagctca 360

<210> 83
<211> 318
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 83
gatatcgaac tgacccagcc gccgagcgtg agcgtgagcc cgggccagac cgcgagcatt 60

acctgtagcg gcgatgctat cggtactaaa ttcgctcatt ggtaccagca gaaaccgggc 120

caggcgccgg tgctggtgat ctactacgac catgaacgtc cgagcggcat cccggaacgt 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac ccaggcggaa 240

gacgaagcgg attattactg ctactctcgt gcttcttcta acctggtgtt tggcggcggc 300

acgaagttaa ccgtccta 318

<210> 84
<211> 14
<212> PRT

<213> 人工序列

<220>
<223> 合成肽

<400> 84

Thr Gly Thr Ser Ser Asp Val Gly Arg Tyr Asn Phe Val Ser
1 5 10

<210> 85
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 85

Arg Val Ser Asn Arg Pro Ser
1 5

<210> 86
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 86

Gln Ser Trp Thr Thr Tyr Ser Asn Val Val
1 5 10

<210> 87
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 87

Ser Tyr Ala Leu Asn
1 5

<210> 88
<211> 19

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 88

Arg Ile Lys Ser Lys Thr Tyr Gly Gly Ser Thr Asp Tyr Ala Ala Pro
1 5 10 15

Val Lys Gly

<210> 89
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 89

Asp Arg Gly Gly Tyr Val Gly Phe Asp Ser
1 5 10

<210> 90
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 90

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Leu Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Lys Ser Lys Thr Tyr Gly Gly Ser Thr Asp Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Asp Arg Gly Gly Tyr Val Gly Phe Asp Ser Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 91
<211> 110
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 91

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Arg Tyr
20 25 30

Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Arg Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Thr Thr Tyr
85 90 95

Ser Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 92
<211> 363
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 92
caggtgcaat tggtggaaag cggcggtggc ctggtgaaac caggcggcag cctgcgcctg 60

agctgcgccg cctccggatt caccttttct tcttacgctc tgaactgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtgggccgt atcaaatcta aaacttacgg tggttctact 180

gactatgccg ccccagtgaa aggccgcttt accattagcc gcgatgattc gaaaaacacc 240

ctgtatctgc aaatgaacag cctgaaaacc gaagatacgg ccgtgtatta ttgcgcgcgt 300

gaccgtggtg gttacgttgg tttcgattct tggggccaag gcaccctggt gactgttagc 360

tca 363

<210> 93
<211> 330
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 93
gatatcgcgc tgacccagcc ggcgagcgtg agcggtagcc cgggccagag cattaccatt 60

agctgcaccg gcaccagcag cgatgtgggc cgttacaact tcgtgtcttg gtaccagcag 120

catccgggca aggcgccgaa actgatgatc taccgtgttt ctaaccgtcc gagcggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattactgc cagtcttgga ctacttactc taacgttgtg 300

tttggcggcg gcacgaagtt aaccgtccta 330

<210> 94
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 94

Ser Gly Asp Ser Ile Gly Ser Lys Tyr Ala Gln
1 5 10

<210> 95
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 95

Tyr Asn Ser Glu Arg Pro Ser
1 5

<210> 96
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 96

Gln Ser Trp Asp Gly Gln Ser Thr Ile Arg Val
1 5 10

<210> 97
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 97

Arg Tyr Trp Met Asp
1 5

<210> 98
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 98

Arg Ile Lys Ser Lys Ala Asn Gly Gly Ile Thr Asp Tyr Ala Ala Pro
1 5 10 15

Val Lys Gly

<210> 99
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 99

Gly Met Thr Phe Leu Gly Ile
1 5

<210> 100
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 100

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Lys Ser Lys Ala Asn Gly Gly Ile Thr Asp Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

85 90 95

Tyr Cys Ala Arg Gly Met Thr Phe Leu Gly Ile Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 101
<211> 108
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 101

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Ser Ile Gly Ser Lys Tyr Ala
20 25 30

Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asn Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Gly Gln Ser Thr Ile
85 90 95

Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 102
<211> 354
<212> DNA
<213> 人工序列

<220>

<223> 合成聚核苷酸

<400> 102
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agctgcgccg cctccggatt caccttttct cgttactgga tggactgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtgggccgt atcaaatcta aagctaacgg tggtatcact 180

gactatgccg ccccagtgaa aggccgcttt accattagcc gcgatgattc gaaaaacacc 240

ctgtatctgc aaatgaacag cctgaaaacc gaagatacgg ccgtgtatta ttgcgcgcgt 300

ggtatgactt tcctgggtat ctggggccaa ggcaccctgg tgactgttag ctca 354

<210> 103
<211> 324
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 103
gatatcgaac tgacccagcc gccgagcgtg agcgtgagcc cgggccagac cgcgagcatt 60

acctgtagcg gcgattctat cggttctaaa tacgctcagt ggtaccagca gaaaccgggc 120

caggcgccgg tgctggtgat ctactacaac tctgaacgtc cgagcggcat cccggaacgt 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac ccaggcggaa 240

gacgaagcgg attattactg ccagtcttgg gacggtcagt ctactatccg tgtgtttggc 300

ggcggcacga agttaaccgt ccta 324

<210> 104
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 104

Arg Ala Ser Gln Ser Ile Ser Phe Tyr Leu Ala
1 5 10

<210> 105
<211> 7
<212> PRT

<213> 人工序列

<220>
<223> 合成肽

<400> 105

Gly Ala Ser Thr Leu Gln Ser
1 5

<210> 106
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 106

His Gln Tyr Ser Tyr Trp Leu Arg Thr
1 5

<210> 107
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 107

Ser Tyr Ala Leu His
1 5

<210> 108
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 108

Tyr Ile Phe Tyr Asp Ser Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 109
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 109

Phe Leu Tyr Ser Ala Tyr Gly Val Ala Asn
1 5 10

<210> 110
<211> 119
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 110

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Phe Tyr Asp Ser Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Phe Leu Tyr Ser Ala Tyr Gly Val Ala Asn Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser

115

<210> 111
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 111

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Phe Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Tyr Ser Tyr Trp Leu Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 112
<211> 357
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 112
caggtgcaat tgctggaaag cggcggtggc ctggtgcagc cgggtggcag cctgcgtctg 60

agctgcgcgg cgtccggatt caccttttct tcttacgctc tgcattgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtttcctac atcttctacg actcttcttc tacctactat 180

gcggatagcg tgaaaggccg ctttaccatc agccgcgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtttcctg 300

tactctgctt acggtgttgc taactggggc caaggcaccc tggtgactgt tagctca 357

<210> 113
<211> 321
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 113
gatatccaga tgacccagag cccgagcagc ctgagcgcca gcgtgggcga tcgcgtgacc 60

attacctgca gagccagcca gtctatttct ttctacctgg cttggtacca gcagaaaccg 120

ggcaaagcgc cgaaactatt aatctacggt gcttctactc tgcaaagcgg cgtgccgagc 180

cgctttagcg gcagcggatc cggcaccgat ttcaccctga ccattagctc tctgcaaccg 240

gaagactttg cgacctatta ttgccatcag tactcttact ggctgcgtac ctttggccag 300

ggcacgaaag ttgaaattaa a 321

<210> 114
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 114

Arg Ala Ser Gln Gly Ile Phe Thr Tyr Leu Asn
1 5 10

<210> 115
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 115

Ala Ala Ser Thr Leu Gln Ser

1 5

<210> 116
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 116

Gln Gln Tyr Tyr Ser Thr Ser Leu Thr
1 5

<210> 117
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 117

Ser Asn Ser Ala Ala Trp Asn
1 5

<210> 118
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 118

Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 119
<211> 10
<212> PRT
<213> 人工序列

<220>

<223> 合成肽

<400> 119

Glu Arg Ser Tyr Arg Asp Tyr Phe Asp Tyr
1 5 10

<210> 120
<211> 122
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 120

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Arg Ser Tyr Arg Asp Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 121
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 121

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Phe Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Ser Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Ser Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 122
<211> 366
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 122
caggtgcaat tgcagcagag cggtccgggc ctggtgaaac cgagccagac cctgagcctg 60

acctgcgcga tttccggaga tagcgtgagc tctaactctg ctgcttggaa ctggattcgt 120

cagagcccga gccgtggcct cgagtggctg ggccgtatct actaccgtag caaatggtac 180

aacgactatg ccgtgagcgt gaaaagccgc attaccatta acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtgaacgtt cttaccgtga ctacttcgat tactggggcc aaggcaccct ggtgactgtt 360

agctca 366

<210> 123
<211> 321
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 123
gatatccaga tgacccagag cccgagcagc ctgagcgcca gcgtgggcga tcgcgtgacc 60

attacctgca gagccagcca gggtattttc acttacctga actggtacca gcagaaaccg 120

ggcaaagcgc cgaaactatt aatctctgct gcttctactc tgcaaagcgg cgtgccgagc 180

cgctttagcg gcagcggatc cggcaccgat ttcaccctga ccattagctc tctgcaaccg 240

gaagactttg cgacctatta ttgccagcag tactactcta cttctctgac ctttggccag 300

ggcacgaaag ttgaaattaa a 321

<210> 124
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 124

Ser Gly Asp Asn Ile Arg Lys Tyr Val Val His
1 5 10

<210> 125
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 125

Arg Asp Asn Asn Arg Pro Ser
1 5

<210> 126
<211> 10
<212> PRT

<213> 人工序列

<220>
<223> 合成肽

<400> 126

Gln Ser Trp Asp Ser Phe Leu Ala Val Val
1 5 10

<210> 127
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 127

Ser Tyr Ala Met His
1 5

<210> 128
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 128

Phe Ile Ser Ser Leu Gly Ser Tyr Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 129
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 129

Glu Thr Ala Gly Tyr Gly Tyr Ala Phe Asp Pro
1 5 10

<210> 130
<211> 120
<212> PRT
<213> 合成肽

<400> 130

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Ser Ser Leu Gly Ser Tyr Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Thr Ala Gly Tyr Gly Tyr Ala Phe Asp Pro Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 131
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 131

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Ile Arg Lys Tyr Val Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Arg Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ser Phe Leu Ala Val
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 132
<211> 360
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 132
caggtgcaat tgctggaaag cggcggtggc ctggtgcagc cgggtggcag cctgcgtctg 60

agctgcgcgg cgtccggatt caccttttct tcttacgcta tgcattgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtttccttc atctcttctc tgggttctta cacctactat 180

gcggatagcg tgaaaggccg ctttaccatc agccgcgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgaaact 300

gctggttacg gttacgcttt cgatccgtgg ggccaaggca ccctggtgac tgttagctca 360

<210> 133
<211> 321
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 133

gatatcgaac tgacccagcc gccgagcgtg agcgtgagcc cgggccagac cgcgagcatt 60

acctgtagcg gcgataacat ccgtaaatac gttgttcatt ggtaccagca gaaaccgggc 120

caggcgccgg tgctggtgat ctaccgtgac aacaaccgtc cgagcggcat cccggaacgt 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac ccaggcggaa 240

gacgaagcgg attattactg ccagtcttgg gactctttcc tggctgttgt gtttggcggc 300

ggcacgaagt taaccgtcct a 321

<210> 134
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 134

Ser Gly Ser Ser Ser Asn Ile Gly Leu Asp Tyr Val Asn
1 5 10

<210> 135
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 135

Arg Asn Lys Gln Arg Pro Ser
1 5

<210> 136
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 136

Gln Ala Trp Ala Gly Arg Thr Asn Tyr Val Val
1 5 10

<210> 137
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 137

Asn Tyr Trp Ile Gly
1 5

<210> 138
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 138

Phe Ile Asp Pro Gly Val Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 139
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 139

Val Leu Ala His Ser Thr Glu Tyr Asn Trp Pro Ala Phe
1 5 10

<210> 140
<211> 122
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 140

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Phe Ile Asp Pro Gly Val Ser Tyr Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Val Leu Ala His Ser Thr Glu Tyr Asn Trp Pro Ala Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 141
<211> 110
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 141

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Leu Asp
20 25 30

Tyr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Lys Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Ala Gly Arg Thr
85 90 95

Asn Tyr Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 142
<211> 366
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 142
caggtgcaat tggtgcagag cggtgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gctccggata tagcttcact aactactgga tcggttgggt gcgccagatg 120

ccgggcaaag gtctcgagtg gatgggcttc atcgacccgg gtgttagcta cacccgttat 180

agcccgagct ttcagggcca ggtgaccatt agcgcggata aaagcatcag caccgcgtat 240

ctgcaatgga gcagcctgaa agcgagcgat accgcgatgt attattgcgc gcgtgttctg 300

gctcattcta ctgaatacaa ctggccggct ttctggggcc aaggcaccct ggtgactgtt 360

agctca 366

<210> 143
<211> 330
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 143
gatatcgtgc tgacccagcc gccgagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagcagcag caacattggt ctggactacg tgaactggta ccagcagctg 120

ccgggcacgg cgccgaaact gctgatctac cgtaacaaac agcgcccgag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagacg aagcggatta ttactgccag gcttgggctg gtcgtactaa ctacgttgtg 300

tttggcggcg gcacgaagtt aaccgtccta 330

<210> 144
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 144

Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr Asn Tyr Val Ser
1 5 10

<210> 145
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 145

Tyr Val Ser Asn Arg Pro Ser
1 5

<210> 146
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 146

Ala Ser Tyr Thr His Gln Gly Ser Trp Val
1 5 10

<210> 147
<211> 5
<212> PRT
<213> 人工序列

<220>

<223> 合成肽

<400> 147

Thr Tyr Tyr Met His
1 5

<210> 148
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 148

Val Ile Ser Ser Asp Gly Ser Phe Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 149
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 149

His Gly Tyr Gly Ala Phe Asp Tyr
1 5

<210> 150
<211> 117
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 150

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr

20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Ser Ser Asp Gly Ser Phe Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg His Gly Tyr Gly Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 151
<211> 110
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 151

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Tyr Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Thr His Gln
85 90 95

Gly Ser Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 152
<211> 351
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 152
caggtgcaat tgctggaaag cggcggtggc ctggtgcagc cgggtggcag cctgcgtctg 60

agctgcgcgg cgtccggatt cacctttttct acttactaca tgcattgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtttccgtt atctcttctg acggttcttt caccttctat 180

gcggatagcg tgaaaggccg ctttaccatc agccgcgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcatggt 300

tacggtgctt tcgattactg gggccaaggc accctggtga ctgttagctc a 351

<210> 153
<211> 330
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 153
gatatcgcgc tgacccagcc ggcgagcgtg agcggtagcc cgggccagag cattaccatt 60

agctgcaccg gcaccagcag cgatgtgggc tcttacaact acgtgtcttg gtaccagcag 120

catccgggca aggcgccgaa actgatgatc tactacgttt ctaaccgtcc gagcggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattactgc gcttcttaca ctcatcaggg ttcttgggtg 300

tttggcggcg gcacgaagtt aaccgtccta 330

<210> 154

<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 154

Arg Ala Ser Gln Ser Ile Ser Leu Trp Leu Asn
1 5 10

<210> 155
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 155

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 156
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 156

Gln Gln Tyr Tyr Thr Ser Pro Tyr Thr
1 5

<210> 157
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 157

Ser Tyr Ala Met Ser
1 5

<210> 158
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 158

Val Ile Arg Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 159
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 159

Gly Gly Gly Tyr Phe Asp Tyr
1 5

<210> 160
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 160

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Arg Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 161
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 161

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Leu Trp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Thr Ser Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 162
<211> 348
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 162
caggtgcagc tgctggaatc aggcggcgga ctggtgcaac ctggcggatc cctgaggctg 60

agctgcgctg ctagtggctt caccttctct agctacgcta tgagctgggt ccgccaggcc 120

cctggtaaag gcctcgagtg ggtgtcagtg attagatcta gcggctctag cacctactac 180

gccgatagcg tgaagggccg gttcactatc tctagggata actctaagaa caccctgtac 240

ctgcagatga actccctgag ggccgaggac accgccgtct actactgcgc tagaggcgga 300

ggctacttcg actactgggg tcaaggcacc ctggtcaccg tgtctagc 348

<210> 163
<211> 321
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 163
gatattcaga tgactcagtc acctagtagc ctgagcgcta gtgtgggcga tagagtgact 60

atcacctgta gagcctctca gtctattagc ctgtggctga actggtatca gcagaagccc 120

ggtaaagccc ctaagctgct gatctacgcc gcctctaccc tgcagtcagg cgtgccctct 180

aggtttagcg gtagcggtag tggcaccgac ttcaccctga ctatctctag cctgcagccc 240

gaggacttcg ctacctacta ctgtcagcag tactacacta gcccctacac cttcggtcag 300

ggcactaagg tcgagattaa g 321

<210> 164
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 164

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 165
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 165

Ala Val Ser Thr Leu Gln Ser
1 5

<210> 166
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 166

Gln Gln Ser Gly Thr Phe Pro Pro Thr Thr
1 5 10

<210> 167
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 167

Ser His Gly Met His
1 5

<210> 168
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 168

Val Ile Ser Gly Ser Gly Ser Asn Thr Gly Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 169
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 169

Gln Trp Gly Ser Tyr Ala Phe Asp Ser
1 5

<210> 170
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 170

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Ser Gly Ser Gly Ser Asn Thr Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Arg Gln Trp Gly Ser Tyr Ala Phe Asp Ser Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 171
<211> 108
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 171

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Val Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Thr Phe Pro Pro
85 90 95

Thr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 172
<211> 354
<212> DNA
<213> 人工序列

<220>

<223> 合成聚核苷酸

<400> 172
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agctgcgctg ctagtggctt cacctttagc tctcacggaa tgcactgggt ccgccaggcc 120

cctggtaaag gcctcgagtg ggtgtcagtg attagcggta gcggctctaa caccggctac 180

gccgatagcg tgaagggccg gttcactatc tctagggata actctaagaa caccctgtac 240

ctgcagatga actccctgag ggccgaggac accgccgtct actactgcgc tagacagtgg 300

ggctcctacg ccttcgatag ctggggtcaa ggcaccctgg tcaccgtgtc tagc 354

<210> 173
<211> 324
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 173
gatattcaga tgactcagtc acctagtagc ctgagcgcta gtgtgggcga tagagtgact 60

atcacctgta gagcctctca gtctatctct agctacctga actggtatca gcagaagccc 120

ggtaaagccc ctaagctgct gatctacgcc gtgtctaccc tgcagtcagg cgtgccctct 180

aggtttagcg gtagcggtag tggcaccgac ttcaccctga ctattagtag cctgcagccc 240

gaggacttcg ctacctacta ctgtcagcag tcaggcacct tccccctac taccttcggt 300

cagggcacta aggtcgagat taag 324

<210> 174
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 174

Ser Gly Asp Asn Leu Arg Ser Tyr Tyr Val His
1 5 10

<210> 175
<211> 7
<212> PRT

<213> 人工序列

<220>
<223> 合成肽

<400> 175

Gly Asn Asn Lys Arg Pro Ser
1 5

<210> 176
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 176

Gly Val Tyr Thr Leu Ser Ser Val Val
1 5

<210> 177
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 177

Ser Asn Ser Ala Ala Trp Asn
1 5

<210> 178
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 178

Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 179
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 179

Gly Leu Val Gly Arg Tyr Gly Gln Pro Tyr His Phe Asp Val
1 5 10

<210> 180
<211> 126
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 180

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Gly Leu Val Gly Arg Tyr Gly Gln Pro Tyr His
100 105 110

Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115 120 125

<210> 181
<211> 106
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 181

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Leu Arg Ser Tyr Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Asn Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Val Tyr Thr Leu Ser Ser Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 182
<211> 378
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 182
caggtgcaat tgcagcagag cggtccgggc ctggtgaaac cgagccagac cctgagcctg 60

acctgcgcga tttccggaga tagcgtgagc tctaactctg ctgcttggaa ctggattcgt 120

cagagcccga gccgtggcct cgagtggctg ggccgtatct actaccgtag caaatggtac 180

aacgactatg ccgtgagcgt gaaaagccgc attaccatta acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtggtctgg ttggtcgtta cggtcagccg taccatttcg atgtttgggg ccaaggcacc 360

ctggtgactg ttagctca 378

<210> 183
<211> 318
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 183
gatatcgaac tgacccagcc gccgagcgtg agcgtgagcc cgggccagac cgcgagcatt 60

acctgtagcg gcgataacct gcgttcttac tacgttcatt ggtaccagca gaaaccgggc 120

caggcgccgg tgctggtgat ctacggtaac aacaaacgtc cgagcggcat cccggaacgt 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac ccaggcggaa 240

gacgaagcgg attattactg cggtgtttac actctgtctt ctgttgtgtt tggcggcggc 300

acgaagttaa ccgtccta 318

<210> 184
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 184

Ser Gly Asp Lys Ile Pro Thr Tyr Thr Val His
1 5 10

<210> 185
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 185

Asp Asp Asn Lys Arg Pro Ser
1 5

<210> 186
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 186

Gln Ser Thr Ala Ser Gly Thr Val Val
1 5

<210> 187
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 187

Ser Tyr Ala Leu His
1 5

<210> 188
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 188

Arg Ile Lys Ser Lys Thr Asn Gly Gly Thr Thr Asp Tyr Ala Ala Pro
1 5 10 15

Val Lys Gly

<210> 189
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 189

Val Asp Ala Thr Tyr Ser Tyr Ser Gly Tyr Tyr Tyr Pro Met Asp Tyr
1 5 10 15

<210> 190
<211> 127
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 190

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Ala Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Lys Ser Lys Thr Asn Gly Gly Thr Thr Asp Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Val Asp Ala Thr Tyr Ser Tyr Ser Gly Tyr Tyr Tyr
100 105 110

Pro Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 191
<211> 106
<212> PRT

<213> 人工序列

<220>
<223> 合成肽

<400> 191

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Ile Pro Thr Tyr Thr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Asp Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Thr Ala Ser Gly Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 192
<211> 381
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 192
caggtgcaat tggtggaaag cggcggtggc ctggtgaaac caggcggcag cctgcgcctg 60

agctgcgccg cctccggatt cacctttaac tcttacgctc tgcattgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtgggccgt atcaaatcta aaactaacgg tggtactact 180

gactatgccg ccccagtgaa aggccgcttt accattagcc gcgatgattc gaaaaacacc 240

ctgtatctgc aaatgaacag cctgaaaacc gaagatacgg ccgtgtatta ttgcgcgcgt 300

gttgacgcta cttactctta ctctggttac tactacccga tggattactg gggccaaggc 360

accctggtga ctgttagctc a 381

<210> 193
<211> 318
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 193
gatatcgaac tgacccagcc gccgagcgtg agcgtgagcc cgggccagac cgcgagcatt 60

acctgtagcg gcgataaaat cccgacttac actgttcatt ggtaccagca gaaaccgggc 120

caggcgccgg tgctggtgat ctacgacgac aacaaacgtc cgagcggcat cccggaacgt 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac ccaggcggaa 240

gacgaagcgg attattactg ccagtctact gcttctggta ctgttgtgtt tggcggcggc 300

acgaagttaa ccgtccta 318

<210> 194
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 194

Arg Ala Ser Gln Ser Ile Val Ser Tyr Leu Asn
1 5 10

<210> 195
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 195

Asp Ala Ser Ser Leu Gln Ser
1 5

<210> 196

<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 196

Gln Gln Ser Gly Ser His Ser Ile Thr
1 5

<210> 197
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 197

Ser His Trp Val His
1 5

<210> 198
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 198

Val Ile Ser Tyr Met Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 199
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 199

Gly Ser Tyr Asp Met Ala Phe Asp Val
1 5

<210> 200
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 200

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
20 25 30

Trp Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Ser Tyr Met Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ser Tyr Asp Met Ala Phe Asp Val Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 201
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 201

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Val Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser His Ser Ile
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 202
<211> 354
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 202
caggtgcagc tgctggaatc aggcggcgga ctggtgcagc ctggcggtag cctgagactg 60

agctgcgctg ctagtggctt cacctttagc tctcactggg tgcactgggt cagacaggcc 120

cctggtaaag gcctggagtg ggtgtcagtg attagctata tgggctctag cacctactac 180

gccgatagcg tgaagggccg gttcactatc tctagggata actctaagaa caccctgtac 240

ctgcagatga atagcctgag agccgaggac accgccgtct actactgcgc tagaggctcc 300

tacgatatgg ccttcgacgt gtggggtcag ggcaccctgg tcaccgtgtc tagc 354

<210> 203
<211> 321
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 203
gatattcaga tgactcagtc acctagtagc ctgagcgcta gtgtgggcga tagagtgact 60

atcacctgta gagcctctca gtctatcgtc agctacctga actggtatca gcagaagccc 120

ggtaaagccc ctaagctgct gatctacgac gcctctagcc tgcagtcagg cgtgccctct 180

aggtttagcg gtagcggtag tggcaccgac ttcaccctga ctattagtag cctgcagccc 240

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ggcactaagg tcgagattaa g 321

<210> 204
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 204

Ser Gly Asp Asn Ile Gly Ser Met Thr Ala His
1 5 10

<210> 205
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 205

Asp Lys Asn Glu Arg Pro Ser
1 5

<210> 206
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 206

Gln Ser Trp Asp Asp Ser Tyr Asn Ser Val Val
1 5 10

<210> 207
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 207

Ser Asn Ser Ala Gly Trp Asn
1 5

<210> 208
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 208

Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 209
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 209

Glu Lys Tyr Thr Val Ser Phe Tyr Asp Phe Phe Asp Tyr
1 5 10

<210> 210
<211> 125
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 210

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Gly Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Lys Tyr Thr Val Ser Phe Tyr Asp Phe Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 211
<211> 108
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 211

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Ile Gly Ser Met Thr Ala
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Asp Lys Asn Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Asp Ser Tyr Asn Ser
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 212
<211> 375
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 212
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acctgcgcga tttccggaga tagcgtgagc tctaactctg ctggttggaa ctggattcgt 120

cagagcccga gccgtggcct cgagtggctg ggccgtatct actaccgtag caaatggtac 180

aacgactatg ccgtgagcgt gaaaagccgc attaccatta acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtgaaaaat acactgtttc tttctacgac ttcttcgatt actggggcca aggcaccctg 360

gtgactgtta gctca 375

<210> 213
<211> 324
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 213
gatatcgaac tgacccagcc gccgagcgtg agcgtgagcc cgggccagac cgcgagcatt 60

acctgtagcg gcgataacat cggttctatg actgctcatt ggtaccagca gaaaccgggc 120

caggcgccgg tgctggtgat ctacgacaaa aacgaacgtc cgagcggcat cccggaacgt 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac ccaggcggaa 240

gacgaagcgg attattactg ccagtcttgg gacgactctt acaactctgt tgtgtttggc 300

ggcggcacga agttaaccgt ccta 324

<210> 214
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 214

Ser Gly Asp Ala Ile Gly Thr Lys Phe Ala His
1 5 10

<210> 215
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 215

Tyr Asp His Glu Arg Pro Ser
1 5

<210> 216
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 216

Tyr Ser Arg Ala Ser Ser Asn Leu Val
1 5

<210> 217

<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 217

Asp His Ala Ile Asp
1 5

<210> 218
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 218

Val Ile Ala Gly Ser Gly Ser Ile Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 219
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 219

Asp Thr Gly Val Tyr Arg Glu Tyr Met Asp Val
1 5 10

<210> 220
<211> 120
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 220

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp His
20 25 30

Ala Ile Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Ala Gly Ser Gly Ser Ile Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Gly Val Tyr Arg Glu Tyr Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 221
<211> 106
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 221

Ser Tyr Glu Leu Thr Gln Pro Leu Ser Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Ile Gly Thr Lys Phe Ala
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp His Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Arg Ala Ser Ser Asn Leu Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 222
<211> 360
<212> DNA
<213> 人工序列

<220>
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<400> 222
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agctgcgcgg cgtccggatt caccttttct gaccatgcta tcgactgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtttccgtt atcgctggta gcggttctat cacctactat 180

gcggatagcg tgaaaggccg ctttaccatc agccgcgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgacact 300

ggtgtttacc gtgaatacat ggatgtttgg ggccaaggca ccctggtgac tgttagctca 360

<210> 223
<211> 318
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 223
agctatgaac tgacccagcc gctgagcgtg agcgtggcgc tgggccagac cgcgcgcatt 60

acctgtagcg gcgatgctat cggtactaaa ttcgctcatt ggtaccagca gaaaccgggc 120

caggcgccgg tgctggtgat ctactacgac catgaacgtc cgagcggcat cccggaacgt 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagccgcgc gcaggcgggc 240

gacgaagcgg attattactg ctactctcgt gcttcttcta acctggtgtt tggcggcggc 300

acgaagttaa ccgtccta 318

<210> 224
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 224

Arg Ala Ser Gln Gly Ile Phe Thr Tyr Leu Asn
1 5 10

<210> 225
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 225

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 226
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 226

Gln Gln Tyr Tyr Ser Thr Ser Leu Thr
1 5

<210> 227
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 227

Ser Gln Ser Ala Ala Trp Asn
1 5

<210> 228
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 228

Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 229
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 229

Glu Arg Ser Tyr Arg Asp Tyr Phe Asp Tyr
1 5 10

<210> 230
<211> 122
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 230

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Gln
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Arg Ser Tyr Arg Asp Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 231
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 231

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Phe Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Ser Leu

85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 232
<211> 366
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 232
caggtgcagc tgcagcagtc aggccctggc ctggtcaagc ctagtcagac cctgagcctg 60

acctgcgcta ttagcggcga tagtgtgtct agtcagtcag ccgcctggaa ctggattaga 120

cagtcaccct ctaggggcct ggagtggctg ggtagaatct actataggtc taagtggtat 180

aacgactacg ccgtcagcgt gaagtctagg atcactatta accccgacac ctctaagaat 240

cagtttagcc tgcagctgaa tagcgtgacc cccgaggaca ccgccgtcta ctactgcgct 300

agagagcggt cctatagaga ctacttcgac tactggggtc agggcaccct ggtcaccgtg 360

tctagc 366

<210> 233
<211> 321
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 233
gatattcaga tgactcagtc acctagtagc ctgagcgcta gtgtgggcga tagagtgact 60

atcacctgta gagcctctca gggaatcttc acctacctga actggtatca gcagaagccc 120

ggtaaagccc ctaagctgct gatctacgcc gcctctaccc tgcagtcagg cgtgccctct 180

aggtttagcg gtagcggtag tggcaccgac ttcaccctga ctatctctag cctgcagccc 240

gaggacttcg ctacctacta ctgtcagcag tactactcta ctagcctgac cttcggtcag 300

ggcactaagg tcgagattaa g 321

<210> 234
<211> 11

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 234

Ser Gly Asp Asn Ile Gly Ser Met Thr Ala His
1 5 10

<210> 235
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 235

Asp Lys Asn Glu Arg Pro Ser
1 5

<210> 236
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 236

Gln Ser Trp Asp Asp Ser Tyr Thr Ser Val Val
1 5 10

<210> 237
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 237

Ser Gln Ser Ala Gly Trp Asn
1 5

<210> 238

<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 238

Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 239
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 239

Glu Lys Tyr Thr Val Ser Phe Tyr Asp Phe Phe Asp Tyr
1 5 10

<210> 240
<211> 125
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 240

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Gln
20 25 30

Ser Ala Gly Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Lys Tyr Thr Val Ser Phe Tyr Asp Phe Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 241
<211> 108
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 241

Ser Tyr Glu Leu Thr Gln Pro Leu Ser Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Asn Ile Gly Ser Met Thr Ala
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Asp Lys Asn Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Asp Ser Tyr Thr Ser
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 242
<211> 375
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 242
caggtgcaat tgcagcagag cggtccgggc ctggtgaaac cgagccagac cctgagcctg 60

acctgcgcga tttccggaga tagcgtgagc tctcagtctg ctggttggaa ctggattcgt 120

cagagcccga gccgtggcct cgagtggctg ggccgtatct actaccgtag caaatggtac 180

aacgactatg ccgtgagcgt gaaaagccgc attaccatta acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtgaaaaat acactgtttc tttctacgac ttcttcgatt actggggcca aggcaccctg 360

gtgactgtta gctca 375

<210> 243
<211> 324
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<400> 243
agctatgaac tgacccagcc gctgagcgtg agcgtggcgc tgggccagac cgcgcgcatt 60

acctgtagcg gcgataacat cggttctatg actgctcatt ggtaccagca gaaaccgggc 120

caggcgccgg tgctggtgat ctacgacaaa aacgaacgtc cgagcggcat cccggaacgt 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagccgcgc gcaggcgggc 240

gacgaagcgg attattactg ccagtcttgg gacgactctt acacctctgt tgtgtttggc 300

ggcggcacga agttaaccgt ccta 324

<210> 244
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 244

Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly Asn Ser Ala Lys
1 5 10 15

Val Val Tyr

<210> 245
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 245

Ile Gln Thr Leu His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His
1 5 10 15

Gln Phe Ser Phe
20

<210> 246
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 246

Phe Leu Leu Glu Glu Tyr Thr Gly Ser Asp
1 5 10

<210> 247
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 247

Ala Lys Val Val Tyr Ser Ile Leu
1 5

<210> 248
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 248

Gln Gly Gln Pro Tyr Phe Ser Val Glu Ser Glu Thr Gly Ile Ile Lys
1 5 10 15

Thr Ala Leu

<210> 249
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 249

Asp Arg Glu Asn Arg Glu Gln Tyr Gln Val Val Ile Gln
1 5 10

<210> 250
<211> 28
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 250

Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile
1 5 10 15

Lys Ala Ser Asp Ala Asp Val Gly Glu Asn Ala Glu
20 25

<210> 251
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 251

Ile Glu Tyr Ser Ile Thr Asp Gly Glu Gly Leu Asp Met
1 5 10

<210> 252
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 252

Phe Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr
1 5 10 15

<210> 253
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 253

Val Lys Lys Leu Leu Asp
1 5

<210> 254
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 254

Phe Glu Lys Lys Lys Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro
1 5 10 15

Tyr Val Glu Pro Arg Phe
20

<210> 255
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 255

Phe Glu Lys Lys Lys Val Tyr Thr Leu
1 5

<210> 256
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 256

Val Arg Ile Val Val Glu Asp
1 5

<210> 257
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 257

Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro Val Lys Tyr Ser Val Asp
1 5 10 15

Arg His Thr Asp Met
20

<210> 258
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 258

Ile Ala Thr Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu
1 5 10 15

Tyr Ile Lys Val Leu Asp Val Asn Asp Asn Ala Pro Glu Phe
20 25 30

<210> 259
<211> 23
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 259

Tyr Leu Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro Val Gln Ser
1 5 10 15

Ser Thr Gly Thr Val Thr Val
20

<210> 260
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 260

Ala Asp Val Gly Glu Asn Ala Glu Ile Glu Tyr Ser Ile Thr Asp Gly
1 5 10 15

Glu Gly Leu Asp Met
20

<210> 261
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 261

Tyr Glu Thr Phe Val Cys Glu Lys Ala Lys Ala Asp Gln Leu
1 5 10

<210> 262
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 262

Thr Arg Lys Asn Gly Tyr Asn Arg His Glu Met Ser Thr
1 5 10

<210> 263
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 263

Asp Asn Asp Tyr Pro Val Gln Ser Ser Thr Gly Thr Val Thr Val
1 5 10 15

<210> 264
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 264

Tyr Glu Thr Phe Val Cys Glu Lys Ala Lys Ala Asp Gln Leu
1 5 10

<210> 265
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 265

His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser Phe
1 5 10 15

<210> 266
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 266

Asn Lys Asp Asn Thr Ala Gly Ile Leu
1 5

<210> 267
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 267

Cys Asp His His Gly Asn Met Gln Ser Cys His Ala Glu Ala
1 5 10

<210> 268
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 268

Val Asp Lys Asp Asp Pro Tyr Ser Gly His Gln
1 5 10

<210> 269
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 269

Leu Glu Glu Tyr Thr Gly Ser Asp
1 5

<210> 270
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 270

Tyr Gln Tyr Val Gly Lys Leu
1 5

<210> 271
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 271

Tyr Gln Tyr Val Gly Lys Leu His Ser Asp Gln Asp Arg Gly Asp Gly
1 5 10 15

Ser Leu

<210> 272
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 272

Tyr Gln Tyr Val Gly Lys Leu His Ser Asp Gln Asp Arg Gly Asp Gly
1 5 10 15

Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly Ala Gly Asp Leu
20 25 30

<210> 273
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 273

Tyr Ile Leu Ser Gly Asp Gly Ala Gly Asp Leu
1 5 10

<210> 274
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 274

Phe Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala
1 5 10

<210> 275
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 275

Phe Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu
1 5 10 15

Asp Arg Glu Glu Lys Pro Val Tyr
20

<210> 276
<211> 26
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 276

Phe Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu
1 5 10 15

Asp Arg Glu Glu Lys Pro Val Tyr Ile Leu
20 25

<210> 277
<211> 28
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 277

Phe Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu
1 5 10 15

Asp Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala
20 25

<210> 278
<211> 23
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 278

Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu Asp
1 5 10 15

Arg Glu Glu Lys Pro Val Tyr
20

<210> 279
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 279

Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu Asp Arg Glu Glu Lys
1 5 10 15

Pro Val Tyr

<210> 280
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 280

Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu Asp Arg Glu Glu Lys
1 5 10 15

Pro Val Tyr Ile Leu
20

<210> 281
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 281

Thr Lys Arg Leu Asp Arg Glu Glu Lys Pro Val Tyr
1 5 10

<210> 282
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 282

Ile Leu Arg Ala Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu
1 5 10 15

Pro Glu Ser Glu
20

<210> 283
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 283

Ile Leu Arg Ala Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu
1 5 10 15

Pro Glu Ser Glu Phe
20

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<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 284

Arg Ala Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu Pro Glu
1 5 10 15

Ser Glu

<210> 285
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 285

Arg Ala Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu Pro Glu
1 5 10 15

Ser Glu Phe

<210> 286
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 286

Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu
1 5 10 15

<210> 287
<211> 17
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<213> 人工序列

<220>
<223> 合成肽

<400> 287

Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu
1 5 10 15

Phe

<210> 288
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 288

Phe Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe
1 5 10 15

<210> 289
<211> 18
<212> PRT
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<220>
<223> 合成肽

<400> 289

Phe Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr
1 5 10 15

Lys Glu

<210> 290
<211> 14
<212> PRT
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<220>
<223> 合成肽

<400> 290

Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe
1 5 10

<210> 291
<211> 15
<212> PRT
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<220>
<223> 合成肽

<400> 291

Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr
1 5 10 15

<210> 292
<211> 16
<212> PRT
<213> 人工序列

<220>
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<400> 292

Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr Lys
1 5 10 15

<210> 293
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 293

Thr Lys Glu Val Tyr Thr Ala Thr Val Pro Glu Met Ser Asp Val Gly
1 5 10 15

Thr

<210> 294
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 294

Thr Lys Glu Val Tyr Thr Ala Thr Val Pro Glu Met Ser Asp Val Gly
1 5 10 15

Thr Phe

<210> 295
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 295

Val Tyr Thr Ala Thr Val Pro Glu Met Ser Asp Val Gly Thr Phe
1 5 10 15

<210> 296
<211> 8
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<400> 296

Phe Val Val Gln Val Thr Ala Thr
1 5

<210> 297
<211> 7
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<213> 人工序列

<220>
<223> 合成肽

<400> 297

Val Val Gln Val Thr Ala Thr
1 5

<210> 298
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 298

Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly Asn
1 5 10 15

Ser

<210> 299
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 299

Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly Asn
1 5 10 15

Ser Ala Lys Val Val Tyr
20

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<211> 15
<212> PRT
<213> 人工序列

<220>
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<400> 300

Asp Ala Asp Asp Pro Thr Tyr Gly Asn Ser Ala Lys Val Val Tyr
1 5 10 15

<210> 301
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<212> PRT
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<220>
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<400> 301

Ser Ile Leu Gln Gly Gln Pro Tyr Phe
1 5

<210> 302
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<220>
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<400> 302

Gln Gly Gln Pro Tyr Phe Ser Val Glu
1 5

<210> 303
<211> 13
<212> PRT
<213> 人工序列

<220>
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<400> 303

Ser Val Glu Ser Glu Thr Gly Ile Ile Lys Thr Ala Leu
1 5 10

<210> 304
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 304

Ser Glu Thr Gly Ile Ile Lys Thr Ala Leu
1 5 10

<210> 305
<211> 9
<212> PRT
<213> 人工序列

<220>
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<400> 305

Thr Gly Ile Ile Lys Thr Ala Leu Leu
1 5

<210> 306
<211> 11
<212> PRT
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<220>
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<400> 306

Leu Asn Met Asp Arg Glu Asn Arg Glu Gln Tyr
1 5 10

<210> 307
<211> 12
<212> PRT
<213> 人工序列

<220>
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<400> 307

Leu Asn Met Asp Arg Glu Asn Arg Glu Gln Tyr Gln
1 5 10

<210> 308
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 308

Asp Arg Glu Asn Arg Glu Gln Tyr Gln
1 5

<210> 309
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 309

Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile
1 5 10 15

Lys Ala Ser Asp
20

<210> 310
<211> 26
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 310

Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile
1 5 10 15

Lys Ala Ser Asp Ala Asp Val Gly Glu Asn
20 25

<210> 311
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 311

Tyr Ser Ile Thr Asp Gly Glu Gly Leu Asp Met
1 5 10

<210> 312
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 312

Ser Ile Thr Asp Gly Glu Gly Leu Asp Met
1 5 10

<210> 313
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 313

Phe Asp Val Ile Thr Asp Gln Glu Thr Gln Glu
1 5 10

<210> 314
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 314

Phe Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val
1 5 10 15

Lys Lys Leu Leu Asp
20

<210> 315
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 315

Phe Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val
1 5 10 15

Lys Lys Leu Leu Asp Phe
20

<210> 316
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 316

Phe Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val
1 5 10 15

Lys Lys Leu Leu Asp Phe Glu Lys Lys Lys Val Tyr Thr Leu
20 25 30

<210> 317
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 317

Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys
1 5 10 15

Lys Leu Leu Asp
20

<210> 318
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 318

Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys
1 5 10 15

Lys Leu Leu Asp Phe
20

<210> 319
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 319

Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys
1 5 10 15

Leu Leu Asp Phe
20

<210> 320
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 320

Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
1 5 10

<210> 321
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 321

Gly Ile Ile Thr Val Lys Lys Leu Leu Asp Phe
1 5 10

<210> 322
<211> 28
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 322

Val Lys Lys Leu Leu Asp Phe Glu Lys Lys Lys Val Tyr Thr Leu Lys
1 5 10 15

Val Glu Ala Ser Asn Pro Tyr Val Glu Pro Arg Phe
20 25

<210> 323
<211> 8
<212> PRT
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<220>
<223> 合成肽

<400> 323

Glu Lys Lys Lys Val Tyr Thr Leu
1 5

<210> 324
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 324

Lys Val Glu Ala Ser Asn Pro Tyr Val Glu Pro Arg Phe
1 5 10

<210> 325
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 325

Val Arg Ile Val Val Glu Asp Val Asp Glu Pro Pro Val Phe Ser Lys
1 5 10 15

Leu

<210> 326
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 326

Asp Val Asp Glu Pro Pro Val Phe
1 5

<210> 327
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 327

Asp Val Asp Glu Pro Pro Val Phe Ser Lys Leu
1 5 10

<210> 328
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 328

Val Asp Glu Pro Pro Val Phe
1 5

<210> 329
<211> 10
<212> PRT
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<220>
<223> 合成肽

<400> 329

Val Asp Glu Pro Pro Val Phe Ser Lys Leu
1 5 10

<210> 330
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 330

Ala Arg Asn Pro Val Lys Tyr Ser Val Asp Arg His Thr Asp Met
1 5 10 15

<210> 331
<211> 8
<212> PRT
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<220>
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<400> 331

Ser Val Asp Arg His Thr Asp Met
1 5

<210> 332
<211> 14
<212> PRT

<213> 人工序列

<220>
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<400> 332

Asp Arg Ile Phe Asn Ile Asp Ser Gly Asn Gly Ser Ile Phe
1 5 10

<210> 333
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 333

Thr Ser Lys Leu Leu Asp Arg Glu Thr Leu
1 5 10

<210> 334
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 334

Leu Asp Arg Glu Thr Leu Leu
1 5

<210> 335
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 335

Ile Ala Thr Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu
1 5 10 15

Tyr

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<211> 14
<212> PRT
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<220>
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<400> 336

Thr Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu
1 5 10

<210> 337
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 337

Thr Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr
1 5 10 15

<210> 338
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 338

Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu
1 5 10

<210> 339
<211> 14
<212> PRT
<213> 人工序列

<220>
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<400> 339

Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr

1 5 10

<210> 340
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<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 340

Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr Ile Lys
1 5 10 15

Val Leu Asp Val Asn Asp Asn Ala Pro Glu Phe
20 25

<210> 341
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 341

Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr
1 5 10

<210> 342
<211> 14
<212> PRT
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<220>
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<400> 342

Tyr Ile Lys Val Leu Asp Val Asn Asp Asn Ala Pro Glu Phe
1 5 10

<210> 343
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<220>

<223> 合成肽

<400> 343

Ile Lys Val Leu Asp Val Asn Asp Asn Ala Pro Glu Phe
1 5 10

<210> 344
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 344

Val Cys Glu Lys Ala Lys Ala Asp Gln Leu
1 5 10

<210> 345
<211> 17
<212> PRT
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<220>
<223> 合成肽

<400> 345

Ile Gln Thr Leu His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His
1 5 10 15

Gln

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<211> 13
<212> PRT
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<220>
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<400> 346

His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His Gln
1 5 10

<210> 347

<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 347

His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser
1 5 10 15

<210> 348
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 348

Val Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser Phe
1 5 10

<210> 349
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 349

Arg Val Cys Ala Cys Asp His His Gly Asn Met Gln Ser Cys His Ala
1 5 10 15

<210> 350
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 350

Cys Asp His His Gly Asn Met Gln Ser Cys His Ala
1 5 10

<210> 351
<211> 10
<212> PRT
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<220>
<223> 合成肽

<400> 351

Gln Phe Lys Thr Pro Glu Ser Ser Pro Pro
1 5 10

<210> 352
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 352

Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile
1 5 10 15

Lys Ala Ser Asp
20

<210> 353
<211> 21
<212> PRT
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<220>
<223> 合成肽

<400> 353

Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly Arg Ile
1 5 10 15

Lys Ala Ser Asp Ala
20

<210> 354
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 354

Pro Pro Gly Thr Pro Ile Gly Arg Ile Lys Ala Ser Asp
1 5 10

<210> 355
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 355

Ala Asp Val Gly Glu Asn Ala Glu
1 5

<210> 356
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<212> PRT
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<220>
<223> 合成肽

<400> 356

Ile Glu Tyr Ser Ile Thr Asp Gly Glu Gly
1 5 10

<210> 357
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 357

Ser Ile Thr Asp Gly Glu Gly
1 5

<210> 358
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 358

Thr Asp Gly Glu Gly Leu Asp Met
1 5

<210> 359
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<220>
<223> 合成肽

<400> 359

Phe Asp Val Ile Thr Asp Gln Glu
1 5

<210> 360
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<220>
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<400> 360

Phe Asp Val Ile Thr Asp Gln Glu Thr Gln Glu
1 5 10

<210> 361
<211> 21
<212> PRT
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<220>
<223> 合成肽

<400> 361

Phe Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val
1 5 10 15

Lys Lys Leu Leu Asp
20

<210> 362
<211> 22
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<220>
<223> 合成肽

<400> 362

Phe Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val
1 5 10 15

Lys Lys Leu Leu Asp Phe
20

<210> 363
<211> 14
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<213> 人工序列

<220>
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<400> 363

Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr
1 5 10

<210> 364
<211> 20
<212> PRT
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<220>
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<400> 364

Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys
1 5 10 15

Lys Leu Leu Asp
20

<210> 365
<211> 19
<212> PRT
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<220>
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<400> 365

Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys
1 5 10 15

Leu Leu Asp

<210> 366
<211> 7
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<220>
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<400> 366

Thr Asp Gln Glu Thr Gln Glu
1 5

<210> 367
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<400> 367

Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
1 5 10 15

<210> 368
<211> 17
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<400> 368

Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
1 5 10 15

Phe

<210> 369
<211> 14
<212> PRT
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<220>
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<400> 369

Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
1 5 10

<210> 370
<211> 13
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<400> 370

Thr Gln Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
1 5 10

<210> 371
<211> 10
<212> PRT
<213> 人工序列

<220>
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<400> 371

Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
1 5 10

<210> 372
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<400> 372

Gly Ile Ile Thr Val Lys Lys Leu Leu Asp Phe

1 5 10

<210> 373
<211> 10
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<400> 373

Ile Ile Thr Val Lys Lys Leu Leu Asp Phe
1 5 10

<210> 374
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<213> 人工序列

<220>
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<400> 374

Ile Thr Val Lys Lys Leu Leu Asp
1 5

<210> 375
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<220>
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<400> 375

Ile Thr Val Lys Lys Leu Leu Asp Phe
1 5

<210> 376
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<400> 376

Thr Val Lys Lys Leu Leu Asp
1 5

<210> 377
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<400> 377

Thr Val Lys Lys Leu Leu Asp Phe
1 5

<210> 378
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<220>
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<400> 378

Val Lys Lys Leu Leu Asp Phe
1 5

<210> 379
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<400> 379

Phe Glu Lys Lys Lys Val Tyr Thr
1 5

<210> 380
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<220>
<223> 合成肽

<400> 380

Glu Lys Lys Lys Val Tyr Thr Leu
1 5

<210> 381
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<400> 381

Lys Val Glu Ala Ser Asn Pro Tyr Val Glu Pro Arg Phe
1 5 10

<210> 382
<211> 11
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<400> 382

Glu Ala Ser Asn Pro Tyr Val Glu Pro Arg Phe
1 5 10

<210> 383
<211> 11
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<220>
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<400> 383

Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala Thr
1 5 10

<210> 384
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<400> 384

Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala Thr Val
1 5 10

<210> 385
<211> 9
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<220>
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<400> 385

Leu Gly Pro Phe Lys Asp Ser Ala Thr
1 5

<210> 386
<211> 14
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<220>
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<400> 386

Val Arg Ile Val Val Glu Asp Val Asp Glu Pro Pro Val Phe
1 5 10

<210> 387
<211> 17
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<220>
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<400> 387

Val Arg Ile Val Val Glu Asp Val Asp Glu Pro Pro Val Phe Ser Lys
1 5 10 15

Leu

<210> 388
<211> 11
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<213> 人工序列

<220>
<223> 合成肽

<400> 388

Val Val Glu Asp Val Asp Glu Pro Pro Val Phe
1 5 10

<210> 389
<211> 8
<212> PRT
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<220>
<223> 合成肽

<400> 389

Asp Val Asp Glu Pro Pro Val Phe
1 5

<210> 390
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<400> 390

Asp Val Asp Glu Pro Pro Val Phe Ser Lys Leu
1 5 10

<210> 391
<211> 13
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<220>
<223> 合成肽

<400> 391

Asp Val Asp Glu Pro Pro Val Phe Ser Lys Leu Ala Tyr
1 5 10

<210> 392
<211> 7

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 392

Val Asp Glu Pro Pro Val Phe
1 5

<210> 393
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 393

Val Asp Glu Pro Pro Val Phe Ser Lys Leu
1 5 10

<210> 394
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 394

Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro Val Lys Tyr
1 5 10

<210> 395
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 395

Ala Arg Asn Pro Val Lys Tyr Ser Val Asp Arg His Thr Asp Met
1 5 10 15

<210> 396

<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 396

Val Asp Arg His Thr Asp Met
1 5

<210> 397
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 397

Asp Arg Ile Phe Asn Ile Asp Ser Gly Asn Gly Ser Ile Phe
1 5 10

<210> 398
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 398

Thr Ser Lys Leu Leu Asp Arg Glu Thr Leu
1 5 10

<210> 399
<211> 7
<212> PRT
<213> 人工序列

<220>
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<400> 399

Leu Asp Arg Glu Thr Leu Leu
1 5

<210> 400
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 400

Ile Ala Thr Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu
1 5 10 15

<210> 401
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 401

Ile Ala Thr Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu
1 5 10 15

Tyr

<210> 402
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 402

Thr Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr
1 5 10 15

<210> 403
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 403

Thr Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr Ile
1 5 10 15

Lys Val

<210> 404
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 404

Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu
1 5 10

<210> 405
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 405

Glu Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr
1 5 10

<210> 406
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 406

Ile Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr
1 5 10

<210> 407
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 407

Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu
1 5 10

<210> 408
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 408

Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr Ile
1 5 10

<210> 409
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 409

Tyr Ile Lys Val Leu Asp Val Asn Asp Asn Ala Pro Glu Phe
1 5 10

<210> 410
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 410

Ile Lys Val Leu Asp Val Asn Asp
1 5

<210> 411
<211> 13
<212> PRT

<213> 人工序列

<220>
<223> 合成肽

<400> 411

Ile Lys Val Leu Asp Val Asn Asp Asn Ala Pro Glu Phe
1 5 10

<210> 412
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 412

Lys Val Leu Asp Val Asn Asp Asn Ala Pro Glu Phe
1 5 10

<210> 413
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 413

Leu Asp Val Asn Asp Asn Ala Pro Glu Phe
1 5 10

<210> 414
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 414

Phe Val Cys Glu Lys Ala Lys Ala Asp Gln Leu
1 5 10

<210> 415
<211> 10

OnCusp
Ex. 1002

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 415

Val Cys Glu Lys Ala Lys Ala Asp Gln Leu
1 5 10

<210> 416
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 416

Lys Ala Lys Ala Asp Gln Leu
1 5

<210> 417
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 417

Ile Gln Thr Leu His Ala Val Asp
1 5

<210> 418
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 418

Ile Gln Thr Leu His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His
1 5 10 15

Gln

<210> 419
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 419

Ile Gln Thr Leu His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His
1 5 10 15

Gln Phe Ser

<210> 420
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 420

Ile Gln Thr Leu His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His
1 5 10 15

Gln Phe Ser Phe
20

<210> 421
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 421

His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His Gln
1 5 10

<210> 422
<211> 15

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 422

His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser
1 5 10 15

<210> 423
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 423

Val Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser Phe
1 5 10

<210> 424
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 424

Ile Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu Met Ser Thr
1 5 10 15

<210> 425
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 425

Arg Lys Asn Gly Tyr Asn Arg His Glu Met Ser Thr
1 5 10

<210> 426

<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 426

Tyr Leu Leu Pro Val Val Ile Ser
1 5

<210> 427
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 427

Tyr Leu Leu Pro Val Val Ile Ser Asp Asn Asp Tyr
1 5 10

<210> 428
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 428

Tyr Leu Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro Val Gln
1 5 10 15

<210> 429
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 429

Pro Val Val Ile Ser Asp Asn Asp Tyr Pro Val Gln Ser Ser Thr Gly
1 5 10 15

Thr Val Thr Val
20

<210> 430
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 430

Arg Val Cys Ala Cys Asp His His Gly Asn Met Gln Ser Cys
1 5 10

<210> 431
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 431

Arg Val Cys Ala Cys Asp His His Gly Asn Met Gln Ser Cys His Ala
1 5 10 15

<210> 432
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 432

Cys Asp His His Gly Asn Met Gln Ser Cys
1 5 10

<210> 433
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 433

Cys Asp His His Gly Asn Met Gln Ser Cys His Ala
1 5 10

<210> 434
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 434

Asp His His Gly Asn Met Gln Ser Cys His Ala
1 5 10

<210> 435
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 435

Leu Ile His Pro Thr Gly Leu Ser Thr Gly Ala Gly Ser Glu
1 5 10

<210> 436
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 436

Phe Arg His Asp Ser Gly Leu
1 5

<210> 437
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 437

Phe Arg His Asp Ser Gly Leu Asn Asp
1 5

<210> 438
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 438

Glu Ala Gln Lys Ile Glu Trp His
1 5

<210> 439
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 439

Glu Ala Gln Lys Ile Glu Trp His Glu
1 5

<210> 440
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 440

Glu Phe Arg His Asp Ser
1 5

<210> 441
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 441

Leu Glu Val Leu Phe Gln Gly Pro
1 5

<210> 442
<211> 790
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 442

Met Arg Thr Tyr Arg Tyr Phe Leu Leu Leu Phe Trp Val Gly Gln Pro
1 5 10 15

Tyr Pro Thr Leu Ser Thr Pro Leu Ser Lys Arg Thr Ser Gly Phe Pro
20 25 30

Ala Lys Lys Arg Ala Leu Glu Leu Ser Gly Asn Ser Lys Asn Glu Leu
35 40 45

Asn Arg Ser Lys Arg Ser Trp Met Trp Asn Gln Phe Phe Leu Leu Glu
50 55 60

Glu Tyr Thr Gly Ser Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp
65 70 75 80

Gln Asp Arg Gly Asp Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly
85 90 95

Ala Gly Asp Leu Phe Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala
100 105 110

Thr Lys Arg Leu Asp Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala
115 120 125

Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu
130 135 140

Phe Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr
145 150 155 160

Lys Glu Val Tyr Thr Ala Thr Val Pro Glu Met Ser Asp Val Gly Thr
165 170 175

Phe Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly
180 185 190

Asn Ser Ala Lys Val Val Tyr Ser Ile Leu Gln Gly Gln Pro Tyr Phe
195 200 205

Ser Val Glu Ser Glu Thr Gly Ile Ile Lys Thr Ala Leu Leu Asn Met
210 215 220

Asp Arg Glu Asn Arg Glu Gln Tyr Gln Val Val Ile Gln Ala Lys Asp
225 230 235 240

Met Gly Gly Gln Met Gly Gly Leu Ser Gly Thr Thr Thr Val Asn Ile
245 250 255

Thr Leu Thr Asp Val Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr
260 265 270

Tyr Gln Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly
275 280 285

Arg Ile Lys Ala Ser Asp Ala Asp Val Gly Glu Asn Ala Glu Ile Glu
290 295 300

Tyr Ser Ile Thr Asp Gly Glu Gly Leu Asp Met Phe Asp Val Ile Thr
305 310 315 320

Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
325 330 335

Phe Glu Lys Lys Lys Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro
340 345 350

Tyr Val Glu Pro Arg Phe Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala
355 360 365

Thr Val Arg Ile Val Val Glu Asp Val Asp Glu Pro Pro Val Phe Ser

370 375 380

Lys Leu Ala Tyr Ile Leu Gln Ile Arg Glu Asp Ala Gln Ile Asn Thr
385 390 395 400

Thr Ile Gly Ser Val Thr Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro
405 410 415

Val Lys Tyr Ser Val Asp Arg His Thr Asp Met Asp Arg Ile Phe Asn
420 425 430

Ile Asp Ser Gly Asn Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp Arg
435 440 445

Glu Thr Leu Leu Trp His Asn Ile Thr Val Ile Ala Thr Glu Ile Asn
450 455 460

Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr Ile Lys Val Leu Asp
465 470 475 480

Val Asn Asp Asn Ala Pro Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val
485 490 495

Cys Glu Lys Ala Lys Ala Asp Gln Leu Ile Gln Thr Leu His Ala Val
500 505 510

Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser Phe Ser Leu Ala
515 520 525

Pro Glu Ala Ala Ser Gly Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp
530 535 540

Asn Thr Ala Gly Ile Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu
545 550 555 560

Met Ser Thr Tyr Leu Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro
565 570 575

Val Gln Ser Ser Thr Gly Thr Val Thr Val Arg Val Cys Ala Cys Asp
580 585 590

His His Gly Asn Met Gln Ser Cys His Ala Glu Ala Leu Ile His Pro
595 600 605

Thr Gly Leu Ser Thr Gly Ala Leu Val Ala Ile Leu Leu Cys Ile Val
610 615 620

Ile Leu Leu Val Thr Val Val Leu Phe Ala Ala Leu Arg Arg Gln Arg
625 630 635 640

Lys Lys Glu Pro Leu Ile Ile Ser Lys Glu Asp Ile Arg Asp Asn Ile
645 650 655

Val Ser Tyr Asn Asp Glu Gly Gly Gly Glu Glu Asp Thr Gln Ala Phe
660 665 670

Asp Ile Gly Thr Leu Arg Asn Pro Glu Ala Ile Glu Asp Asn Lys Leu
675 680 685

Arg Arg Asp Ile Val Pro Glu Ala Leu Phe Leu Pro Arg Arg Thr Pro
690 695 700

Thr Ala Arg Asp Asn Thr Asp Val Arg Asp Phe Ile Asn Gln Arg Leu
705 710 715 720

Lys Glu Asn Asp Thr Asp Pro Thr Ala Pro Pro Tyr Asp Ser Leu Ala
725 730 735

Thr Tyr Ala Tyr Glu Gly Thr Gly Ser Val Ala Asp Ser Leu Ser Ser
740 745 750

Leu Glu Ser Val Thr Thr Asp Ala Asp Gln Asp Tyr Asp Tyr Leu Ser
755 760 765

Asp Trp Gly Pro Arg Phe Lys Lys Leu Ala Asp Met Tyr Gly Gly Val
770 775 780

Asp Ser Asp Lys Asp Ser
785 790

<210> 443
<211> 119
<212> PRT

<213> 人工序列

<220>
<223> 合成肽

<400> 443

Glu Phe Tyr Glu Thr Phe Val Cys Glu Lys Ala Lys Ala Asp Gln Leu
1 5 10 15

Ile Gln Thr Leu His Ala Val Asp Lys Asp Asp Pro Tyr Ser Gly His
20 25 30

Gln Phe Ser Phe Ser Leu Ala Pro Glu Ala Ala Ser Gly Ser Asn Phe
35 40 45

Thr Ile Gln Asp Asn Lys Asp Asn Thr Ala Gly Ile Leu Thr Arg Lys
50 55 60

Asn Gly Tyr Asn Arg His Glu Met Ser Thr Tyr Leu Leu Pro Val Val
65 70 75 80

Ile Ser Asp Asn Asp Tyr Pro Val Gln Ser Ser Thr Gly Thr Val Thr
85 90 95

Val Arg Val Cys Ala Cys Asp His His Gly Asn Met Gln Ser Cys His
100 105 110

Ala Glu Ala Leu Ile His Pro
115

<210> 444
<211> 225
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 444

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Ser Gly Ser Gly Ser Asn Thr Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Trp Gly Ser Tyr Ala Phe Asp Ser Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His
225

<210> 445

OnCusp
Ex. 1002

<211> 215
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 445

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Val Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Thr Phe Pro Pro
85 90 95

Thr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 446
<211> 223
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 446

Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Arg Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

<210> 447
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 447

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Leu Trp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Thr Ser Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

申請專利範圍

1. 一種抗體藥結合物，其具有下式：

$$Ab\text{-}(L\text{-}(D)_m)_n$$

或其醫藥學上可接受之鹽；其中

Ab為特異性結合CDH6之胞外域(SEQ ID NO: 4)的抗體或其抗原結合片段；

L為連接子；

D為藥物部分；

m為整數1至8；及

n為整數1至10。

2. 如請求項1之抗體藥結合物，其中該抗體或抗原結合片段特異性結合至SEQ ID NO: 443之人類CDH6抗原決定基。

3. 如請求項1至2中任一項之抗體藥結合物，其中該抗體或其抗原結合片段包含：

(i)輕鏈可變區，其包含(a) SEQ ID NO: 164之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 165之LCDR2、(c) SEQ ID NO: 166之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 167之HCDR1、(e) SEQ ID NO: 168之HCDR2及(f) SEQ ID NO: 169之HCDR3；

(ii)輕鏈可變區，其包含(a) SEQ ID NO: 154之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 155之LCDR2、(c) SEQ ID NO: 156之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 157之HCDR1、(e) SEQ ID NO: 158之HCDR2及(f) SEQ ID NO: 159之HCDR3；

(iii)輕鏈可變區，其包含(a) SEQ ID NO: 194之LCDR1 (CDR-

互補決定區)、(b) SEQ ID NO: 195之LCDR2、(c) SEQ ID NO: 196之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 197之HCDR1、(e) SEQ ID NO: 198之HCDR2及(f) SEQ ID NO: 199之HCDR3；

(iv)輕鏈可變區，其包含(a) SEQ ID NO: 224之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 225之LCDR2、(c) SEQ ID NO: 226之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 227之HCDR1、(e) SEQ ID NO: 228之HCDR2及(f) SEQ ID NO: 229之HCDR3；

(v)輕鏈可變區，其包含(a) SEQ ID NO: 14之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 15之LCDR2、(c) SEQ ID NO: 16之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 17之HCDR1、(e) SEQ ID NO: 18之HCDR2及(f) SEQ ID NO: 19之HCDR3；

(vi)輕鏈可變區，其包含(a) SEQ ID NO: 24之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 25之LCDR2、(c) SEQ ID NO: 26之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 27之HCDR1、(e) SEQ ID NO: 28之HCDR2及(f) SEQ ID NO: 29之HCDR3；

(vii)輕鏈可變區，其包含(a) SEQ ID NO: 34之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 35之LCDR2、(c) SEQ ID NO: 36之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 37之HCDR1、(e) SEQ ID NO: 38之HCDR2及(f) SEQ ID NO: 39之HCDR3；

(viii)輕鏈可變區，其包含(a) SEQ ID NO: 44之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 45之LCDR2、(c) SEQ ID NO: 46

之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 47之HCDR1、(e) SEQ ID NO: 48之HCDR2及(f) SEQ ID NO: 49之HCDR3；

(ix)輕鏈可變區，其包含(a) SEQ ID NO: 54之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 55之LCDR2、(c) SEQ ID NO: 56之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 57之HCDR1、(e) SEQ ID NO: 58之HCDR2及(f) SEQ ID NO: 59之HCDR3；

(x)輕鏈可變區，其包含(a) SEQ ID NO: 64之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 65之LCDR2、(c) SEQ ID NO: 66之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 67之HCDR1、(e) SEQ ID NO: 68之HCDR2及(f) SEQ ID NO: 69之HCDR3；

(xi)輕鏈可變區，其包含(a) SEQ ID NO: 74之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 75之LCDR2、(c) SEQ ID NO: 76之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 77之HCDR1、(e) SEQ ID NO: 78之HCDR2及(f) SEQ ID NO: 79之HCDR3；

(xii)輕鏈可變區，其包含(a) SEQ ID NO: 84之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 85之LCDR2、(c) SEQ ID NO: 86之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 87之HCDR1、(e) SEQ ID NO: 88之HCDR2及(f) SEQ ID NO: 89之HCDR3；

(xiii)輕鏈可變區，其包含(a) SEQ ID NO: 94之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 95之LCDR2、(c) SEQ ID NO: 96之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 97之

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HCDR1、(e) SEQ ID NO: 98之HCDR2及(f) SEQ ID NO: 99之HCDR3；

(xiv)輕鏈可變區，其包含(a) SEQ ID NO: 104之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 105之LCDR2、(c) SEQ ID NO: 106之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 107之HCDR1、(e) SEQ ID NO: 108之HCDR2及(f) SEQ ID NO: 109之HCDR3；

(xv)輕鏈可變區，其包含(a) SEQ ID NO: 114之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 115之LCDR2、(c) SEQ ID NO: 116之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 117之HCDR1、(e) SEQ ID NO: 118之HCDR2及(f) SEQ ID NO: 119之HCDR3；

(xvi)輕鏈可變區，其包含(a) SEQ ID NO: 124之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 125之LCDR2、(c) SEQ ID NO: 126之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 127之HCDR1、(e) SEQ ID NO: 128之HCDR2及(f) SEQ ID NO: 129之HCDR3；

(xvii)輕鏈可變區，其包含(a) SEQ ID NO: 134之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 135之LCDR2、(c) SEQ ID NO: 136之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 137之HCDR1、(e) SEQ ID NO: 138之HCDR2及(f) SEQ ID NO: 139之HCDR3；

(xviii)輕鏈可變區，其包含(a) SEQ ID NO: 144之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 145之LCDR2、(c) SEQ ID NO: 146之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 147之HCDR1、(e) SEQ ID NO: 148之HCDR2及(f) SEQ ID NO: 149

之HCDR3；

(xix)輕鏈可變區，其包含(a) SEQ ID NO: 174之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 175之LCDR2、(c) SEQ ID NO: 176之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 177之HCDR1、(e) SEQ ID NO: 178之HCDR2及(f) SEQ ID NO: 179之HCDR3；

(xx)輕鏈可變區，其包含(a) SEQ ID NO: 184之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 185之LCDR2、(c) SEQ ID NO: 186之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 187之HCDR1、(e) SEQ ID NO: 188之HCDR2及(f) SEQ ID NO: 189之HCDR3；

(xxi)輕鏈可變區，其包含(a) SEQ ID NO: 204之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 205之LCDR2、(c) SEQ ID NO: 206之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 207之HCDR1、(e) SEQ ID NO: 208之HCDR2及(f) SEQ ID NO: 209之HCDR3；

(xxii)輕鏈可變區，其包含(a) SEQ ID NO: 214之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 215之LCDR2、(c) SEQ ID NO: 216之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 217之HCDR1、(e) SEQ ID NO: 218之HCDR2及(f) SEQ ID NO: 219之HCDR3；或

(xxiii)輕鏈可變區，其包含(a) SEQ ID NO: 234之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 235之LCDR2、(c) SEQ ID NO: 236之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 237之HCDR1、(e) SEQ ID NO: 238之HCDR2及(f) SEQ ID NO: 239之HCDR3。

4. 如請求項1或2之抗體藥結合物，其中CDR內之至少一個胺基酸經表5或6中之另一種抗CDH6抗體之相應CDR之相應殘基取代。

5. 如請求項1或2之抗體藥結合物，其中CDR內之一或兩個胺基酸已經修飾、缺失或取代。

6. 如請求項1或2之抗體藥結合物，其中該抗體或其抗原結合片段包含：

(i)包含SEQ ID NO: 170之重鏈可變區(vH)及包含SEQ ID NO: 171之輕鏈可變區(vL)；

(ii)包含SEQ ID NO: 160之重鏈可變區(vH)及包含SEQ ID NO: 161之輕鏈可變區(vL)；

(iii)包含SEQ ID NO: 200之重鏈可變區(vH)及包含SEQ ID NO: 201之輕鏈可變區(vL)；

(iv)包含SEQ ID NO: 230之重鏈可變區(vH)及包含SEQ ID NO: 231之輕鏈可變區(vL)；

(v)包含SEQ ID NO: 20之重鏈可變區(vH)及包含SEQ ID NO: 21之輕鏈可變區(vL)；

(vi)包含SEQ ID NO: 30之重鏈可變區(vH)及包含SEQ ID NO: 31之輕鏈可變區(vL)；

(vii)包含SEQ ID NO: 40之重鏈可變區(vH)及包含SEQ ID NO: 41之輕鏈可變區(vL)；

(viii)包含SEQ ID NO: 50之重鏈可變區(vH)及包含SEQ ID NO: 51之輕鏈可變區(vL)；

(ix)包含SEQ ID NO: 60之重鏈可變區(vH)及包含SEQ ID NO: 61之輕鏈可變區(vL)；

(x)包含SEQ ID NO: 70之重鏈可變區(vH)及包含SEQ ID NO: 71之輕鏈可變區(vL)；

(xi)包含SEQ ID NO: 80之重鏈可變區(vH)及包含SEQ ID NO: 81之輕鏈可變區(vL)；

(xii)包含SEQ ID NO: 90之重鏈可變區(vH)及包含SEQ ID NO: 91之輕鏈可變區(vL)；

(xiii)包含SEQ ID NO: 100之重鏈可變區(vH)及包含SEQ ID NO: 101之輕鏈可變區(vL)；

(xiv)包含SEQ ID NO: 110之重鏈可變區(vH)及包含SEQ ID NO: 111之輕鏈可變區(vL)；

(xv)包含SEQ ID NO: 120之重鏈可變區(vH)及包含SEQ ID NO: 121之輕鏈可變區(vL)；

(xvi)包含SEQ ID NO: 130之重鏈可變區(vH)及包含SEQ ID NO: 131之輕鏈可變區(vL)；

(xvii)包含SEQ ID NO: 140之重鏈可變區(vH)及包含SEQ ID NO: 141之輕鏈可變區(vL)；

(xviii)包含SEQ ID NO: 150之重鏈可變區(vH)及包含SEQ ID NO: 151之輕鏈可變區(vL)；

(xix)包含SEQ ID NO: 180之重鏈可變區(vH)及包含SEQ ID NO: 181之輕鏈可變區(vL)；

(xx)包含SEQ ID NO: 190之重鏈可變區(vH)及包含SEQ ID NO: 191之輕鏈可變區(vL)；

(xxi)包含SEQ ID NO: 210之重鏈可變區(vH)及包含SEQ ID NO: 211之輕鏈可變區(vL)；

(xxii)包含SEQ ID NO: 220之重鏈可變區(vH)及包含SEQ ID NO: 221之輕鏈可變區(vL)；或

(xxiii)包含SEQ ID NO: 240之重鏈可變區(vH)及包含SEQ ID NO: 241之輕鏈可變區(vL)。

7. 如請求項1或2之抗體藥結合物，其中該抗體為單株抗體、嵌合抗體、人類化抗體、經工程改造之人類抗體、人類抗體、單鏈抗體(scFv)或抗體片段。

8. 如請求項1或2之抗體藥結合物，其中該連接子衍生自選自由以下組成之群的交聯試劑：N-丁二醯亞胺基-4-(2-吡啶基二硫基)2-磺基-丁酸酯(磺基-SPDB)、N-丁二醯亞胺基-3-(2-吡啶基二硫基)丙酸酯(SPDP)、N-丁二醯亞胺基4-(2-吡啶基二硫基)戊酸酯(SPP)、N-丁二醯亞胺基4-(2-吡啶基二硫基)丁酸酯(SPDB)、N-丁二醯亞胺基碘乙酸酯(SIA)、N-丁二醯亞胺基(4-碘乙醯基)胺基苯甲酸酯(SIAB)、順丁烯二醯亞胺PEG NHS、N-丁二醯亞胺基4-(順丁烯二醯亞胺基甲基)環己烷甲酸酯(SMCC)、N-磺基丁二醯亞胺基4-(順丁烯二醯亞胺基甲基)環己烷甲酸酯(磺基-SMCC)或17-(2,5-二側氧基-2,5-二氫-1H-吡咯-1-基)-5,8,11,14-四側氧基-4,7,10,13-四氮雜十七烷-1-酸2,5-二側氧基吡咯啶-1-基酯(CX1-1)。

9. 如請求項8之抗體藥結合物，其中該連接子衍生自N-丁二醯亞胺基-4-(2-吡啶基二硫基)2-磺基-丁酸酯(磺基-SPDB)。

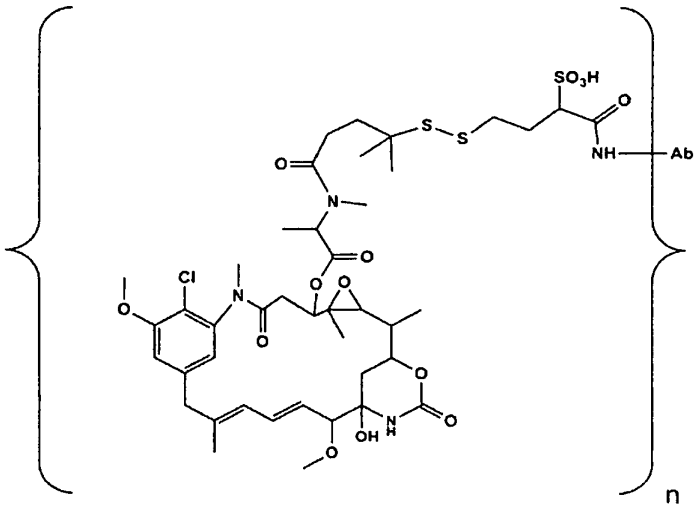
10. 如請求項1或2之抗體藥結合物，其中該藥物部分(D)係選自由以下組成之群：類美登素(maytansinoid)、V-ATP酶抑制劑、促細胞凋亡劑、Bcl2抑制劑、MCL1抑制劑、HSP90抑制劑、IAP抑制劑、mTor抑制劑、微管穩定劑、微管去穩定劑、奧瑞他汀(auristatin)、海兔毒素(dolastatin)、MetAP (甲硫胺酸胺基肽酶)、核輸出蛋白CRM1之抑制劑、DPPIV抑制劑、蛋白酶體抑制劑、粒線體中之磷醯基轉移反應之抑制劑、蛋白質合成抑制劑、激酶抑制劑、CDK2抑制劑、CDK9抑制劑、驅動蛋白抑制劑、HDAC抑制劑、DNA損傷劑、DNA烷化劑、DNA嵌入劑、

DNA小凹槽結合劑及DHFR抑制劑。

11. 如請求項10之抗體藥結合物，其中該類美登素為N(2')-去乙醯基-N2-(4-巰基-4-甲基-1-側氧基戊基)-美登素(DM4)或N(2')-去乙醯基-N(2')-(3-巰基-1-側氧基丙基)-美登素(DM1)。

12. 如請求項1或2之抗體藥結合物，其與表18中所列之治療劑組合。

13. 一種抗體藥結合物，其具有下式：



Ab-磺基-SPDB-DM4

或其醫藥學上可接受之鹽，其中：

Ab為在(SEQ ID NO: 4)處特異性結合至人類CDH6抗原決定基的抗體或其抗原結合片段，且n為整數1至10。

14. 如請求項13之抗體藥結合物，其中該抗體或其抗原結合片段在(SEQ ID NO: 443)處特異性結合人類CDH6。

15. 如請求項13之抗體藥結合物，其中該Ab為包含以下之抗體或其抗原結合片段：

(i)輕鏈可變區，其包含(a) SEQ ID NO: 164之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 165之LCDR2、(c) SEQ ID NO: 166之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 167之

HCDR1、(e) SEQ ID NO: 168之HCDR2及(f) SEQ ID NO: 169之HCDR3；

(ii)輕鏈可變區，其包含(a) SEQ ID NO: 154之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 155之LCDR2、(c) SEQ ID NO: 156之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 157之HCDR1、(e) SEQ ID NO: 158之HCDR2及(f) SEQ ID NO: 159之HCDR3；

(iii)輕鏈可變區，其包含(a) SEQ ID NO: 194之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 195之LCDR2、(c) SEQ ID NO: 196之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 197之HCDR1、(e) SEQ ID NO: 198之HCDR2及(f) SEQ ID NO: 199之HCDR3；

(iv)輕鏈可變區，其包含(a) SEQ ID NO: 224之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 225之LCDR2、(c) SEQ ID NO: 226之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 227之HCDR1、(e) SEQ ID NO: 228之HCDR2及(f) SEQ ID NO: 229之HCDR3；

(v)輕鏈可變區，其包含(a) SEQ ID NO: 14之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 15之LCDR2、(c) SEQ ID NO: 16之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 17之HCDR1、(e) SEQ ID NO: 18之HCDR2及(f) SEQ ID NO: 19之HCDR3；

(vi)輕鏈可變區，其包含(a) SEQ ID NO: 24之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 25之LCDR2、(c) SEQ ID NO: 26之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 27之HCDR1、(e) SEQ ID NO: 28之HCDR2及(f) SEQ ID NO: 29之

HCDR3；

(vii)輕鏈可變區，其包含(a) SEQ ID NO: 34之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 35之LCDR2、(c) SEQ ID NO: 36之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 37之HCDR1、(e) SEQ ID NO: 38之HCDR2及(f) SEQ ID NO: 39之HCDR3；

(viii)輕鏈可變區，其包含(a) SEQ ID NO: 44之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 45之LCDR2、(c) SEQ ID NO: 46之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 47之HCDR1、(e) SEQ ID NO: 48之HCDR2及(f) SEQ ID NO: 49之HCDR3；

(ix)輕鏈可變區，其包含(a) SEQ ID NO: 54之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 55之LCDR2、(c) SEQ ID NO: 56之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 57之HCDR1、(e) SEQ ID NO: 58之HCDR2及(f) SEQ ID NO: 59之HCDR3；

(x)輕鏈可變區，其包含(a) SEQ ID NO: 64之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 65之LCDR2、(c) SEQ ID NO: 66之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 67之HCDR1、(e) SEQ ID NO: 68之HCDR2及(f) SEQ ID NO: 69之HCDR3；

(xi)輕鏈可變區，其包含(a) SEQ ID NO: 74之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 75之LCDR2、(c) SEQ ID NO: 76之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 77之HCDR1、(e) SEQ ID NO: 78之HCDR2及(f) SEQ ID NO: 79之HCDR3；

(xii)輕鏈可變區，其包含(a) SEQ ID NO: 84之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 85之LCDR2、(c) SEQ ID NO: 86之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 87之HCDR1、(e) SEQ ID NO: 88之HCDR2及(f) SEQ ID NO: 89之HCDR3；

(xiii)輕鏈可變區，其包含(a) SEQ ID NO: 94之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 95之LCDR2、(c) SEQ ID NO: 96之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 97之HCDR1、(e) SEQ ID NO: 98之HCDR2及(f) SEQ ID NO: 99之HCDR3；

(xiv)輕鏈可變區，其包含(a) SEQ ID NO: 104之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 105之LCDR2、(c) SEQ ID NO: 106之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 107之HCDR1、(e) SEQ ID NO: 108之HCDR2及(f) SEQ ID NO: 109之HCDR3；

(xv)輕鏈可變區，其包含(a) SEQ ID NO: 114之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 115之LCDR2、(c) SEQ ID NO: 116之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 117之HCDR1、(e) SEQ ID NO: 118之HCDR2及(f) SEQ ID NO: 119之HCDR3；

(xvi)輕鏈可變區，其包含(a) SEQ ID NO: 124之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 125之LCDR2、(c) SEQ ID NO: 126之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 127之HCDR1、(e) SEQ ID NO: 128之HCDR2及(f) SEQ ID NO: 129之HCDR3；

(xvii)輕鏈可變區，其包含(a) SEQ ID NO: 134之LCDR1 (CDR-

互補決定區)、(b) SEQ ID NO: 135之LCDR2、(c) SEQ ID NO: 136之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 137之HCDR1、(e) SEQ ID NO: 138之HCDR2及(f) SEQ ID NO: 139之HCDR3；

(xviii)輕鏈可變區，其包含(a) SEQ ID NO: 144之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 145之LCDR2、(c) SEQ ID NO: 146之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 147之HCDR1、(e) SEQ ID NO: 148之HCDR2及(f) SEQ ID NO: 149之HCDR3；

(xix)輕鏈可變區，其包含(a) SEQ ID NO: 174之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 175之LCDR2、(c) SEQ ID NO: 176之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 177之HCDR1、(e) SEQ ID NO: 178之HCDR2及(f) SEQ ID NO: 179之HCDR3；

(xx)輕鏈可變區，其包含(a) SEQ ID NO: 184之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 185之LCDR2、(c) SEQ ID NO: 186之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 187之HCDR1、(e) SEQ ID NO: 188之HCDR2及(f) SEQ ID NO: 189之HCDR3；

(xxi)輕鏈可變區，其包含(a) SEQ ID NO: 204之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 205之LCDR2、(c) SEQ ID NO: 206之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 207之HCDR1、(e) SEQ ID NO: 208之HCDR2及(f) SEQ ID NO: 209之HCDR3；

(xxii)輕鏈可變區，其包含(a) SEQ ID NO: 214之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 215之LCDR2、(c) SEQ ID NO:

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216之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 217之HCDR1、(e) SEQ ID NO: 218之HCDR2及(f) SEQ ID NO: 219之HCDR3；或

(xxiii)輕鏈可變區，其包含(a) SEQ ID NO: 234之LCDR1(CDR-互補決定區)、(b) SEQ ID NO: 235之LCDR2、(c) SEQ ID NO: 236之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 237之HCDR1、(e) SEQ ID NO: 238之HCDR2及(f) SEQ ID NO: 239之HCDR3。

16. 如請求項15之抗體藥結合物，其中該抗體或其抗原結合片段包含：

(i)包含SEQ ID NO: 170之重鏈可變區(vH)及包含SEQ ID NO: 171之輕鏈可變區(vL)；

(ii)包含SEQ ID NO: 160之重鏈可變區(vH)及包含SEQ ID NO: 161之輕鏈可變區(vL)；

(iii)包含SEQ ID NO: 200之重鏈可變區(vH)及包含SEQ ID NO: 201之輕鏈可變區(vL)；

(iv)包含SEQ ID NO: 230之重鏈可變區(vH)及包含SEQ ID NO: 231之輕鏈可變區(vL)；

(v)包含SEQ ID NO: 20之重鏈可變區(vH)及包含SEQ ID NO: 21之輕鏈可變區(vL)；

(vi)包含SEQ ID NO: 30之重鏈可變區(vH)及包含SEQ ID NO: 31之輕鏈可變區(vL)；

(vii)包含SEQ ID NO: 40之重鏈可變區(vH)及包含SEQ ID NO: 41之輕鏈可變區(vL)；

(viii)包含SEQ ID NO: 50之重鏈可變區(vH)及包含SEQ ID NO: 51之輕鏈可變區(vL)；

(ix)包含SEQ ID NO: 60之重鏈可變區(vH)及包含SEQ ID NO: 61之輕鏈可變區(vL)；

(x)包含SEQ ID NO: 70之重鏈可變區(vH)及包含SEQ ID NO: 71之輕鏈可變區(vL)；

(xi)包含SEQ ID NO: 80之重鏈可變區(vH)及包含SEQ ID NO: 81之輕鏈可變區(vL)；

(xii)包含SEQ ID NO: 90之重鏈可變區(vH)及包含SEQ ID NO: 91之輕鏈可變區(vL)；

(xiii)包含SEQ ID NO: 100之重鏈可變區(vH)及包含SEQ ID NO: 101之輕鏈可變區(vL)；

(xiv)包含SEQ ID NO: 110之重鏈可變區(vH)及包含SEQ ID NO: 111之輕鏈可變區(vL)；

(xv)包含SEQ ID NO: 120之重鏈可變區(vH)及包含SEQ ID NO: 121之輕鏈可變區(vL)；

(xvi)包含SEQ ID NO: 130之重鏈可變區(vH)及包含SEQ ID NO: 131之輕鏈可變區(vL)；

(xvii)包含SEQ ID NO: 140之重鏈可變區(vH)及包含SEQ ID NO: 141之輕鏈可變區(vL)；

(xviii)包含SEQ ID NO: 150之重鏈可變區(vH)及包含SEQ ID NO: 151之輕鏈可變區(vL)；

(xix)包含SEQ ID NO: 180之重鏈可變區(vH)及包含SEQ ID NO: 181之輕鏈可變區(vL)；

(xx)包含SEQ ID NO: 190之重鏈可變區(vH)及包含SEQ ID NO: 191之輕鏈可變區(vL)；

(xxi)包含SEQ ID NO: 210之重鏈可變區(vH)及包含SEQ ID NO: 211之輕鏈可變區(vL)；

(xxii)包含SEQ ID NO: 220之重鏈可變區(vH)及包含SEQ ID NO: 221之輕鏈可變區(vL)；或

(xxiii)包含SEQ ID NO: 240之重鏈可變區(vH)及包含SEQ ID NO: 241之輕鏈可變區(vL)。

17. 如請求項13至16中任一項之抗體藥結合物，其中該抗體為單株抗體、嵌合抗體、人類化抗體、經工程改造之人類抗體、人類抗體、單鏈抗體(scFv)或抗體片段。

18. 如請求項13至16中任一項之抗體藥結合物，其中該n為整數2至8。

19. 如請求項1、2及13至16中任一項之抗體藥結合物，其用作藥物。

20. 如請求項1、2及13至16中任一項之抗體藥結合物，或如請求項19之醫藥組合物，其用於治療CDH6陽性卵巢癌、腎癌、肝癌或甲狀腺癌。

21. 一種核酸，其編碼如請求項1至17中任一項之抗體或抗原結合片段。

22. 一種載體及宿主細胞，其包含如請求項21之核酸。

23. 一種抗體或其抗原結合片段，其包含：

(i)輕鏈可變區，其包含(a) SEQ ID NO: 164之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 165之LCDR2、(c) SEQ ID NO: 166之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 167之HCDR1、(e) SEQ ID NO: 168之HCDR2及(f) SEQ ID NO: 169之HCDR3；

(ii)輕鏈可變區，其包含(a) SEQ ID NO: 154之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 155之LCDR2、(c) SEQ ID NO: 156之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 157之

HCDR1、(e) SEQ ID NO: 158之HCDR2及(f) SEQ ID NO: 159之HCDR3；

(iii)輕鏈可變區，其包含(a) SEQ ID NO: 194之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 195之LCDR2、(c) SEQ ID NO: 196之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 197之HCDR1、(e) SEQ ID NO: 198之HCDR2及(f) SEQ ID NO: 199之HCDR3；

(iv)輕鏈可變區，其包含(a) SEQ ID NO: 224之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 225之LCDR2、(c) SEQ ID NO: 226之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 227之HCDR1、(e) SEQ ID NO: 228之HCDR2及(f) SEQ ID NO: 229之HCDR3；

(v)輕鏈可變區，其包含(a) SEQ ID NO: 14之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 15之LCDR2、(c) SEQ ID NO: 16之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 17之HCDR1、(e) SEQ ID NO: 18之HCDR2及(f) SEQ ID NO: 19之HCDR3；

(vi)輕鏈可變區，其包含(a) SEQ ID NO: 24之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 25之LCDR2、(c) SEQ ID NO: 26之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 27之HCDR1、(e) SEQ ID NO: 28之HCDR2及(f) SEQ ID NO: 29之HCDR3；

(vii)輕鏈可變區，其包含(a) SEQ ID NO: 34之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 35之LCDR2、(c) SEQ ID NO: 36之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 37之HCDR1、(e) SEQ ID NO: 38之HCDR2及(f) SEQ ID NO: 39之

HCDR3；

(viii)輕鏈可變區，其包含(a) SEQ ID NO: 44之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 45之LCDR2、(c) SEQ ID NO: 46之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 47之HCDR1、(e) SEQ ID NO: 48之HCDR2及(f) SEQ ID NO: 49之HCDR3；

(ix)輕鏈可變區，其包含(a) SEQ ID NO: 54之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 55之LCDR2、(c) SEQ ID NO: 56之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 57之HCDR1、(e) SEQ ID NO: 58之HCDR2及(f) SEQ ID NO: 59之HCDR3；

(x)輕鏈可變區，其包含(a) SEQ ID NO: 64之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 65之LCDR2、(c) SEQ ID NO: 66之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 67之HCDR1、(e) SEQ ID NO: 68之HCDR2及(f) SEQ ID NO: 69之HCDR3；

(xi)輕鏈可變區，其包含(a) SEQ ID NO: 74之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 75之LCDR2、(c) SEQ ID NO: 76之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 77之HCDR1、(e) SEQ ID NO: 78之HCDR2及(f) SEQ ID NO: 79之HCDR3；

(xii)輕鏈可變區，其包含(a) SEQ ID NO: 84之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 85之LCDR2、(c) SEQ ID NO: 86之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 87之HCDR1、(e) SEQ ID NO: 88之HCDR2及(f) SEQ ID NO: 89之HCDR3；

(xiii)輕鏈可變區，其包含(a) SEQ ID NO: 94之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 95之LCDR2、(c) SEQ ID NO: 96之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 97之HCDR1、(e) SEQ ID NO: 98之HCDR2及(f) SEQ ID NO: 99之HCDR3；

(xiv)輕鏈可變區，其包含(a) SEQ ID NO: 104之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 105之LCDR2、(c) SEQ ID NO: 106之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 107之HCDR1、(e) SEQ ID NO: 108之HCDR2及(f) SEQ ID NO: 109之HCDR3；

(xv)輕鏈可變區，其包含(a) SEQ ID NO: 114之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 115之LCDR2、(c) SEQ ID NO: 116之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 117之HCDR1、(e) SEQ ID NO: 118之HCDR2及(f) SEQ ID NO: 119之HCDR3；

(xvi)輕鏈可變區，其包含(a) SEQ ID NO: 124之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 125之LCDR2、(c) SEQ ID NO: 126之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 127之HCDR1、(e) SEQ ID NO: 128之HCDR2及(f) SEQ ID NO: 129之HCDR3；

(xvii)輕鏈可變區，其包含(a) SEQ ID NO: 134之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 135之LCDR2、(c) SEQ ID NO: 136之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 137之HCDR1、(e) SEQ ID NO: 138之HCDR2及(f) SEQ ID NO: 139之HCDR3；

(xviii)輕鏈可變區，其包含(a) SEQ ID NO: 144之LCDR1

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(CDR-互補決定區)、(b) SEQ ID NO: 145之LCDR2、(c) SEQ ID NO: 146之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 147之HCDR1、(e) SEQ ID NO: 148之HCDR2及(f) SEQ ID NO: 149之HCDR3；

(xix)輕鏈可變區，其包含(a) SEQ ID NO: 174之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 175之LCDR2、(c) SEQ ID NO: 176之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 177之HCDR1、(e) SEQ ID NO: 178之HCDR2及(f) SEQ ID NO: 179之HCDR3；

(xx)輕鏈可變區，其包含(a) SEQ ID NO: 184之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 185之LCDR2、(c) SEQ ID NO: 186之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 187之HCDR1、(e) SEQ ID NO: 188之HCDR2及(f) SEQ ID NO: 189之HCDR3；

(xxi)輕鏈可變區，其包含(a) SEQ ID NO: 204之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 205之LCDR2、(c) SEQ ID NO: 206之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 207之HCDR1、(e) SEQ ID NO: 208之HCDR2及(f) SEQ ID NO: 209之HCDR3；

(xxii)輕鏈可變區，其包含(a) SEQ ID NO: 214之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 215之LCDR2、(c) SEQ ID NO: 216之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 217之HCDR1、(e) SEQ ID NO: 218之HCDR2及(f) SEQ ID NO: 219之HCDR3；或

(xxiii)輕鏈可變區，其包含(a) SEQ ID NO: 234之LCDR1 (CDR-互補決定區)、(b) SEQ ID NO: 235之LCDR2、(c) SEQ ID

NO: 236之LCDR3；及重鏈可變區，其包含：(d) SEQ ID NO: 237之HCDR1、(e) SEQ ID NO: 238之HCDR2及(f) SEQ ID NO: 239之HCDR3。

24. 如請求項23之抗體或其抗原結合片段，其中該抗體或其抗原結合片段包含：

(i)包含SEQ ID NO: 170之重鏈可變區(vH)及包含SEQ ID NO: 171之輕鏈可變區(vL)；

(ii)包含SEQ ID NO: 160之重鏈可變區(vH)及包含SEQ ID NO: 161之輕鏈可變區(vL)；

(iii)包含SEQ ID NO: 200之重鏈可變區(vH)及包含SEQ ID NO: 201之輕鏈可變區(vL)；

(iv)包含SEQ ID NO: 230之重鏈可變區(vH)及包含SEQ ID NO: 231之輕鏈可變區(vL)；

(v)包含SEQ ID NO: 20之重鏈可變區(vH)及包含SEQ ID NO: 21之輕鏈可變區(vL)；

(vi)包含SEQ ID NO: 30之重鏈可變區(vH)及包含SEQ ID NO: 31之輕鏈可變區(vL)；

(vii)包含SEQ ID NO: 40之重鏈可變區(vH)及包含SEQ ID NO: 41之輕鏈可變區(vL)；

(viii)包含SEQ ID NO: 50之重鏈可變區(vH)及包含SEQ ID NO: 51之輕鏈可變區(vL)；

(ix)包含SEQ ID NO: 60之重鏈可變區(vH)及包含SEQ ID NO: 61之輕鏈可變區(vL)；

(x)包含SEQ ID NO: 70之重鏈可變區(vH)及包含SEQ ID NO: 71之輕鏈可變區(vL)；

(xi)包含SEQ ID NO: 80之重鏈可變區(vH)及包含SEQ ID NO:

81之輕鏈可變區(vL)；

(xii)包含SEQ ID NO: 90之重鏈可變區(vH)及包含SEQ ID NO: 91之輕鏈可變區(vL)；

(xiii)包含SEQ ID NO: 100之重鏈可變區(vH)及包含SEQ ID NO: 101之輕鏈可變區(vL)；

(xiv)包含SEQ ID NO: 110之重鏈可變區(vH)及包含SEQ ID NO: 111之輕鏈可變區(vL)；

(xv)包含SEQ ID NO: 120之重鏈可變區(vH)及包含SEQ ID NO: 121之輕鏈可變區(vL)；

(xvi)包含SEQ ID NO: 130之重鏈可變區(vH)及包含SEQ ID NO: 131之輕鏈可變區(vL)；

(xvii)包含SEQ ID NO: 140之重鏈可變區(vH)及包含SEQ ID NO: 141之輕鏈可變區(vL)；

(xviii)包含SEQ ID NO: 150之重鏈可變區(vH)及包含SEQ ID NO: 151之輕鏈可變區(vL)；

(xix)包含SEQ ID NO: 180之重鏈可變區(vH)及包含SEQ ID NO: 181之輕鏈可變區(vL)；

(xx)包含SEQ ID NO: 190之重鏈可變區(vH)及包含SEQ ID NO: 191之輕鏈可變區(vL)；

(xxi)包含SEQ ID NO: 210之重鏈可變區(vH)及包含SEQ ID NO: 211之輕鏈可變區(vL)；

(xxii)包含SEQ ID NO: 220之重鏈可變區(vH)及包含SEQ ID NO: 221之輕鏈可變區(vL)；或

(xxiii)包含SEQ ID NO: 240之重鏈可變區(vH)及包含SEQ ID NO: 241之輕鏈可變區(vL)。

圖式

藉由FACS測定CDH6 IgG針對OVCAR3細胞的細胞結合EC50

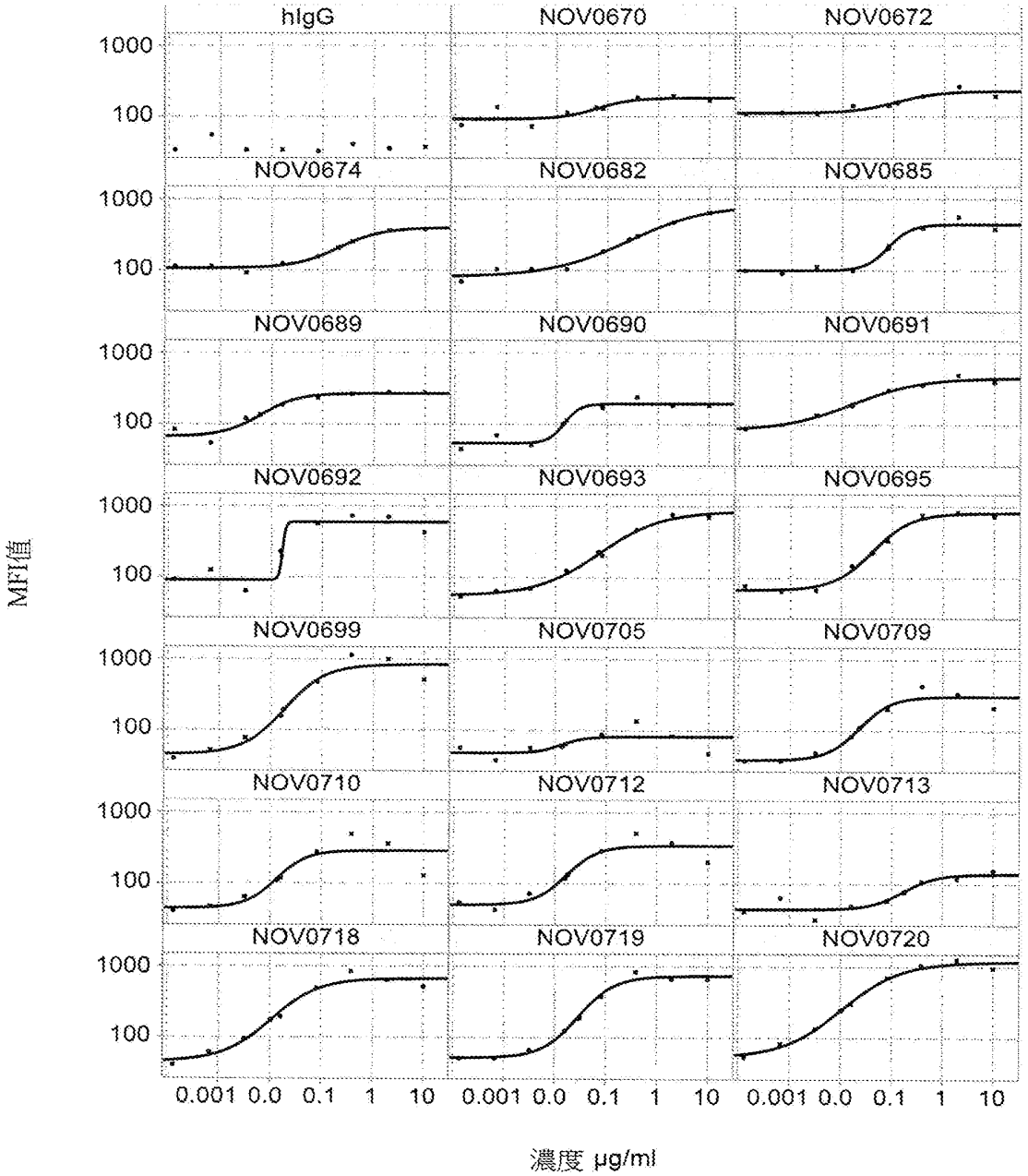


圖1

在Biacore上使用競爭性結合分析對抗CDH6抗體進行抗原決定基分組。

	NOV1126	NOV1127	NOV1132	NOV0692	NOV0710	NOV0712	NOV0719
NOV1126	8.59	16.47	23.7	7.829	15	9.506	25.42
NOV1127	56.62	36.74	39.28	50.79	32.73	24.73	46.9
NOV1132	30.06	17.82	1.08	23.2	10.62	6.004	20.71
NOV0692	18.7	25.45	17.87	-2.84	8.84	5.12	13.48
NOV0710	36.93	30.92	17.84	17.89	-3.562	-3.264	16.15
NOV0712	26.66	22.38	14.3	14.14	-2.167	-1.821	11.05
NOV0719	61.59	51.5	33.65	35.53	21.94	16.48	-2.356

圖2

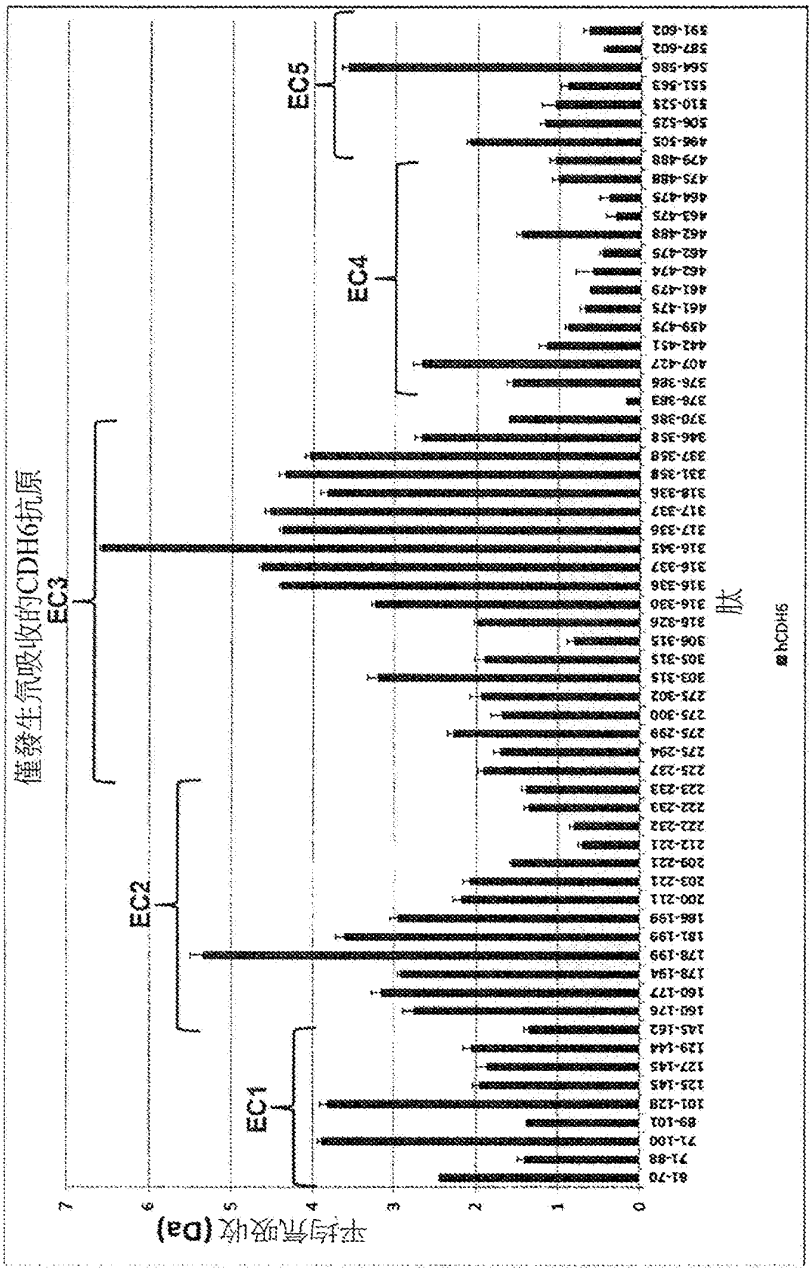


圖3

hCDH6(54-615)離子交換資料概述。

CDH6 EC5/NOV0712及CDH6 EC5/NOV0710複合物結構藉由EC5域之疊合而覆疊於CDH2之全長ECD結構上。灰色條帶為NOV0710，NOV0712以黑色表示。

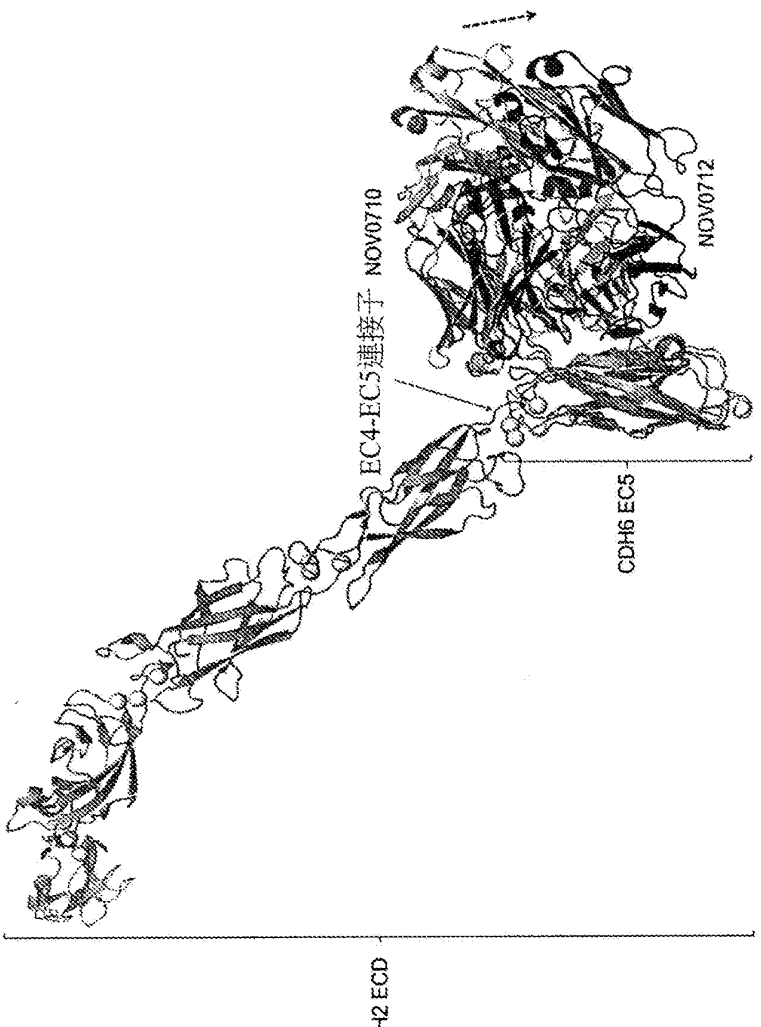


圖4

結合至CDH6之NOV0712的結構。上圖：結合至CDH6 EC5之NOV0712的整體結構(左)及CDH6上之NOV0712抗原決定基殘基的詳細視圖(右，以棒顯示且經標記)。下圖：NOV0712結合CDH6 EC5中之Ca2+結合環之大部分(殘基571-579)且誘導該環之「翻出」構形。

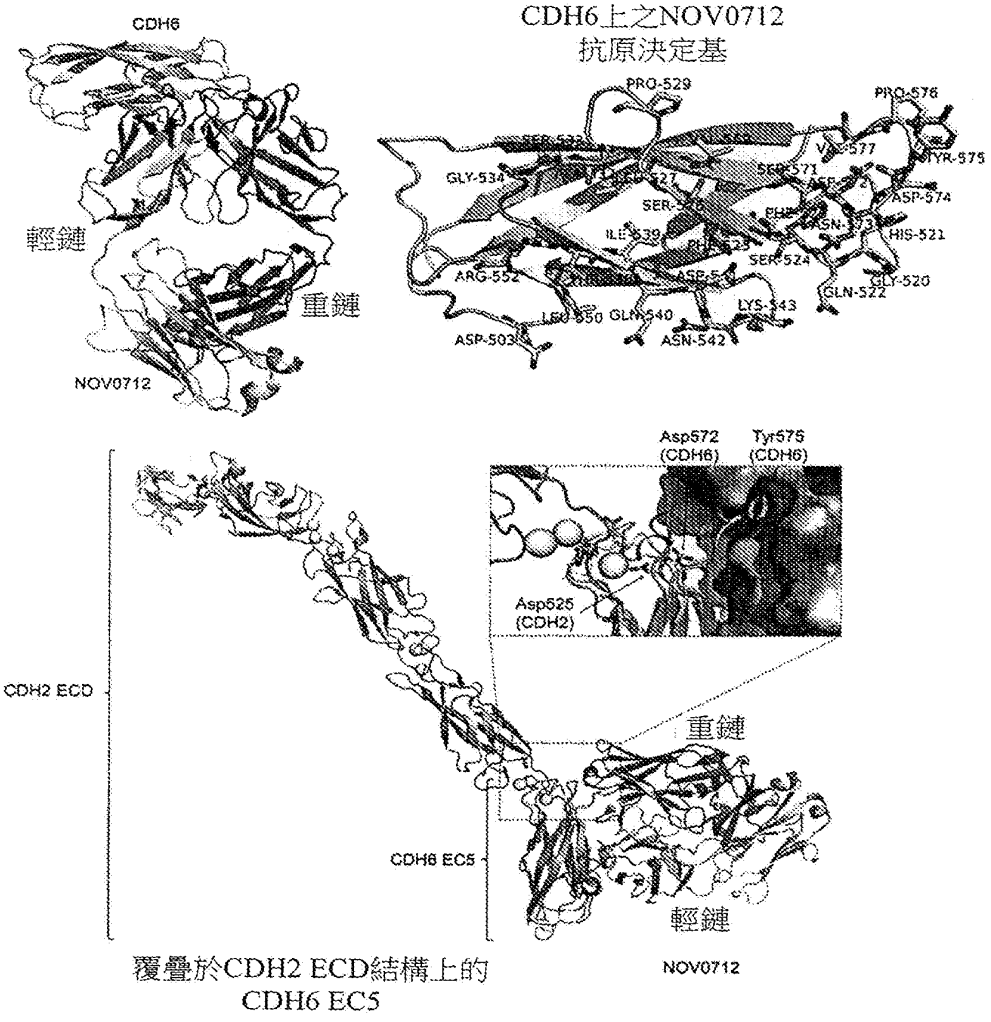


圖5

結合至CDH6之NOV0710之結構。上圖：結合至CDH6 EC5之NOV0710之整體結構(左)及CDH6上之NOV0710抗原決定基殘基之詳細視圖(右，以棒顯示且經標記)。下圖：NOV0710結合CDH6 EC5中之Ca2+結合環之大部分(殘基571-579)且誘導該環之「翻出」構形。

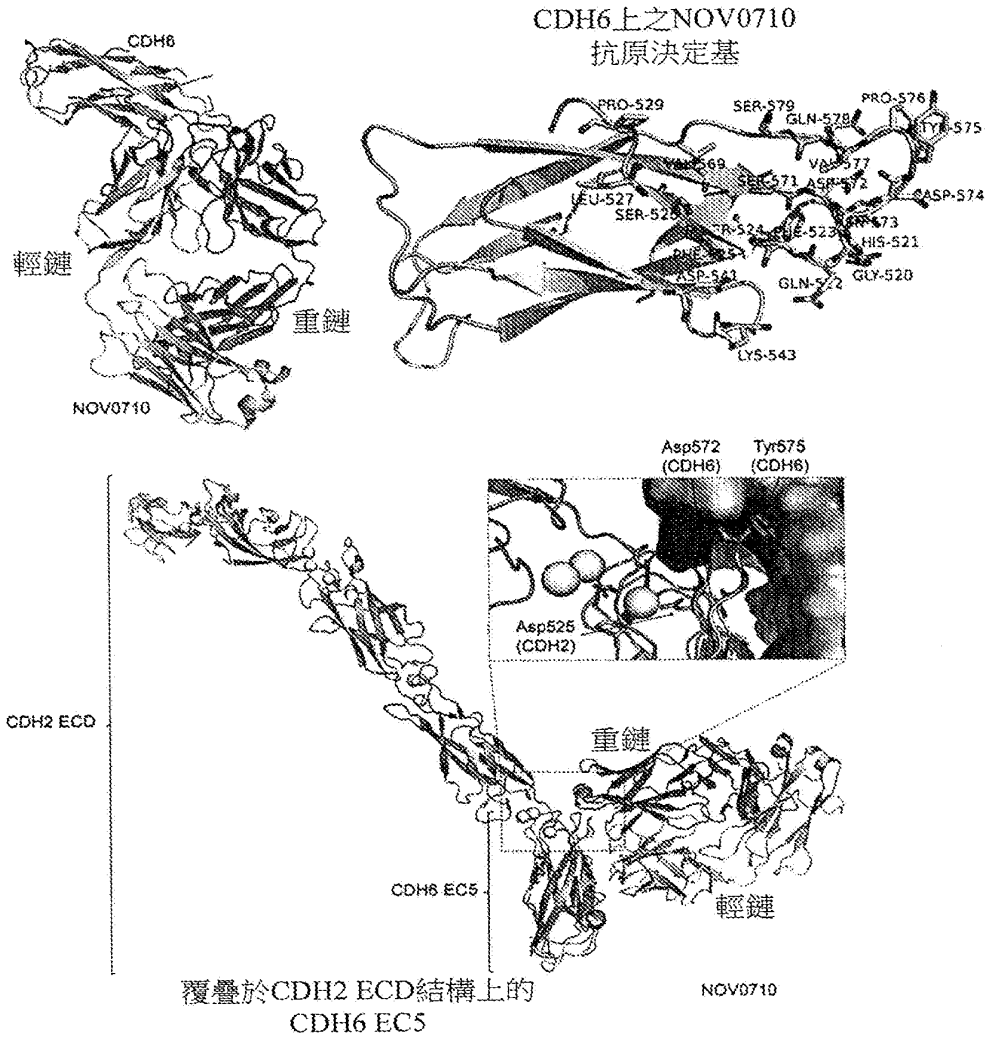


圖6

呈SMCC-DM1及SPDB-DM4結合物形式之抗CDH6 ADC針對卵巢癌細胞株的活體外細胞活性。

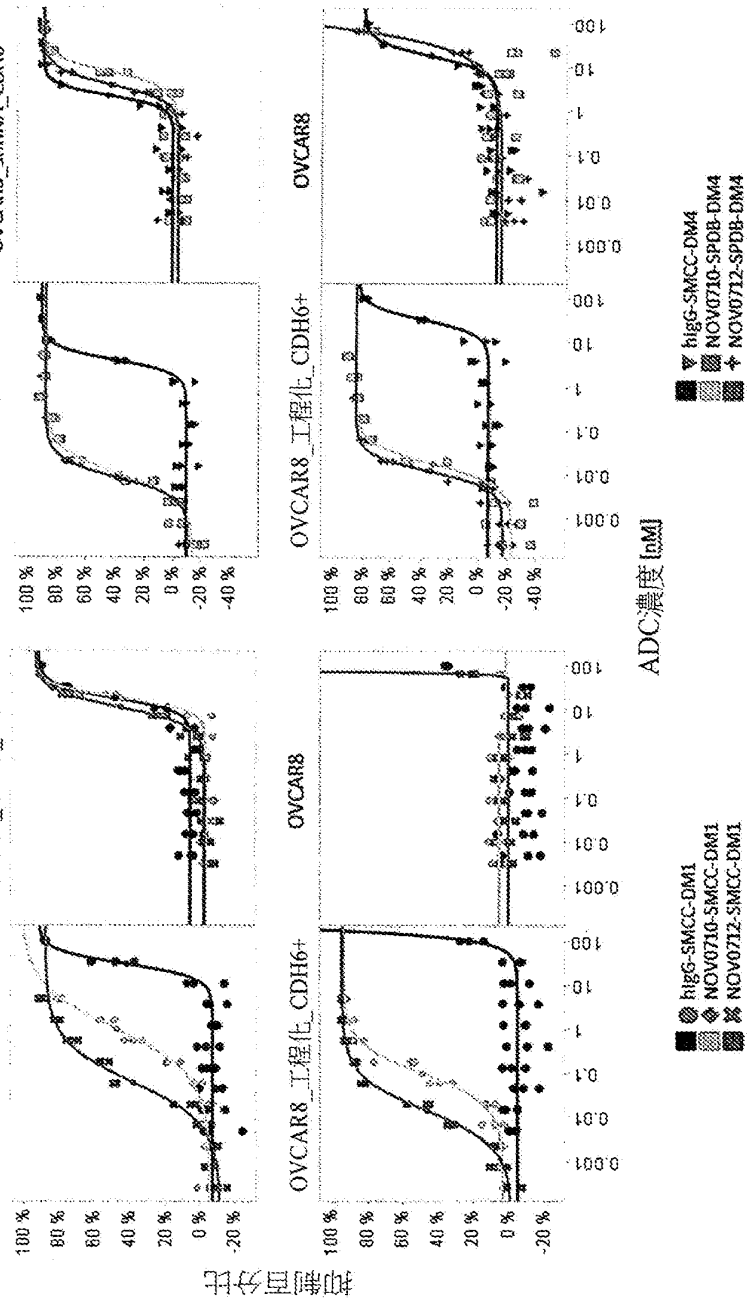


圖7

對卵巢癌細胞株OVCAR3、(OVCAR3_CDH6_shRNA)、OVCAR8及(OVCAR8_工程化_CDH6+)中之CDH6表現的FACS分析。

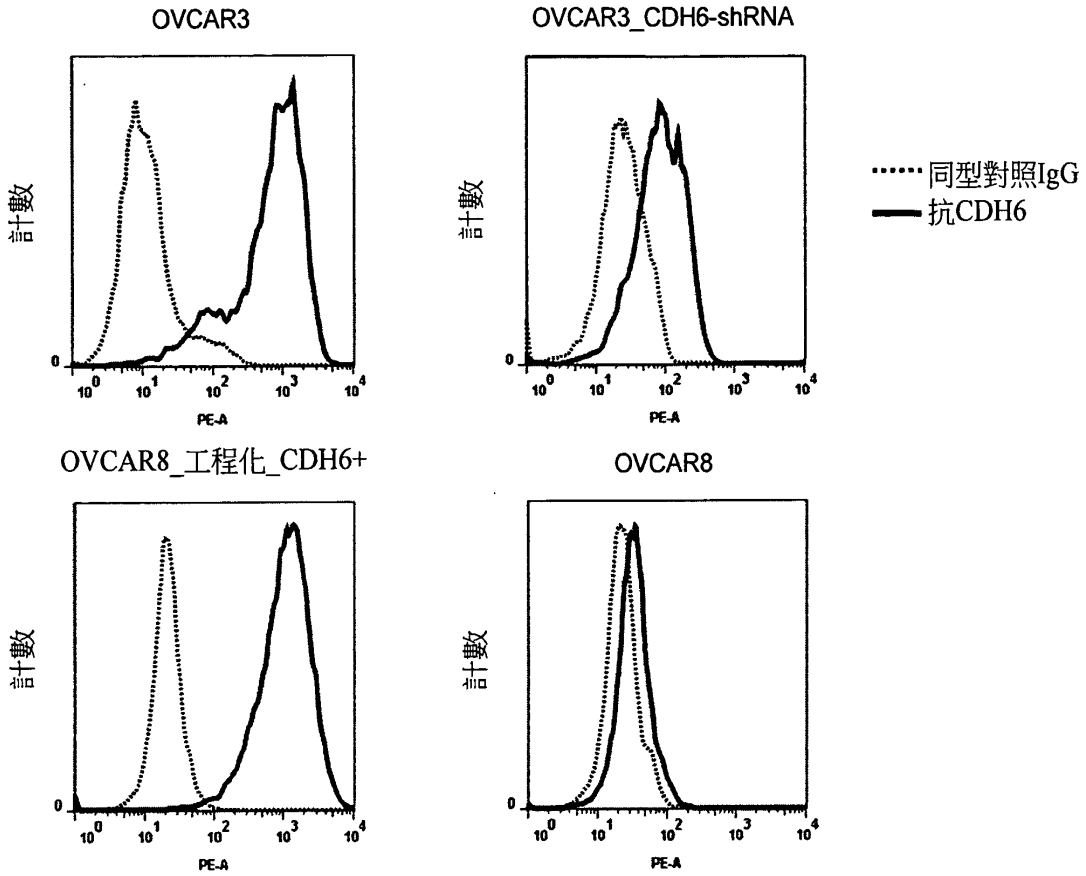


圖8

呈SMCC-DM1結合物形式之抗CDH6抗體在異種移植小鼠卵巢癌模型中的活體內功效。

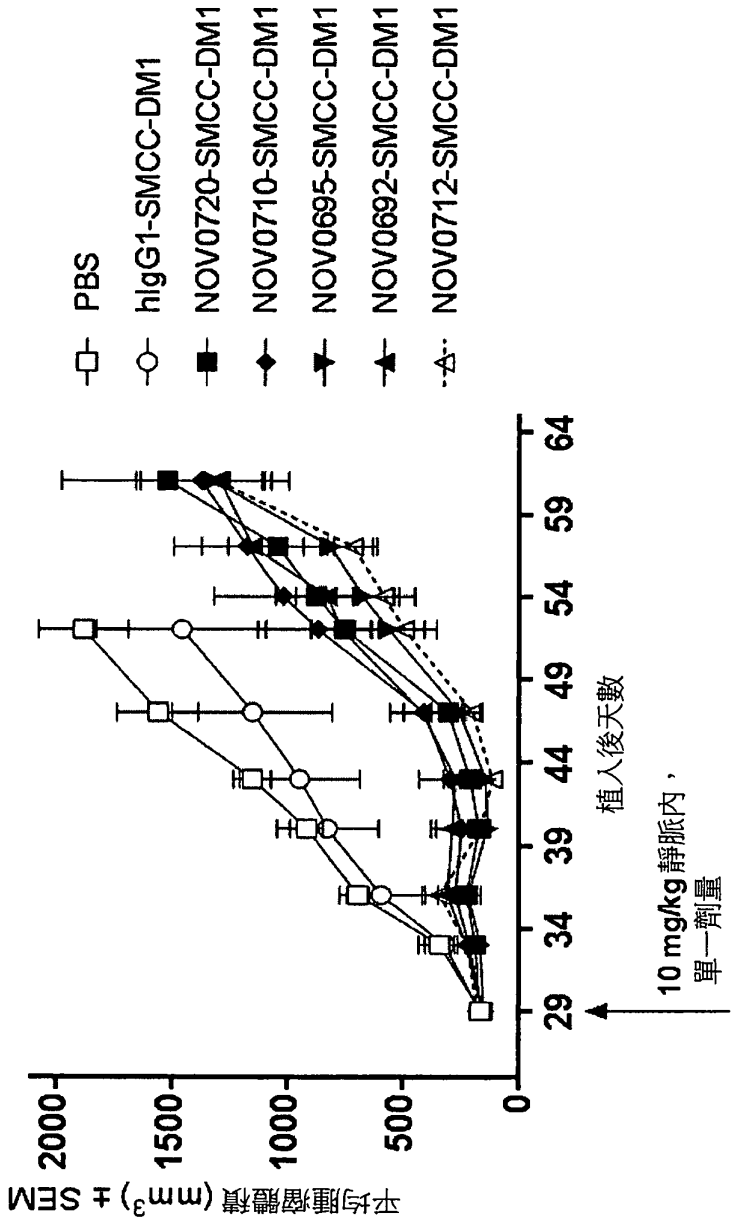


圖9

呈SMCC-DM1結合物形式之抗CDH6抗體在異種移植小鼠卵巢癌模型中的活體內功效。

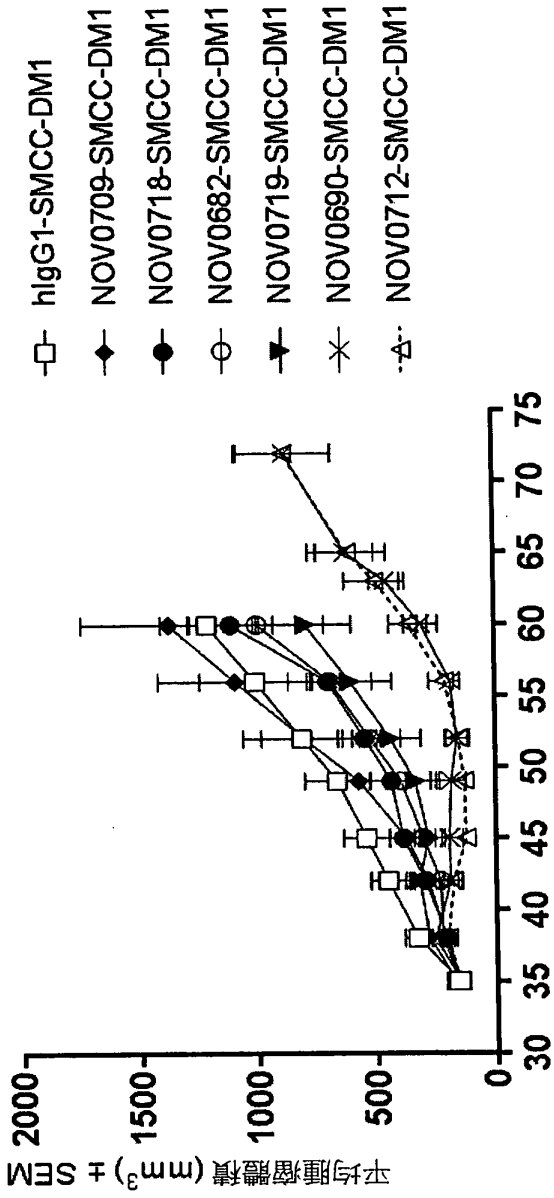


圖10

C191252DA.pdf

呈SPDB-DM4結合物形式之抗CDH6抗體在異種移植小鼠卵巢癌模型中的活體內功效。

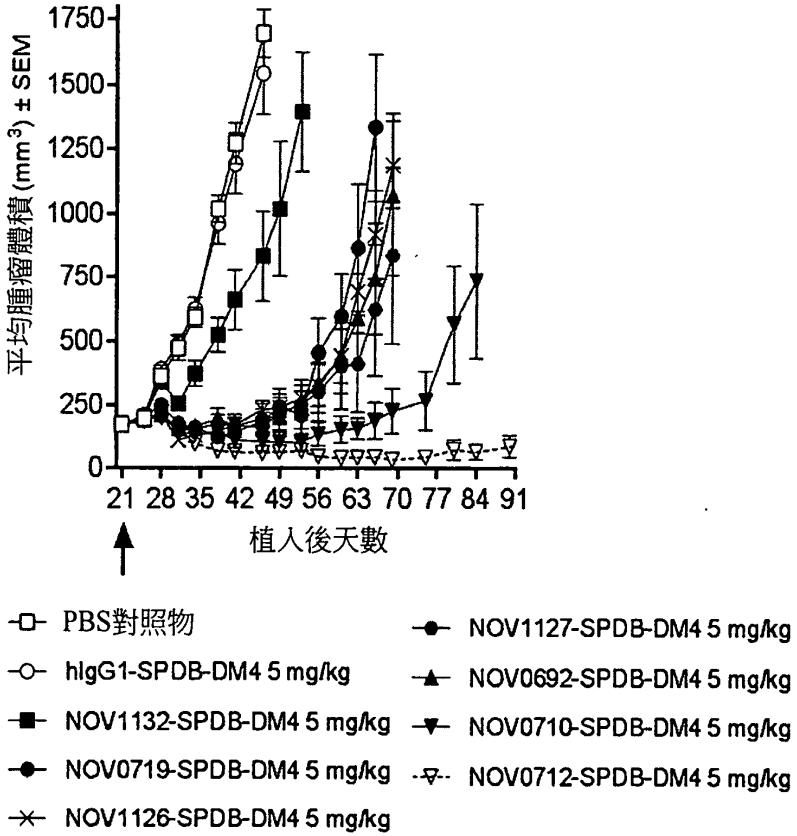


圖11

OnCusp
Ex. 1002

呈SPDB-DM4及SMCC-DM1結合物形式之抗CDH6抗體在異種移植小鼠卵巢癌模型中的活體內功效。

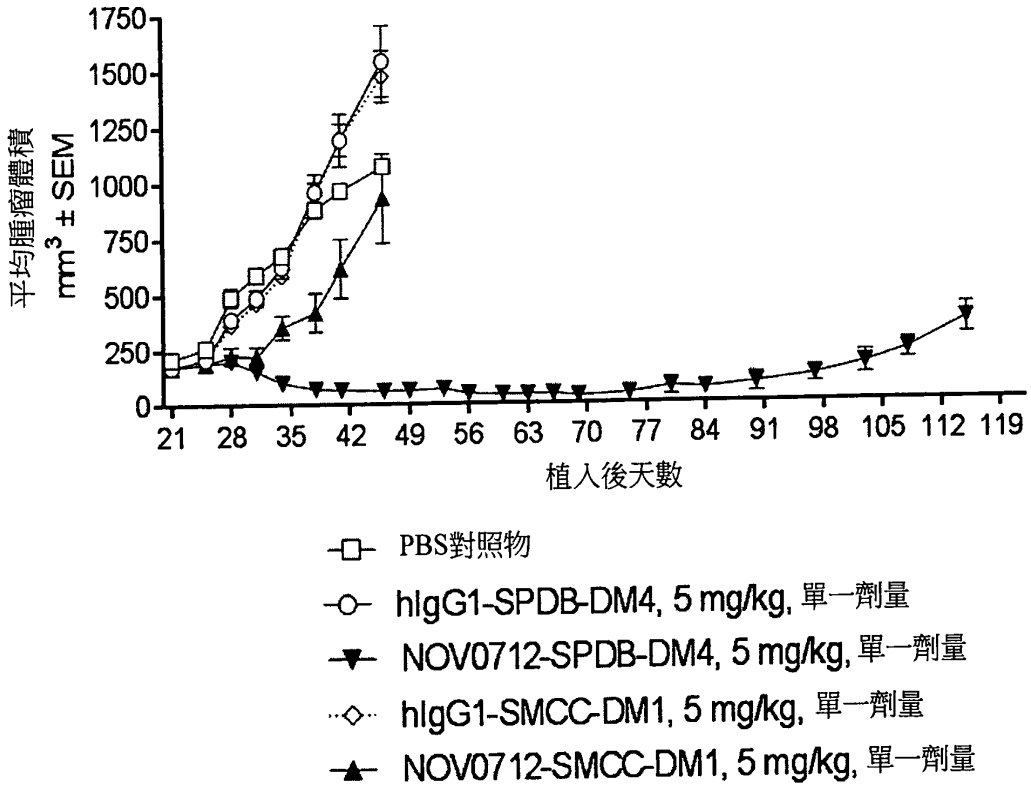


圖12

OnCusp
Ex. 1002

抗CDH6 ADC以不同連接子/有效負載形式在患者源原發腫瘤異種移植小鼠卵巢癌模型中的活體內功效。

圖13

抗CDH6 ADC以不同連接子/有效負載形式在異種移植小鼠卵巢癌模型中的活體內功效。

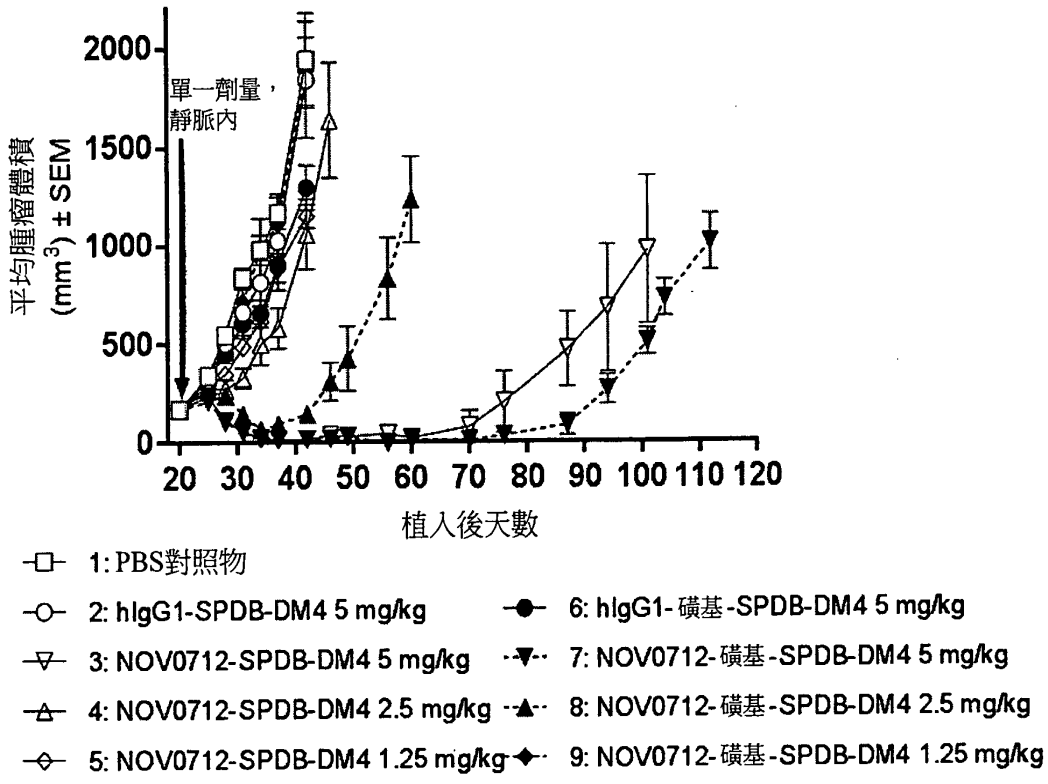


圖14

抗CDH6 ADC以不同連接子/有效負載形式在患者源原發腫瘤異種移植小鼠卵巢癌模型中的活體內功效。

圖15

抄件

files No.:
Shelf life:

Intellectual Property Bureau, Ministry of Economic Affairs Notice of Review Opinion

Office address: 2 Xinhai Road, Daan District, Taipei City
Duan 185, 3rd
Floor Contact: Wu Shujun
Contact number: (02)23765344
e-mail:
pass True: (02)23779875

Recipient:

Pack

Date of issue: May 9, 111, ROC
(111)Zhizhuan two (five) 01343 word
Issue number: 11120455820 *11120455820*

speed do not: * 1 1 1 2 0 4 5 5 8 2 0
* Password and decryption conditions or confidentiality period:
attached file: as text

Subject: Patent application No. 107116035 has been examined and stated in the first statement, please order Submit a reply explanation or amendment within 3 months from the next day of the text. If no explanation or amendment is filed within the time limit, the patent will not be granted in accordance with Article 46, Paragraph 2 of the Patent Law.

Please check.

illustrate:

1、Upon review of this case, it was found that:

(1)This case "Anti-CDH6 antibody and anti-CDH6 antibody-drug combin

Wire

Articles", the applicant filed an amendment to the specificati on January 27, 110

39、40、109、110、125、126、133、134、137-140 Page

At the Bureau, after checking that the amendments did not exceed the scope disclosed in the description, the scope of the patent application or the drawings at the time of the application, the case was examined according to the amendments and the content of the materials submitted at the time of the application. There are 53 claims in this case, of which Nos. 1 and 14, 20, 21, 23, 29, 43, 49, 53, and 53 are independent items, and the rest are

auxiliary items, which are described together first.

(2)Items 49-52, the requested method for the treatment of tumors is for the purpose of treatment, and the object is a living human body, and belongs to the treatment method of human beings or animals. Articles

The provisions of paragraph 2 shall not be patentable.

(3)The description of this case does not comply with the provisions of Article 26(1) of the Patent Law;

Item 1-53 does not comply with the provisions of Article 26(2) of the Patent Law; Items 4-8, 13, 24, 27, 28, 33-37, 40 and 41 of this case do not comply with the provisions of Article 26(4) of the Patent Law ; The sequence listing in this case does not comply with Article 26 of the Patent Law

Clause 4.

1、In claim 1, the requested antibody or a functional fragment of the antibody is defined with the expected properties of "it specifically binds to the amino acid sequence described in SEQ ID NO: 4, and has the ability to be incorporated into cells", and the technical characteristics of things should be defined by structural characteristics such as chemical name, molecular formula, structural formula or sequence, so the necessary technical characteristics to define the invention are not stated, and those with ordinary knowledge in the technical field can only make many products through excessive experimentation. Antibody or the functional fragment of the antibody, and screen out the compound with the specific function, so the patented invention violation can be realized according to the requirements. Again, check the case manual

【0238】 The "Humanized hG019 antibody 4 kinds (strain number: H01L02, H02L02, H02L03 and H04L02) bind to human and Cynomolgus monkey CDH6, but did not bind to mouse and rat CDH6. Neither antibody binds to the empty vector pcDNA3.1 introduced cells as a negative control. On the other hand, the NOV0712 antibody system showed full binding activity to human, cynomolgus monkey, mouse,

and rat CDH6. This result shows that the four humanized hG019 antibodies obtained in this specification are anti-CDH6 antibodies that show different binding properties from the NOV0712 antibody.

body. 」;The specification [0239] of the present application states that "4 humanized hG019 antibodies (strain number H01L02, H02L02, H02L03 and H04L02) bind to full-length hCDH6, EC1 deletion, EC2 deletion, EC4 deletion, and EC5 deletion, but Does not bind to the EC3-deficient body. That is, it was shown that four humanized hG019 antibodies specifically bind to EC3 of hCDH6 as an epitope. On the other hand, anti-CDH6 antibodies Although NOV0712 binds to full-length hCDH6, EC1 deletion, EC2 deletion, EC3 deletion, and EC4 deletion, it does not bind to EC5 deletion. That is, it was shown that the anti-CDH6 antibody NOV0712 antibody specifically binds to EC5 of hCDH6 as an epitope. These results show that NOV0712 and the four humanized hG019 antibodies obtained in this specification are anti-CDH6 antibodies that exhibit different properties." In short, the anti-CDH6 antibody of the present invention specifically recognizes the EC domain 3 (EC3) of CDH6, while the known anti-CDH6 antibody NOV0712 specifically recognizes the EC domain 5 (EC5) of CDH6; check the description of the present case [0239]] "These antibodies have different epitopes and the binding is not cooperating."; the description of the case

【0242】 "Humanized hG019 antibody 4 in 3 cells"

In any of the strains, the internalization rate predicted from the cell survival rate was about 50 to 75%, showing a very high internalization activity, which was higher than that of NOV0712. 」;Description of the case

[0250] "Compared with NOV0712-drug conjugates, four humanized hG019-drug conjugates showed tumor cell proliferation inhibitory activity and high anti-tumor activity from a lower concentration."; "NOV0712-DM4 was used in this tumor model, and the dosage of either 1 and 3 mg/kg showed no anti-tumor effect. another

On the one hand, H01L02-DXd was administered at either 1 or 3 mg/kg, the tumor volume was significantly reduced, and the effect of tumor regression was exerted (FIG. 13). In addition, the results of the comparison of the pharmacological effects of the H01L02 antibody or NOV0712 antibody obtained in this specification by conjugating the same drug DXd to the sample, the doses of H01L02-DXd of either 1 and 3 mg/kg were higher than those of H01L02-DXd. NOV0712-DXd exerts a strong antitumor effect. That is, it was shown that the H01L02 antibody of the present invention is a better antibody than the NOV0712 antibody as an antibody as an antibody-drug conjugate of an antitumor agent (FIG. 13). 」;″NOV0712-DM4" described in the specification of the present application [0254] showed no anti-tumor effect at all at 1 mg/kg, but showed anti-tumor effect at 3 mg/kg, but it was considered that there was tumor re-proliferation after 2 weeks of administration. On the other hand, the dosage of H01L02-DXd at either 1 and 3 mg/kg significantly inhibited the increase in tumor volume after administration, especially at 3 mg/kg, tumor proliferation was inhibited for a long period of 31 days after administration. The effect lasts. (Figure 14)."; contained in the description of this case [0255]

"NOV0712-DM4 in this tumor model, at either 1 and 3 mg/kg None of the dosages showed significant anti-tumor effect. On the other hand, H01L02-DXd was dosed at either 1 and 3 mg/kg, and tumor volume was reduced after administration, especially at 3 mg/kg, which was considered to have significant tumor regression, between 20 days after administration, and The tumor regression effect was sustained (Figure 15). 」;According to the specification [0256] of the present case, "In this tumor model that does not express CDH6, the dosage of either H01L02-DXd and NOV0712-DM4 showed no antitumor effect at all. From these results, it is

considered that the anti-tumor effects of the antibody-drug conjugates in the CDH6 positive tumor models shown in Examples 9)-1, 9)-2, 9)-3, and 9)-4

It is a selective and safe anti-tumor agent that depends on the expression of CDH6 in tumor cells, shows specific anti-tumor effect on CDH6-positive tumors, and does not cause cell disturbance in CDH6-negative normal tissues (Fig. 16)". In short, the anti-CDH6 antibody-drug conjugate H01L02-DXd of the present invention showed obvious tumor regression compared with the known antibody-drug conjugate NOV0712-DM4. To sum up, the examples of this case only confirm that four humanized hG019 antibodies, including H01L02, H02L02, H02L03 and H04L02, can specifically recognize the EC3 of CDH6 (ie, the amino acid sequence of SEQ ID NO: 4), and the anti-CDH6 antibody-drug The conjugate H01L02-DXd has better anti-tumor efficacy. However, the requested antibody or its antigen-binding fragment is not clearly defined by its structural features (such as the light/heavy chain variable region composition sequences of H01L02, H02L02, H02L03, H04L02) according to the specification, which makes the requested scope too large. Generality is not clear. Furthermore, in fact, the 6 CDR sequences of the antibody represent the specificity and activity of the antibody, so if the CDR amino acid sequence is changed or modified to be different, it may cause different antibody activities, and the arrangement and combination of the CDR sequences will also affect the antibody. activity, so an antibody must in principle at least be derived from

3 HCDR1~3 "and" 3 LCDR1~3 of "same antibody"

The technical characteristics of the antibody and the definition of the specific binding properties of the "specific antigen" (CDH6) can make the antibody have a definite structural feature and can produce the claimed specific efficacy; In addition to being determined by the sequence of the CDRs, the relative configuration of the CDRs will also affect the binding properties of the antibody. Therefore, mutations in the sequence of the CDRs or the sequence of the variable region

(such as the framework region) other than the CDRs may lead to antibody binding. The antigen-binding properties have changed, according to the case

H01L02, H02L02, H02L03 and H04L02 disclosed in the manual 4 Structural characteristics and preparation methods of various humanized hG019 antibodies, "six CDRs and framework regions" or "complete light chain variable region and heavy chain variable region" constitute the EC3 that specifically recognizes CDH6 and has high The important technical features of the anti-CDH6 antibody with internalization activity, but the requested technical feature has not been fully defined, and the overall technical means of the requested invention cannot be presented. Clause 2 of Article 26. In addition, for the contents disclosed in the corresponding instructions, it is also impossible to confirm the specific structure of the requested antibody and whether it is indeed "can specifically recognize EC3 of CDH6, has high internalization activity, and has excellent anti-tumor activity without excessive realization. It is difficult to say that the description complies with the requirements for realizing the effect", so it does not comply with the provisions of Article 26, Paragraph 1 of the Patent Law. another request

2-53 In order to directly or indirectly depend on or refer to claim 1, the same as above
reason.

2、In claims 1-13, the antibody or the functional fragment of the antibody should be defined as CDH6 to which the antibody binds to be definite.

3、Claim 2, the reason is as described in (3)-1, the requested antibody or the functional fragment of the antibody is only based on "its binding to the amino acid sequence described in SEQ ID NO: 4, has the However, it is known that even if the antigenic epitopes of the antibodies are not identical, they may cross-compete with each other, in other words, antibodies that cross-compete with each other It does not necessarily have the same function, and those with

ordinary knowledge in the technical field to which the invention belongs cannot infer the requested antibody or the function of the antibody based on the content of the description. Both sex fragments can bind to CDH6 and have high internalization activity, and have

It has excellent anti-tumor effect, so the request cannot be supported by the instructions. Another claim 3-53 is directly or indirectly dependent on or citing claim 2, the same reason as above.

4、Claims 3, 4, and 6, the reasons are as described in (3)-1, the scope of the antibody is requested to further define the options of its CDR, light/heavy chain variable region sequence, because the description of this case only discloses specific antibodies H01L02, The effects of H02L02, H02L03 and H04L02 cannot reasonably be expected by a person of ordinary knowledge in the art based on the content of the aforementioned specification, as long as the CDR sequences as defined in the request are included, the claim in this case that "can specifically recognize EC3 of CDH6 and has high internalization" can be achieved. active, and has excellent anti-tumor effect, etc. Moreover, the requested covers a wide range of CDRs or any combination of light/heavy chain variable regions, and it cannot be confirmed by the disclosure content of the description that it has the stated effects, so too many applicants are included. The content is speculated and its effect is difficult to determine, so the request is not clear and cannot be supported by the description. The other claims 5, 13-53 are directly or indirectly dependent on or citing claims 3, 4, and 6, and the reasons above are the same.

5、Claims 25-27, the subject of the request is "antibodies", but the at[illegible]d The subject matter of claim 24 is "antibody or a functional fragment of the antibody", and the subject matter is inconsistent, making the claim unclear.

6、Request item 28, said ″if ″selected to include″ request item...", it is suggested to delete the "selected to include" for clarity. Also, the statement "in order to enhance the activity of antibody-dependent cell damage, and the modification of sugar chains is regulated" is only defined by the expected effect, but does not limit the technical

means necessary to achieve the effect. The invention belongs to Those with ordinary knowledge in the technical field cannot understand the specific structure of the antibody or the functional fragment of the antibody based on these characteristics, and cannot understand the "glycan".

It is unclear what structural features of the chain modification are regulated. In addition, referring to 2.4.2 of Chapter 1, Chapter 1 of my country's Inventive Entity Examination Standards, the description of the request should be concise. Except for the necessary technical characteristics, it should not explain the reasons, reasons or background for the effect, purpose or use achieved by the technical means. Make unnecessary records and specify them.

7、Claims 4-8, 13, 24, 27, 28, 33-37, 40, and 41 are a number of sub-items, but they are directly or indirectly dependent on a number of sub-items, which are inconsistent with Article 26, item 4 of the Patent Law and its implementing regulations. Clause 5 of Article 18.

8、The numerical identification number <110> of the sequence listing in this case should be recorded in the format prescribed by the Bureau. The name of the applicant must be expressed in Chinese, and the foreigner must attach the original foreign language or English or Latin letters, and the content of the record should not contain invention. name of the person; <140> should record the application number of this case; <141> should record the application date of this case, otherwise it will not comply with Article 26 of the Patent Law.

4 Article 17, Paragraph 6 of the Enforcement Regulations of the same law.

(4)According to the contents disclosed in Citation 1, the claims 1-53 of this case do not comply with Article 1 of the Patent Law.

22 Clause 2 of the article.

1、Claims 1-13, Citation 1 [Abstract; page 40 of the specification] discloses anti-CDH6 antibodies, antibody fragments, antibody-drug conjugates, and uses thereof for the treatment of cancer, particularly with regard to binding to CDH6 and internalization after such binding Antibodies and antibody fragments (eg, antigen-binding fragments); Citation 1

【Manual page 17】 It is disclosed that the antibody -drug conjugate is used to prepare a pharmaceutical composition, and to treat CDH6-positive cancers in patients in need, such as ovarian cancer, kidney cancer, liver cancer or thyroid cancer, etc.; Citation 1

[Example 1; Table 5] reveals the screening and identification of CDH6 antibodies by phage display technology, such as NOV0712; Citation 1 [Example 7; Figure 4]



NOV0712 was revealed to bind to EC domain 5 (EC5) of CDH6; Citation 1

[Example 12; Figure 11] It was revealed that the antibody-drug conjugate NOV0712-SPDB-DM4 caused the greatest antitumor effect and subsided 70 days after administration, and that NOV0710-SPDB-DM4 was the second most active anti-CDH6-SPDB-DM4

DM4; Citation 1 [Fig. 3; pages 156 and 157 of the specification] reveal five EC domains (extracellular domains) of CDH6, wherein EC1 is the amino acid sequence of No. 54-159 of human CDH6; EC2 is the first of human CDH6 Amino acid sequence of No. 160-268; EC3 is No. 269- of human CDH6

383 The amino acid sequence of No. 1; EC4 is the amino acid sequence of No. 384-486 of human CDH6; EC5 is the amino acid sequence of No. 487-608 of human CDH6. Also check the contents of the description [0234] of this case, it can be seen that the anti-CDH6 antibody NOV0712 used in the examples of this case was prepared with reference to the amino acid sequences of the full length of the light chain and the full length of the heavy chain of NOV0712 described in Citation 1. The difference between Citation 1 and the applicant is that Citation 1 reveals that the anti-CDH6 antibody NOV0712 specifically recognizes the EC5 of CDH6, while the anti-CDH6 antibody of the present invention specifically recognizes the EC3 of CDH6 (namely the amino group of SEQ ID NO. 4). acid sequence), and citation 1 does not reveal the same CDRs, light/heavy chain variable regions, light/heavy chain sequences as the antibody requested in this case, but citation 1 has revealed anti-CDH6 that specifically binds to EC5 of CDH6 Antibodies, and five of CDH6 The sequence of each of the EC domains, therefore those with ordinary knowledge in the technical field to which this invention belongs, according to the content of Citation 1, when there is a reasonable motivation to test the efficacy of the antibody

binding to the five different EC domains of CDH6, prepare various combinations in a routine experimental manner. Anti-CDH6 antibodies against five different EC domains of CDH6 were tested, and the efficacy of these antibodies to antigens was tested, and then those who could be used to treat CDH6-positive cancers were screened. Again, as mentioned above

(3) As discussed in -1, 3, and 4, the requested range covers antibodies other than antibodies H01L02, H02L02, H02L03, and H04L02. According to the description of this case, it is impossible to know whether the requested range can produce unexpected effects, so there is no improvement. sex.

2、Claim 14-53, the reason is as stated in (4)-1, the requested polynucleotide, expression vector, host cell, method for producing antibody, antibody-drug conjugate, pharmaceutical composition and pharmaceutical use, etc., are based on this Such antibodies are technical features or medical applications of such antibodies, and those with ordinary knowledge in the technical field to which the invention pertains can be easily inferred based on the content disclosed in Citation 1 and the prior art, so it is a part that can be easily completed, and This case does not disclose the unexpected effect of the claimed scope compared with the prior art in the specification, so the claim is not progressive.

(5)Citation documents:

Citation 1. TW 201613643 A 2016/04/16.

2、If this case is amended or revised, it shall be subject to Article 43, Article 44, Paragraph 3 of the Patent Law.

Articles 36 to 38 of the Enforcement Regulations of the Patent Law shall be handled in accordance with the provisions of the Patent Amendment Application Form and the Patent Mistranslation Correction Application Form.

3、If you need a face-to-face demonstration or explanation, please use the "face-to-face application form" to state the version on which the interview is based, the items to be interviewed and explanations, and pay a fee of NT$1,000. The bureau will notify you when it deems it necessary. Interview location and time.

4、1 copy of the search report for this case was submitted. If the search report of this case is accompanied by non-patent literature for citation, it is only for the personal reference of the

patent applicant. If it involves other acts of making use of the work (such as: printing paper copies to the public, uploading files to the Internet, etc.) The consent or authorization of the copyright owner should be obtained to avoid infringement.

Original: Nippon Business Daiichi Sankyo Co., Ltd. (Agent: Ding Guolong Patent Attorney, Huang Zhengcheng patent attorney)

copy:



appe

Search Report for Patent

Application No. 107116035

1. Application Date: 11 May 107
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associative generation code	Citations and relevant passages	associated request item
X	1. TW 201613643 A 2016/04/16 Abstract; Specification pages 17, 40, 156, 157; Example 1, Example 7, Example 12; Table 5; Figure 3, Figure 4, Figure 11	1-53

Relevance code description:

X: Citation alone is sufficient to deny novelty of the invention or progressive nature. technical level.

Y: Sufficient in combination with one or more other papers recorded in the manual. relevant to denying the progressiveness of the invention publicity/announcement later literature.

O: Documents of particular relevance to the public use, sale or display of a sexual

P: Articles published between the filing date and the priority date are particularly

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A: References of the general document.

D: Documents that have been

E: Application first, offer.

L: Literature cited for other reasons.

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主旨：第107116035號專利申請案經審查有說明一所述情事，請於文到次日起3個月內提出申復說明或修正。屆期未申復說明或修正者，依專利法第46條第2項規定將不予專利，請查照。

說明：

一、本案經審查認為：

(一)本案「抗ＣＤＨ６抗體及抗ＣＤＨ６抗體－藥物結合物」，申請人於 110 年 01 月 27 日提出修正說明書第39、40、109、110、125、126、133、134、137-140 頁到局，經查修正內容未超出申請時說明書、申請專利範圍或圖式所揭露之範圍，本案依該修正及申請時所提資料內容進行審查，本案請求項共53項，其中第1、14、20、21、23、29、43、49、53、53項為獨立項，其餘為附屬項，合先敘明。

(二)請求項 49-52，所請一種腫瘤之治療方法，係以治療為目的，且以有生命的人體為對象，屬於人類或動物之治療方法，為不予發明專利之項目，依專利法第 24 條條第 2 款之規定，不予專利。

(三)本案說明書不符專利法第 26 條第 1 項之規定；本案請求項 1-53 不符專利法第 26 條第 2 項之規定；本案請求項 4-8、13、24、27、28、33-37、40、41 不符專利法第 26 條第 4 項之規定；本案序列表不符專利法第 26 條第 4 項之規定。

1、請求項 1，所請以「其與序列識別號 4 記載之胺基酸序列專一性結合，且具有被併入細胞內的內在化能力」之預期性質界定所請抗體或該抗體之機能性片段，而物之技術特徵應以化學名稱、分子式、結構式或序列等結構特徵予以界定，故未敘明界定發明之必要技術特徵，所屬技術領域具有通常知識者實須過度實驗始可製造眾多之抗體或該抗體之機能性片段，並篩選出具有該特定功能之化合物，因此申請專利之發明違反可據以實現要件。再者，查本案說明書【0238】所載「人類化 hG019 抗體 4 種(株編號為 H01L02、H02L02、H02L03 及 H04L02)會結合於人類及食蟹獼猴 CDH6，但並不會結合於小鼠及大鼠 CDH6。任一抗體皆不會結合於為陰性對照的空載體 pcDNA3.1 導入細胞。另一方面，NOV0712 抗體係顯示對人類、食蟹獼猴、小鼠、及大鼠 CDH6 全部的結合活性。此結果顯示了，於本說明書取得的人類化 hG019 抗體 4 種為顯示與 NOV0712 抗體不同結合性質的抗 CDH6 抗

體。」；本案說明書【0239】所載「人類化 hG019 抗體 4 種(株編號為 H01L02、H02L02、H02L03 及 H04L02)會結合於全長 hCDH6、EC1 缺失體、EC2 缺失體、EC4 缺失體、及 EC5 缺失體，但不會結合於 EC3 缺失體結合。即，顯示了人類化 hG019 抗體 4 種會將 hCDH6 之 EC3 作為抗原決定位而特異性地結合。另一方面，抗 CDH6 抗體 NOV0712 雖會結合於全長 hCDH6、EC1 缺失體、EC2 缺失體、EC3 缺失體、及 EC4 缺失體，但不會結合於 EC5 缺失體。即，顯示了抗 CDH6 抗體 NOV0712 抗體會將 hCDH6 之 EC5 作為抗原決定位而特異性地結合。由此結果顯示了，NOV0712 與於本說明書取得的人類化 hG019 抗體 4 種為顯示不同性質的抗 CDH6 抗體」。簡言之，本案發明之抗 CDH6 抗體，係特異性辨識 CDH6 之 EC 域 3(EC3)，而已知抗 CDH6 抗體 NOV0712，係特異性辨識 CDH6 之 EC 域 5(EC5)；又查本案說明書【0239】所載「此等抗體係抗原決定位不同且結合並非競合。」；本案說明書【0242】所載「人類化 hG019 抗體 4 種於 3 種之細胞株任一者中，由細胞生存率而予測的內在化率皆為約 50~75%，顯示非常高的內在化活性，且與 NOV0712 比較，而顯示更高的內在活性。」；本案說明書【0250】所載「人類化 hG019-藥物結合物 4 種與 NOV0712-藥物結合物比較，自更低添加濃度顯示腫瘤細胞的增殖抑制活性，抗腫瘤活性高。」；本案說明書【0253】所載「NOV0712-DM4 係於本腫瘤模型中，1 及 3mg/kg 任一者之用量皆未顯示抗腫瘤效果。另一

方面，H01L02-DXd 以 1 及 3mg/kg 任一者之用量皆投予後腫瘤體積顯著減少，發揮了使腫瘤縮退的效果（圖 13）。又，比較了將相同藥物 DXd 結合(conjugate)於本說明書中取得的 H01L02 抗體或是 NOV0712 抗體與的檢體之藥效的結果，H01L02-DXd 係 1 及 3mg/kg 任一者之用量都比 NOV0712-DXd 發揮強的抗腫瘤效果。即顯示了，相較於 NOV0712 抗體，就作為抗腫瘤劑之抗體-藥物結合物的抗體而言，本發明之 H01L02 抗體為更優異的抗體(圖 13)。」；本案說明書【0254】所載「NOV0712-DM4，係於 1mg/kg 完全不顯示抗腫瘤效果，而於 3mg/kg 雖顯示抗腫瘤效果，但被認為自投予 2 週後有腫瘤之再增殖。另一方面，H01L02-DXd 係於 1 及 3mg/kg 任一者之用量，皆顯著地抑制投予後腫瘤體積之增加，特別是於 3mg/kg，投予後歷經 31 日的長期間，腫瘤增殖抑制效果持續。(圖 14)。」；本案說明書【0255】所載「NOV0712-DM4 於本腫瘤模型中，於 1 及 3mg/kg 任一者之用量皆未顯示顯著的抗腫瘤效果。另一方面，H01L02-DXd 係於 1 及 3mg/kg 任一者之用量，投予後腫瘤體積皆減少，特別是於 3mg/kg 被認為有顯著的腫瘤的退縮，投予後 20 日之間，且腫瘤退縮效果維持續(圖 15)。」；本案說明書【0256】所載「於不表現 CDH6 的本腫瘤模型中，H01L02-DXd 及 NOV0712-DM4 係任一者之用量皆完全未顯示抗腫瘤效果。由此結果認為，於實施例 9)-1、9)-2、9)-3、9)-4 所示的 CDH6 陽性腫瘤模型之抗體-藥物結合物之抗腫瘤效

果，係依賴於腫瘤細胞之 CDH6 表現而產生的效果，對 CDH6 陽性之腫瘤顯示特異性抗腫瘤效果，於 CDH6 陰性之正常組織不會造成細胞障礙之有選擇性且安全的抗腫瘤藥劑(圖 16)」。簡言之，本案發明之抗 CDH6 抗體-藥物結合物 H01L02-DXd 與已知的抗體藥物結合物 NOV0712-DM4 相比，表現出明顯的腫瘤消退。綜上論述，本案實施例僅證實 H01L02、H02L02、H02L03 及 H04L02 等 4 種人類化 hG019 抗體，能特異性辨識 CDH6 之 EC3(即序列識別號 4 之胺基酸序列)，以及抗 CDH6 抗體-藥物結合物 H01L02-DXd 具有較佳抗腫瘤功效。然而，所請抗體或其抗原結合片段，並未依據說明書可支持者明確以其結構特徵(例如 H01L02、H02L02、H02L03、H04L02 之輕/重鏈可變區組成序列)界定，致使所請範圍過於籠統不明確。再者，事實上抗體 6 個 CDR 序列係代表抗體的專一性及活性，因此若 CDR 胺基酸序列經改變或修飾而不同，可能會造成不同抗體活性，且 CDR 序列經排列組合亦會影響抗體活性，故一抗體原則上必須至少以源自「同一個抗體」的 3 個 HCDR1~3「以及」3 個 LCDR1~3 的技術特徵再加上對於「特定抗原」(CDH6)之特異性結合性質加以界定，才可使該抗體具有一明確的結構特徵而能產生所宣稱之特定功效；又由於抗體的抗原結合特性除了由 CDR 之序列決定之外，CDR 間的相對配置亦會影響抗體的結合特性，故於 CDR 之序列或是 CDR 以外之可變區(如:框架區）序列上進行突變，皆可能導致抗體的抗原結合特性發生改變，根據本案說

明書所揭露之 H01L02、H02L02、H02L03 及 H04L02 等 4 種人類化 hG019 抗體之結構特徵以及製備方式，「6 個 CDRs 與框架區」或「完整的輕鏈可變區及重鏈可變區」係為構成所請特異性辨識 CDH6 之 EC3 且具有高內在化活性之抗 CDH6 抗體的重要技術特徵，但所請並未完整界定該必要技術特徵，無法呈現所請發明之整體技術手段，故所請不明確且無法由說明書予以支持，不符專利法第 26 條第 2 項之規定。此外，對於對應之說明書揭露內容，亦無法在未經過度實現下即可確認所請抗體具體結構及是否確具「能特異性辨識 CDH6 之 EC3 且具有高內在化活性，及具有優異的抗腫瘤效果」之功效，說明書亦難謂符合據以實現要件，故不符專利法第 26 條第 1 項之規定。另請求項 2-53 為直接或間接地依附或引用請求項 1，亦同上述理由。

2、請求項 1-13，所述抗體或該抗體之機能性片段應界定其所結合之抗原為 CDH6，以臻明確。

3、請求項 2，理由如(三)-1 所述，所請抗體或該抗體之機能性片段僅以「其對於序列識別號 4 記載之胺基酸序列的結合，具有與選自包含以下之(1)~(5)的群組之抗體中至少一者的競爭抑制活性」界定，然而，習知即使抗體的抗原決定位不完全相同，也可能會相互交叉競爭，換言之，相互交叉競爭的抗體不一定具有相同功能，該發明所屬技術領域中具有通常知識者無法僅就說明書內容而能推論所請抗體或該抗體之機能性片段均能與 CDH6 結合且具有高內在化活性，及具

有優異的抗腫瘤效果之功效，故所請無法為說明書所支持。另請求項 3-53 為直接或間接地依附或引用請求項 2，亦同上述理由。

4、請求項 3、4、6，理由如(三)-1 所述，所請進一步對抗體之範圍，界定其 CDR、輕/重鏈可變區序列之選項，由於本案說明書僅揭示特定抗體 H01L02、H02L02、H02L03 及 H04L02 的效果，所屬領域之通常知識者根據前述說明書內容無法合理預期只要包含有所請定義之 CDR 序列，即可達到本案所宣稱「能特異性辨識 CDH6 之 EC3 且具有高內在化活性，及具有優異的抗腫瘤效果」等功效，況且，所請涵蓋廣泛 CDR 或輕/重鏈可變區之任意組合，亦無法由說明書揭露內容證實確具所述功效，故所請包含過多申請人推測內容而其效果實難以確定，因此所請不明確且無法為說明書所支持。另請求項 5、13-53 為直接或間接地依附或引用請求項 3、4、6，亦同上述理由。

5、請求項 25-27，所請之標的為「抗體」，然而所依附之請求項 24 之標的為「抗體或該抗體之機能性片段」，標的不一致，致請求項不明確。

6、請求項 28，所述「如“選自包含”請求項…」，建議刪除該「選自包含」，以臻明確。又所述「其為了使抗體依賴性細胞傷害活性增強，而糖鏈修飾被調節」，僅以預期達到所述的效果來界定，但沒有限定實現所述效果所必需的技術手段，該發明所屬技術領域中具有通常知識者就該等特徵無法理解所述抗體或該抗體之機能性片段的具體結構為何，無法了解「糖

鏈修飾被調節」具有何種結構特徵，導致所請不明確。另參酌我國發明實體審查基準第 2 篇第 1 章 2.4.2，請求項之記載應簡潔，除記載必要技術特徵外，不得對技術手段達成之功效、目的或用途的原因、理由或背景說明，作不必要之記載，併予指明。

7、請求項 4-8、13、24、27、28、33-37、40、41 係多項附屬項，惟其直接或間接依附於多項附屬項，不符專利法第 26 條第 4 項暨其施行細則第 18 條第 5 項之規定。

8、本案序列表數字識別號<110>，請依本局訂定之格式記載，申請人的姓名或名稱須以中文表示，外國人須附記外文原文或英文或拉丁字母，且該項記載內容應不含發明人姓名；＜140＞應記載本案申請案號；＜141＞應記載本案申請日，否則不符專利法第 26 條第 4 項及同法施行細則第 17 條第 6 項之規定。

(四)依據引證 1 揭示內容，本案請求項 1-53 不符專利法第 22 條第 2 項之規定。

1、請求項 1-13，引證 1【摘要；說明書第 40 頁】揭示抗 CDH6 抗體、抗體片段、抗體藥結合物及其用於治療癌症的用途，特別是關於結合至 CDH6 且此結合後內化的抗體及抗體片段(例如抗原結合片段)；引證 1【說明書第 17 頁】揭示所述抗體藥結合物用來製備醫藥組合物，及治療有需要之患者之 CDH6 陽性癌症，如卵巢癌、腎癌、肝癌或甲狀腺癌等；引證 1【實例 1；表 5】揭示藉由噬菌體呈現技術篩選及鑑別 CDH6 抗體，如 NOV0712；引證 1【實例 7；圖 4】

揭示 NOV0712 與 CDH6 之 EC 域 5(EC5)結合；引證 1【實例 12；圖 11】揭示抗體藥結合物 NOV0712-SPDB-DM4 引起最大的抗腫瘤作用，給藥後 70 天消退，以及 NOV0710-SPDB-DM4 為活性次最強的抗 CDH6-SPDB-DM4；引證 1【圖 3；說明書第 156、157 頁】揭示 CDH6 之五個 EC 域(細胞外域)，其中 EC1 為人類 CDH6 之第 54-159 號之胺基酸序列；EC2 為人類 CDH6 之第 160-268 號之胺基酸序列；EC3 為人類 CDH6 之第 269-383 號之胺基酸序列；EC4 為人類 CDH6 之第 384-486 號之胺基酸序列；EC5 為人類 CDH6 之第 487-608 號之胺基酸序列。另查本案說明書【0234】之內容，可知本案實施例所使用的抗 CDH6 抗體 NOV0712 係參照引證 1 所載之 NOV0712 之輕鏈全長、及重鏈全長之胺基酸序列而製作。引證 1 與所請者之差異在於，引證 1 揭示抗 CDH6 抗體 NOV0712，係特異性辨識 CDH6 之 EC5，而本案發明之抗 CDH6 抗體，係特異性辨識 CDH6 之 EC3(即序列識別號 4 之胺基酸序列)，以及引證 1 並未揭示與本案所請抗體相同之 CDR、輕/重鏈可變區、輕/重鏈之序列，但是引證 1 已揭示與 CDH6 之 EC5 特異性地結合之抗 CDH6 抗體，及 CDH6 之五個 EC 域各自之序列，因此該發明所屬技術領域中具有通常知識者根據引證 1 內容當有合理動機測試結合於 CDH6 之五個不同 EC 域之抗體功效，以例行性實驗方式製備出各式結合於 CDH6 之五個不同 EC 域之抗 CDH6 抗體，並測試該等抗體對抗原的親和性等功效，進而篩選出可用來治療 CDH6 陽性癌症者。再者，如前述

(三)-1、3、4 所論述，所請範圍涵蓋抗體 H01L02、H02L02、H02L03、H04L02 以外之抗體，根據本案說明書並無法得知所請範圍是否皆能夠產生無法預期之功效，故不具進步性。

2、請求項 14-53，理由如(四)-1 所述，所請多核苷酸、表現載體、宿主細胞、製造抗體的方法、抗體-藥物結合物、醫藥組成物及製藥用途等，係以該等抗體為技術特徵者或為該等抗體之醫療應用，亦為發明所屬技術領域中具通常知識者依據引證 1 揭示內容及習知技術可輕易推知者，故係屬可輕易完成的部分，而本案於說明書中亦未揭示所請範圍相較先前技術之無法預期的功效，故所請不具進步性。

(五)引證文件：

引證 1、 TW 201613643 A 2016/04/16。

二、本案如有修正、訂正，應依專利法第 43 條、第 44 條第 3 項、專利法施行細則第 36 條至第 38 條之規定辦理，並請依專利修正申請書、專利誤譯訂正申請書之規定撰寫。

三、若需當面示範或說明者，請以「面詢申請書」敘明面詢所依據之版本、面詢事項及說明並繳交規費新台幣 1 千元，本局認為有必要時，將另行通知面詢地點及時間。

四、檢送本案檢索報告 1 份。本案檢索報告如附有引證用之非專利文獻，僅供專利申請人個人參考之用，如涉及其他利用該著作之行為(如：列印紙本對公眾散布、將檔案上傳網路等)，仍應取得著作財產權人之同意或授權，以避免侵權。

正本：日商第一三共股份有限公司（代理人：丁國隆　專利代理人、黃政誠　專利師）

副本：



附件

第107116035號專利申請案檢索報告

1.申 請 日： 107年5月11日	
2.優先權日： 2017年5月15日	
3.本案國際專利分類號(IPC)：	***C07K16/28*** (2006.01) , ***C12N15/13*** (2006.01) ***C12N15/63*** (2006.01) , ***C12P21/08*** (2006.01) ***A61K47/68*** (2017.01) , ***A61K31/4375*** (2006.01) ***A61P35/00*** (2006.01)
4.檢索國際專利分類號(IPC)範圍：	C07K/16/28,C12N/15/13,C12N/15/63,C12P/21/08,A61K/47/68,A61K/31/4375,A61P/35/00 C07K16/28 (2006.01),C12N15/13 (2006.01),C12N15/63 (2006.01),C12P21/08 (2006.01),A61K47/68 (2017.01),A61K31/4375 (2006.01),A61P35/00 (2006.01)
5.檢索使用資料庫名稱：(關鍵詞) TIPO全球/全域專利資料庫、國內外專利資料庫全域系統	

關聯性代碼	引用文獻資料與相關段落處	相關聯請求項
X	1. TW 201613643 A 2016/04/16 摘要；說明書第17、40、156、157頁；實例1、實例7、實例12；表5；圖3、圖4、圖11	1-53

關聯性代碼說明：

X：單獨引用即足以否定發明新穎性或進步性之特別相關的文獻。

Y：結合一或多篇其他文獻後足以否定發明進步性之特別相關的文獻。

A：一般技術水準之參考文獻。

D：說明書已記載之文獻。

E：申請在前、公開／公告在後之專利文獻。

O：公開使用、販賣或展覽陳列之文件。

P：申請日與優先權日間公開之文獻。

L：其他理由引用之文獻。

完成日： 111年5月4日

Electronic Patent Application Fee Transmittal	
Application Number:	16613203
Filing Date:	13-Nov-2019
Title of Invention:	ANTI-CDH6 ANTIBODY AND METHOD OF PRODUCING AN ANTI-CDH6 ANTIBODY-DRUG CONJUGATE
First Named Inventor/Applicant Name:	Atsuko SAITO
Filer:	Michael D. Kaminski/Rebecca Fincutter
Attorney Docket Number:	098065-0249
Filed as Large Entity	

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**260**

Electronic Acknowledgement Receipt	
EFS ID:	46214489
Application Number:	16613203
International Application Number:	
Confirmation Number:	6337
Title of Invention:	ANTI-CDH6 ANTIBODY AND METHOD OF PRODUCING AN ANTI-CDH6 ANTIBODY-DRUG CONJUGATE
First Named Inventor/Applicant Name:	Atsuko SAITO
Customer Number:	22428
Filer:	Michael D. Kaminski/Rebecca Fincutter
Filer Authorized By:	Michael D. Kaminski
Attorney Docket Number:	098065-0249
Receipt Date:	18-JUL-2022
Filing Date:	13-NOV-2019
Time Stamp:	16:31:51
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$260
RAM confirmation Number	E20227HG33013696
Deposit Account	190741
Authorized User	Rebecca Fincutter
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	098065-0249_IDS_F_Transmittal.pdf	145337 d8a4c05ed0d56a56284e901d18fe0dc99b6f59db	no	3
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	098065-0249_SB08_F.pdf	147266 a4edfa196a40c06d1fcb3069e3b7345bf86d6b05	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	F1--TW_201613643A.pdf	18829170 24d5694db240fb37ce41d455ca1e613f288df0ab	no	403
Warnings:					
Information:					
4	Other reference-Patent/Application/ Search Documents	F2--Office_Action_and_Search_Report_issued.pdf	1312880 73428b65f48252965b913a2a4944fb8f4ac0a9e8	no	34
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	38467 403f8f3ae17d8040984b560b8cba33642aeb3c1b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	20473120		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Atty. Dkt. No. 098065-0249

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Atsuko SAITO
Title:	ANTI-CDH6 ANTIBODY AND ANTI-CDH6 ANTIBODY-DRUG CONJUGATE
Application No.:	16/613,203
International Filing Date:	5/14/2018
371(c) Date:	11/13/2019
Examiner:	LANDSMAN, ROBERT S
Art Unit:	1647
Confirmation No.:	6337

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicant does not waive

any rights to take any action, which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

CONCISE EXPLANATION OF RELEVANCE

Reference F1 was cited in an Office Action dated May 10, 2022 issued in corresponding Taiwanese Patent Application No. 107116035. The Taiwanese Office Action is also submitted as Reference F2, with its English-language machine translation.

An English-language abstract is provided for Reference F1.

References F1 and previously cited International Patent Publication No. WO 2016/024195A1 (cited by the Examiner in the Restriction Requirement dated November 12, 2021) belong to the same patent family, whereby the English-language document may assist the Examiner in understanding the content of the foreign-language patent document.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(d), on or before payment of the issue fee.

STATEMENT UNDER 37 CFR §1.97(e)

The undersigned hereby states in accordance with 37 CFR §1.97(e)(1) that each item of information contained in this information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three (3) months prior to filing of this Statement.

FEE

Fees in the amount of $260.00 to cover the fee associated with an information disclosure statement are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required for this application to Deposit Account Number 19-0741.

Atty. Dkt. No. 098065-0249

Respectfully submitted,

Date 2022-07-18

By /Michael D. Kaminski/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5490
Facsimile: (202) 672-5399

Michael D. Kaminski
Attorney for Applicant
Registration No. 32,904

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 05/11/2022
FOLEY & LARDNER LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/613,203	11/13/2019	Atsuko SAITO	098065-0249	6337

TITLE OF INVENTION: ANTI-CDH6 ANTIBODY AND METHOD OF PRODUCING AN ANTI-CDH6 ANTIBODY-DRUG CONJUGATE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	08/11/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
LANDSMAN, ROBERT S	1647	424-181100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Foley & Lardner LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: DAIICHI SANKYO COMPANY, LIMITED

(B) RESIDENCE: (CITY and STATE OR COUNTRY): TOKYO, JAPAN

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ☒ Corporation or other private group entity ❑ Government

4a. Fees submitted: ☒ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

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5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Michael D. Kaminski/ Date 2022-08-01

Typed or printed name Michael D. Kaminski Registration No. 32,904

Electronic Patent Application Fee Transmittal

Application Number:	16613203
Filing Date:	13-Nov-2019
Title of Invention:	ANTI-CDH6 ANTIBODY AND METHOD OF PRODUCING AN ANTI-CDH6 ANTIBODY-DRUG CONJUGATE
First Named Inventor/Applicant Name:	Atsuko SAITO
Filer:	Michael D. Kaminski/Audrey Titus
Attorney Docket Number:	098065-0249

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt	
EFS ID:	46312369
Application Number:	16613203
International Application Number:	
Confirmation Number:	6337
Title of Invention:	ANTI-CDH6 ANTIBODY AND METHOD OF PRODUCING AN ANTI-CDH6 ANTIBODY-DRUG CONJUGATE
First Named Inventor/Applicant Name:	Atsuko SAITO
Customer Number:	22428
Filer:	Michael D. Kaminski/Audrey Titus
Filer Authorized By:	Michael D. Kaminski
Attorney Docket Number:	098065-0249
Receipt Date:	01-AUG-2022
Filing Date:	13-NOV-2019
Time Stamp:	16:54:10
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1200
RAM confirmation Number	E202281G55303853
Deposit Account	
Authorized User	
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	098065-0249_IssueFee_2022-08-01.pdf	147011 3f627b7378aa19ab38169f5eba41834f48aced0a	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	38245 7340a4e75092aae1caf688acf296813b87069671	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	185256		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PRINTER RUSH
(PTO ASSISTANCE)

Application: 16613203	Examiner: Landsman	GAU: 1647
From:	Location: RTFM	Creation Date: 08/01/2022

Week Date: 5/9/2022

DOC CODE	DOC DATE	MISCELLANEOUS
[ ] 1449		[ ] Continuing Data
[X] IDS	07/18/2022	[ ] Foreign Priority
[ ] CLM		[ ] Document Legibility
[ ] IIFW/FWCLM		[ ] Fees
[ ] SRFW		[ ] Petition (TC)
[ ] DRW		[ ] Other
[ ] OATH		
[ ] 312		
[ ] SPEC		

[RUSH] Message:

Please respond to the 07/18/22 IDS.

Thank you

[XRUSH] Response:

Initials: _____

Examiner: PUBS contact - James Leija, (703) 756-1197
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REV: AUG 16

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/613,203	11/13/2019	Atsuko SAITO	098065-0249	6337

22428 7590 08/05/2022

FOLEY & LARDNER LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
LANDSMAN, ROBERT S	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
08/05/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@foley.com

Corrected ***Notice of Allowability***	**Application No.** 16/613,203	**Applicant(s)** SAITO et al.	
	Examiner ROBERT S LANDSMAN	**Art Unit** 1647	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the IDS filed 7/18/22.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-13 and 24-28 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ROBERT S LANDSMAN/
Primary Examiner, Art Unit 1647

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/613,203	SAITO et al.
	Examiner	Art Unit
	ROBERT S LANDSMAN	1647

CPC							
Symbol						Type	Version
A61K	/	47	/	6803		F	2017-08-01
A61K	/	47	/	6849		I	2017-08-01
A61P	/	35	/	00		I	2018-01-01
A61K	/	31	/	4745		I	2013-01-01
C07K	/	16	/	28		I	2013-01-01
C07K	/	2317	/	24		A	2013-01-01
C07K	/	2317	/	40		A	2013-01-01
C07K	/	2317	/	41		A	2013-01-01
C07K	/	2317	/	565		A	2013-01-01
C07K	/	2317	/	732		A	2013-01-01
C07K	/	2317	/	76		A	2013-01-01
C07K	/	2317	/	77		A	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	18	
/ROBERT S LANDSMAN/ Primary Examiner, Art Unit 1647	03 August 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office

Part of Paper No.: 20220803

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/613,203	SAITO et al.
	Examiner	**Art Unit**
	ROBERT S LANDSMAN	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K47/68	/	47	/	68	
C07K16/28	/	16	/	28	

NON-CLAIMED					
A61P35/00	/	35	/	00	
A61K31/4745	/	31	/	4745	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	18	
/ROBERT S LANDSMAN/ Primary Examiner, Art Unit 1647	03 August 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office

Part of Paper No.: 20220803

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/613,203	SAITO et al.
	Examiner	**Art Unit**
	ROBERT S LANDSMAN	1647

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10												
	2		11												
	3		12												
	4		13												
	5		24												
	6		25												
	7		26												
	8		27												
	9		28												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 18	
/ROBERT S LANDSMAN/ Primary Examiner, Art Unit 1647 (Primary Examiner)	03 August 2022 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No.: 20220803

PRINTER RUSH
(PTO ASSISTANCE)

Application: 16613203	Examiner: Landsman	GAU: 1647
From:	Location: RTFM	Creation Date: 08/01/2022

Week Date: 5/9/2022

DOC CODE	DOC DATE	MISCELLANEOUS
[ ] 1449		[ ] Continuing Data
[X] IDS	07/18/2022	[ ] Foreign Priority
[ ] CLM		[ ] Document Legibility
[ ] IIFW/FWCLM		[ ] Fees
[ ] SRFW		[ ] Petition (TC)
[ ] DRW		[ ] Other
[ ] OATH		
[ ] 312		
[ ] SPEC		

[RUSH] Message:

Please respond to the 07/18/22 IDS.

Thank you

[XRUSH] Response:

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Initials: /RL/

Examiner: PUBS contact - James Leija, (703) 756-1197
NOTE: This form will be included as part of the official USPTO record with the response document coded as XRUSH.
REV: AUG 16

PTO/SB/08 (modified)

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	16/613,203
				Filing Date	5/14/2018
Date Submitted: July 18, 2022				**First Named Inventor**	Atsuko SAITO
				Art Unit	1647
(use as many sheets as necessary)				Examiner Name	LANDSMAN, ROBERT S
Sheet	1	of	1	Attorney Docket Number	098065-0249

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
/R.S.L/	F1	TW-201613643-A	04-16-2016	NOVARTIS AG	=WO 2016/024195A1	Abs.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
/R.S.L/	F2	Office Action and Search Report issued in corresponding Taiwanese Patent Application No. 107116035 dated May 10, 2022.	✓

Examiner Signature	/ROBERT S LANDSMAN/	Date Considered	08/03/2022

To: ipdocketing@foley.com,,
From: PAIR_eOfficeAction@uspto.gov
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Aug 05, 2022 04:23:24 AM

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Application	Document	Mailroom Date	Attorney Docket No.
16613203	NOA	08/05/2022	098065-0249
	1449	08/05/2022	098065-0249

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	16/613,203
Date Submitted: September 30, 2020				**Filing Date**	5/14/2018
				First Named Inventor	Atsuko SAITO
(use as many sheets as necessary)				Art Unit	1643
				Examiner Name	NOT YET ASSIGNED
Sheet	2	of	12	Attorney Docket Number	098065-0249

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B50	2011/0045587-A1	02-24-2011	SULLIVAN ET AL.	
	B51	2011/0059076-A1	03-10-2011	MCDONAGH ET AL.	=B95
	B52	2011/0070248-A1	03-24-2011	ICHIKAWA ET AL.	
	B53	2011/0229406-A1	09-22-2011	HETTMANN ET AL.	
	B54	2011/0293513-A1	12-01-2011	GOVINDAN ET AL.	
	B55	2012/0121615-A1	05-17-2012	FLYGARE ET AL.	
	B56	2012/0171201-A1	07-05-2012	SAPRA, PUJA	=B74 =B96
	B57	2012/0201809-A1	08-09-2012	BHAT ET AL.	=B97
	B58	2012/0328634-A1	12-27-2012	GOVINDAN, SERENGULAM	
	B59	2013/0089872-A1	04-11-2013	NAKAMURA ET AL.	
	B60	2013/0123178-A1	05-16-2013	DIMARCHI ET AL.	=B98
	B61	2013/0216561-A1	08-22-2013	GOVINDAN	
	B62	2014/0004078-A1	01-02-2014	GOVINDAN, SERENGULAM	
	B63	2015/0297748-A1	10-22-2015	MASUDA ET AL.	
	B64	2015/0352224-A1	12-10-2015	NAITO ET AL.	
	B65	2016/0279259-A1	09-29-2016	MASUDA ET AL.	
	B66	2016/0287722-A1	10-06-2016	~~IMMUNOMEDICS, INC~~.	Govindan
	B67	2017/0021031-A1	01-26-2017	HETTMANN ET AL.	
	B68	2019/0151328-A1	05-23-2019	HETTMANN ET AL.	

Change(s) applied to document
/J.E./
6/3/2022

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B69	CA-2815154-A1	02-09-2012	U3 PHARMA GMBH DE		
	B70	CA-2859255-A1	06-20-2013	SEATTLE GENETICS, INC.		
	B71	CA-2927832-A1	11-24-2011	CERULEAN PHARMA. INC.		
	B72	CN-101023100-A	08-22-2007	GENENTECH INC	=B38	
	B73	CN-101490087-A	07-22-2009	GENENTECH INC		abs
	B74	CN-102481364-A	05-30-2012	ENZON PHARMACEUTICALS INC	=B74	
	B75	CN-1227499-A	09-01-1999	DAIICHI SEIYAKU CO		abs
	B76	CN-1764478-A	04-26-2006	IMMUNOMEDICS INC		abs
	B77	EP-1 155 702-A1	11-21-2001	DAIICHI PHARMACEUTICAL CO., LTD.		
	B78	EP-2 594 589-A1	05-22-2013	SAPPORO MEDICAL UNIVERSITY ET AL.		
	B79	EP-2 799 452-A1	11-05-2014	LIVTECH INC		
	B80	EP-2 907 824-A1	08-19-2015	DAIICHI SANKYO CO LTD		

Examiner Signature		Date Considered	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.S.L/

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/613,203	09/20/2022	11446386	098065-0249	6337

22428 7590 08/31/2022

FOLEY & LARDNER LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 233 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

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Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

Atsuko SAITO, Tokyo, JAPAN;
Tsuyoshi HIRATA, Tokyo, JAPAN;
Kensuke NAKAMURA, Tokyo, JAPAN;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

DAIICHI SANKYO COMPANY, LIMITED, Tokyo, JAPAN;

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Application	Document	Mailroom Date	Attorney Docket No.
16613203	ISSUE.NTF	08/31/2022	098065-0249

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