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(54)名稱

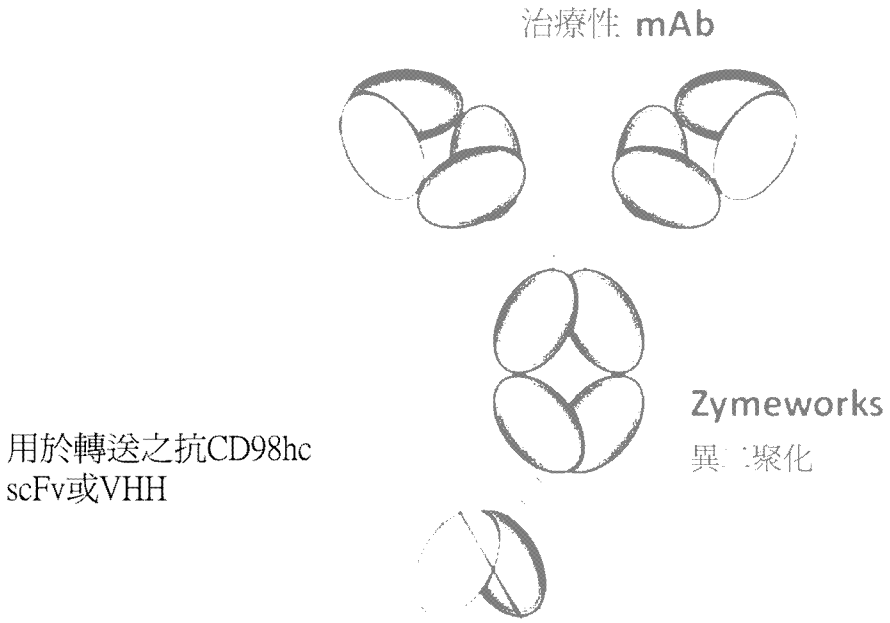
抗 CD98 抗體及其用途

(57)摘要

描述單株抗 CD98 抗體及其抗原結合片段，其用於將劑遞送至有需要之對象的腦部。亦描述接合物及融合建構體，其含有偶合至治療劑或診斷劑（諸如第二抗體及其抗原結合片段）之抗 CD98 抗體或其抗原結合片段，其用於治療或檢測神經病症及/或將治療劑或診斷劑遞送跨過血腦障壁。亦描述編碼該抗體、接合物、及融合建構體之核酸及相關之重組宿主細胞。

Monoclonal anti-CD98 antibodies and antigen-binding fragments thereof for delivering an agent to the brain of a subject in need thereof are described. Also described are conjugates and fusion constructs containing the anti-CD98 antibody or antigen-binding fragment thereof coupled to a therapeutic or diagnostic agent, such as a second antibody and antigen-binding fragment thereof, for treating or detecting a neurological disorder and/or delivering a therapeutic or diagnostic agent across the blood-brain barrier. Also described are nucleic acids encoding the antibodies, conjugates and fusion constructs and related recombinant host cells.

指定代表圖：



【圖1】

202142569

【發明摘要】

【中文發明名稱】　抗CD98抗體及其用途

【英文發明名稱】　ANTI-CD98 ANTIBODIES AND USES THEREOF

【中文】

描述單株抗CD98抗體及其抗原結合片段，其用於將劑遞送至有需要之對象的腦部。亦描述接合物及融合建構體，其含有偶合至治療劑或診斷劑（諸如第二抗體及其抗原結合片段）之抗CD98抗體或其抗原結合片段，其用於治療或檢測神經病症及/或將治療劑或診斷劑遞送跨過血腦障壁。亦描述編碼該抗體、接合物、及融合建構體之核酸及相關之重組宿主細胞。

【英文】

Monoclonal anti-CD98 antibodies and antigen-binding fragments thereof for delivering an agent to the brain of a subject in need thereof are described. Also described are conjugates and fusion constructs containing the anti-CD98 antibody or antigen-binding fragment thereof coupled to a therapeutic or diagnostic agent, such as a second antibody and antigen-binding fragment thereof, for treating or detecting a neurological disorder and/or delivering a therapeutic or diagnostic agent across the blood-brain barrier. Also described are nucleic acids encoding the antibodies, conjugates and fusion constructs and related recombinant host cells.

【指定代表圖】圖1

【代表圖之符號簡單說明】無

【特徵化學式】無

【發明說明書】

【中文發明名稱】　抗CD98抗體及其用途

【英文發明名稱】　ANTI-CD98 ANTIBODIES AND USES THEREOF

相關申請案之交互參照

【0001】　本申請案主張美國臨時專利申請案第63/006,988號（2020年4月8日提出申請）及美國臨時專利申請案第63/035,961號（2020年6月8日提出申請）之優先權，該等專利申請案之揭露全文以引用方式併入本文中。

電子提交序列表之參照

【0002】　本申請案含有序列表，該序列表已以ASCII格式序列表經由EFS-Web電子提交，檔案名稱為「JBI6290WOPCT1_Sequence_ Listing」，創建日期2021年3月31日，檔案大小478 kB。經由EFS-Web提交之序列表係本說明書之一部分，其全文以引用方式併入本文中。

【技術領域】

【0003】　本發明關於一種結合至人類CD98hc之血腦障壁穿梭劑(blood-brain barrier shuttle)及其使用方法。

【先前技術】

【0004】　雖然血腦障壁(BBB)防止有害物質進入腦部且對於腦內恆定(brain homeostasis)是不可或缺的，其也會對於將藥物有效率遞送至腦部造成難以克服的障礙。大分子（諸如單株抗體及其他生物治療劑）對於治療/檢測中樞神經系統(CNS)中之病理學具有相當大的治療/診斷潛力。然而，其等進入腦部之途徑受到BBB阻礙。先前研究已說明，注射在血流中之IgG只有極小百分比（大約0.1%）能夠穿透BBB進入CNS隔室(Felgenhauer, *Klin. Wschr.* 52: 1158-1164, 1974))。由於抗體在CNS內之低濃度，這將會限制任何藥理作用。

【0005】 已研究許多方法以改善治療性單株抗體(mAb)之腦部遞送，包括受體介導之胞吞轉送(RMT)的使用。RMT利用BBB內腔側上大量表現之受體以輸送通過腦部內皮細胞。產生用於將治療性mAb遞送至腦部中之臨床上可行平台的先前努力已著重在抗體工程改造，以提高胞吞轉送之效率，並透過對於結合價、pH依賴性、及親和力之觀察而獲得進展（綜述於Goulatis et al., 2017, *Curr Opin Struct Biol* 45: 109-115中）。然而，轉用於非人類靈長類(non-human primate, NHP)及臨床上已受到下列限制：由於目標介導之藥物動向(target-mediated drug disposition, TMDD)所致之快速末梢清除及由於急性網狀紅血球耗盡所致之安全性(Gadkar K, et al. Eur J Pharm Biopharm. 2016; 101: 53-61)。

【0006】 CD98重鏈次單元(CD98hc)係溶質載劑家族的成員，且與許多CD98輕鏈成員異二聚化以在BBB處形成胺基酸輸送蛋白(Zuchero YJ, et al. Neuron. 2016; 89(1): 70-82, citing Boado RJ, et al. PNAS 1999; 96(21): 12079-84)。CD98hc之胞內部分作用於介導整合素傳訊，其在細胞生長及腫瘤形成兩者中發揮作用(Zuchero YJ, et al. Neuron. 2016; 89(1): 70-82, citing Feral CC, et al. J Cell Biol 2007; 178: 701-711; Cantor JM and Ginsburg MH. J Cell Sci 2012; 125: 1373-82)。CD98hc在人類腦部微血管系統上高度表現，且已使用抗CD98hc雙特異性抗體傳遞治療性抗體至小鼠腦部(Zuchero YJ, et al. Neuron. 2016; 89(1): 70-82)。然而，尚未有針對在人類中安全靶向CD98hc的能力進行研究。

【0007】 因此，需要一種抗CD98單株抗體或其抗原結合片段，其可用於將藥物有效率穿梭進入腦部且其安全性及PK經改善。

【發明內容】

【0008】 本申請案關於一種用於腦部遞送之經最佳化平台，其不僅考量所遞送之劑（諸如治療性單株抗體(mAb)）的腦部濃度，亦考量mAb之治療相關特性（包括mAb之末梢藥物動力學、安全性、及藥效動力學）。平台採用CD98結合分子，尤其是結合至CD98、較佳地人類CD98重鏈(huCD98hc)之抗體或其抗原結合片段，其中CD98結合分子在6.8至7.8之中性pH（諸如生理pH（例如

7.4））及4.5至6.5之酸性pH（諸如常見於內體隔室(endosomal compartment)中之酸性pH）兩者下，具有經最佳化之輸送功能，其由結合速率k_a及解離速率k_d值定義。

【0009】 發明人出乎意料地發現，最佳值不單純是最快的結合速率k_a值及最慢的解離速率k_d值，如在典型抗體-目標交互作用中可能預期的。亦即，對於此系統，不必然會想要使用以相對高速率與CD98「結合」及締合、然後更慢地自CD98解離的分子以具有最長之抗體-目標複合體壽命。而是，在一個實施例中，本文所述之CD98結合劑的經最佳化輸送功能較佳地在生理pH（例如，7.4）及較低pH（例如，6.5或6.0）兩者下具有類似（例如，在相同的數量級內）的k_a速率，但是在較低pH（例如，6.5或6.0）下具有比在生理pH（例如，7.4）下之k_d速率快的解離速率k_d。

【0010】 在一個大致態樣中，本申請案描述一種抗CD98抗體或其抗原結合片段，其用於將治療劑或診斷劑遞送至有需要之對象的腦部，其中該抗CD98抗體或其抗原結合片段在中性pH下以至少1 nM、較佳地1 nM至500 nM之解離常數K_D且在酸性pH、較佳地pH 5下以至少10^{-4} sec^{-1}、較佳地10^{-4}至10^{-1} sec^{-1}之解離速率常數k_d結合至CD98、較佳地人類CD98。

【0011】 在一些實施例中，本申請案之抗CD98抗體或其抗原結合片段在中性pH下具有2×10^{-2}至2×10^{-4} sec^{-1}、較佳地9×10^{-3} sec^{-1}之解離速率常數k_d。

【0012】 在另一實施例中，本文所述之某些CD98結合劑的經最佳化輸送功能較佳地在生理酸性pH（例如，7.4）下，具有至少1.05×10^5之k_a速率及至少9×10^{-3} s^{-1}或更快之k_d速率。前述pH、KD、k_a、及k_d參數僅反映經最佳化之胞吞轉送條件，且絕不會對吾人的發現造成限制，即接合至本文中某些CD98結合劑之某些分子的CD98介導之輸送仍可能在超出所述之較佳參數的情況下發生。

【0013】 在一個大致態樣中，本申請案關於一種抗體或其抗原結合片段，其用於將劑遞送至有需要之對象的腦部，其中該抗體或其抗原結合片段結合至CD98、較佳地人類CD98重鏈(huCD98hc)，該抗體或其抗原結合片段包含

(1) 包含重鏈互補決定區(HCDR) HCDR1、HCDR2、及 HCDR3 之重鏈可變區及包含輕鏈互補決定區(LCDR) LCDR1、LCDR2、及 LCDR3 之輕鏈可變區，其中該 HCDR1、HCDR2、HCDR3、LCDR1、LCDR2、及 LCDR3 具有下列之胺基酸序列：

i) 分別為 SEQ ID NO: 7、8、9、10、11、及 12；

(ii) 分別為 SEQ ID NO: 67、68、69、70、71、及 72；

(iii) 分別為 SEQ ID NO: 89、90、91、92、93、及 94；

(iv) 分別為 SEQ ID NO: 113、114、115、116、117、及 118；

(v) 分別為 SEQ ID NO: 123、124、125、126、127、及 128；

(vi) 分別為 SEQ ID NO: 133、134、135、136、137、及 138；

(vii) 分別為 SEQ ID NO: 150、151、152、153、154、及 155；

(viii) 分別為 SEQ ID NO: 160、161、162、163、164、及 165；

(ix) 分別為 SEQ ID NO: 170、171、172、173、174、及 175；

(x) 分別為 SEQ ID NO: 180、181、182、183、184、及 185；

(xi) 分別為 SEQ ID NO: 194、195、196、197、198、及 199；或

(xii) 分別為 SEQ ID NO: 204、205、206、207、208、及 209；或

(2) 重鏈上之單可變域(VHH)，其包含具有下列之胺基酸序列的重鏈互補決定區(HCDR) HCDR1、HCDR2、及 HCDR3：

(i) 分別為 SEQ ID NO: 29、30、及 31；

(ii) 分別為 SEQ ID NO: 48、49、及 50；或

(iii) 分別為 SEQ ID NO: 143、144、及 145。

【0014】 在某些實施例中，本申請案關於一種抗CD98 VHH片段，其包含與SEQ ID NO: 28、SEQ ID NO: 47、或SEQ ID NO: 142具有至少80%、諸如至少85%、90%、95%、或100%序列同一性之胺基酸序列。

【0015】 在其他實施例中，本申請案關於一種抗CD98單鏈可變片段(scFv)，其包含經由連接子共價連接至輕鏈可變區之重鏈可變區，較佳地該連接子具有

SEQ ID NO: 189之胺基酸序列。更佳地，scFv包含與下列之胺基酸序列具有至少80%、諸如至少85%、90%、95%、或100%序列同一性之胺基酸序列：SEQ ID NO: 6、SEQ ID NO: 66、SEQ ID NO: 88、SEQ ID NO: 112、SEQ ID NO: 122、SEQ ID NO: 132、SEQ ID NO: 149、SEQ ID NO: 159、SEQ ID NO: 169、SEQ ID NO: 179、SEQ ID NO: 193、或SEQ ID NO: 203。

【0016】 本申請案之另一態樣關於一種接合物，其包含偶合至治療劑或診斷劑（諸如神經病症藥物或用於檢測神經病症之劑）之本申請案之抗CD98抗體或其抗原結合片段。較佳地，治療劑或診斷劑係結合至腦部目標之第二抗體或其抗原結合片段。

【0017】 在某些實施例中，本申請案關於一種融合建構體，其包含共價連接至第二抗體或其抗原結合片段的本申請案之抗CD98抗體或其抗原結合片段，該第二抗體或其抗原結合片段結合至腦部目標，諸如選自由下列所組成之群組的腦部目標：β-分泌酶1 (BACE1)、β類澱粉蛋白(Aβ)、表皮生長因子受體(EGFR)、人類表皮生長因子受體2 (HER2)、Tau、載脂蛋白E4 (ApoE4)、α-突觸核蛋白、CD20、亨丁頓蛋白(huntingtin)、普里昂蛋白(PrP)、富白胺酸重複激酶2 (LRRK2)、parkin、早老素1、早老素2、γ分泌酶、死亡受體6 (DR6)、類澱粉蛋白前驅蛋白(APP)、p75神經營養因子受體(p75NTR)、及凋亡蛋白酶6。

【0018】 在某些實施例中，本申請案之融合建構體包含第二抗體或其抗原結合片段，該第二抗體或其抗原結合片段結合至Tau且包含分別具有SEQ ID NO: 213至218之胺基酸序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2、及LCDR3。較佳地，第二抗體係單株抗體，該單株抗體包含具有SEQ ID NO: 110之胺基酸序列的重鏈及具有SEQ ID NO: 111之胺基酸序列的輕鏈。

【0019】 在一個實施例中，本申請案之融合建構體包含本申請案之抗CD98抗體或其抗原結合片段、較佳地抗huCD98hc VHH或scFv片段，該抗TfR抗體或其抗原結合片段經由連接子共價連接至結合至腦部目標之第二抗體或其抗原結合片段之兩個重鏈中僅一者之羧基端。較佳地，連接子具有SEQ ID NO: 190或SEQ ID NO: 191之胺基酸序列。

【0020】 在某些實施例中，第二抗體或其抗原結合片段之兩個重鏈的各者包含經修飾恆定重鏈3 (CH3)域（相較於野生型CH3域），以促進兩個重鏈之間的異二聚體形成。可使用促進兩個重鏈之間的異二聚體形成之任何突變。較佳地，第一重鏈之經修飾CH3域在位置T350、L351、F405、及Y407包含胺基酸修飾，且第二重鏈之經修飾CH3域在位置T350、T366、K392、及T394包含胺基酸修飾。較佳地，在位置T350之胺基酸修飾係T350V、T350I、T350L、或T350M；在位置L351之胺基酸修飾係L351Y；在位置F405之胺基酸修飾係F405A、F405V、F405T、或F405S；在位置Y407之胺基酸修飾係Y407V、Y407A、或Y407I；在位置T366之胺基酸修飾係T366L、T366I、T366V、或T366M，在位置K392之胺基酸修飾係K392F、K392L、或K392M，且在位置T394之胺基酸修飾係T394W。更佳地，第一重鏈之經修飾異二聚體CH3域包含突變T350V、L351Y、F405A、及Y407V，且第二重鏈之經修飾異二聚體CH3域包含突變T350V、T366L、K392L、及T394W。在整份說明書中，抗體中胺基酸殘基之編號係根據如下列中所述之EU索引執行：Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)中所述的EU索引(EU index)，除非另有明確說明。

【0021】 在某些實施例中，第二抗體或其抗原結合片段之可結晶片段區（fragment crystallizable region，Fc區）含有改變（增加或減少）、較佳地消除效應功能（諸如抗體依賴性細胞毒性(ADCC)及/或補體依賴性細胞毒性(CDC)）的取代。較佳地，第二抗體或其抗原結合片段之Fc區包含降低或除去第二抗體或其抗原結合片段與Fcγ受體(FcγR)之結合且避免效應功能介導之毒性的一或多個胺基酸修飾。例如，第二抗體或其抗原結合片段之Fc區可在位置L234、L235、D270、N297、E318、K320、K322、P331、及P329包含一或多個胺基酸修飾，諸如L234A、L235A、及P331S中之一、二、或三個突變，其中胺基酸殘基之編號係根據如Kabat中所陳述之EU索引。

【0022】 在某些實施例中，第二抗體或其抗原結合片段之Fc區含有改變（增加或減少）、較佳地增加第二抗體或其抗原結合片段與新生兒Fc受體(FcRn)之結合的取代。較佳地，一或多個突變增強在酸性pH下之結合，更佳地Fc具有M252Y/S254T/T256E (YTE)突變，其中胺基酸殘基之編號係根據如Kabat中所陳述之EU索引。

【0023】 在某些實施例中，本申請案之融合建構體包含：

(1) 第一重鏈，其具有與選自由下列所組成之群組的胺基酸序列至少80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 13、16、19、22、25、32、35、38、41、44、51、54、57、60、63、73、76、79、82、85、95、98、101、104、107、119、129、139、146、156、166、176、186、200、210、及 219；

(2) 兩個輕鏈，其等各獨立地具有分別與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 14、17、20、23、26、33、36、42、45、52、55、58、61、64、74、77、80、83、86、96、99、102、105、108、120、130、140、147、157、167、177、187、201、211、及 220；及

(3) 第二重鏈，其具有分別與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 15、18、21、24、27、34、37、43、46、53、56、59、62、65、75、78、81、84、87、97、100、103、106、109、121、131、141、148、158、168、178、188、202、212、及 221。

【0024】 本申請案之另一大致態樣關於一種經單離之核酸，其編碼本申請案之抗體或抗原結合片段、接合物、或融合建構體。亦提供一種包含本申請案之經單離之核酸的載體、一種包含本申請案之核酸或載體的宿主細胞。

【0025】 本申請案之另一大致態樣關於一種生產本申請案之抗體或抗原結合片段、接合物、或融合建構體的方法。該方法包含在生產該抗體或抗原結合片段、該接合物、或該融合建構體之條件下，培養包含本申請案之核酸的細胞；

及自該細胞或細胞培養物回收該抗體或抗原結合片段、該接合物、或該融合建構體。

【0026】 進一步提供一種醫藥組成物，其包含本申請案之接合物或融合建構體及醫藥上可接受之載劑。

【0027】 本申請案之另一大致態樣關於一種治療或檢測有需要之對象的神經病症之方法，其包含向該對象投予有效量的本申請案之抗CD98抗體或其抗原結合片段、接合物、或融合建構體、或醫藥組成物。較佳地，神經病症係選自由下列所組成之群組：神經退化性疾病（諸如路易氏體病(Lewy body disease)、脊髓灰質炎後症候群、Shy-Draeger症候群、橄欖體橋腦小腦萎縮、巴金森氏症、多系統萎縮、紋狀體與黑質體退化症、脊髓小腦性失調症、脊髓性肌萎縮）、tau蛋白病(tauopathy)（諸如阿茲海默症及核上神經麻痺症）、普里昂疾病（諸如牛海綿狀腦病、羊搔癢症、庫賈氏症候群(Creutz-feldt-Jakob syndrome)、庫魯病、吉斯曼-史特斯勤-先克病(Gerstmann-Straussler-Scheinker disease)、慢性消耗病、及致死性家族性失眠症）、延髓性麻痺、運動神經元疾病、及神經系統異退化性病症(nervous system heterodegenerative disorder)（諸如Canavan病、亨丁頓舞蹈症(Huntington's disease)、神經元蠟樣脂褐質儲積症、亞歷山大氏病(Alexander's disease)、妥瑞氏症候群(Tourette's syndrome)、Menkes氏捲髮症候群、柯凱因氏症候群(Cockayne syndrome)、Halervorden-Spatz氏症候群、拉弗拉病(lafora disease)、雷特氏症候群(Rett syndrome)、肝豆狀核變性、Lesch-Nyhan氏症候群、及Unverricht-Lundborg氏症候群）、失智症（諸如匹克症(Pick's disease)及脊髓小腦性失調症）、及CNS及/或腦部之癌症（諸如身體其他地方之癌症所致的腦部轉移）。

【0028】 較佳地，本申請案之抗體或其抗原結合片段、接合物、融合建構體、或醫藥組成物經靜脈內投予。

【0029】 亦描述一種將治療劑或診斷劑遞送至有需要之對象的腦部之方法，其包含向該對象投予接合物，該接合物包含偶合至本申請案之抗CD98抗體或其抗原結合片段的治療劑或診斷劑。較佳地，治療劑或診斷劑係結合至腦部目標

之第二抗體或其抗原結合片段。更佳地，將偶合至本申請案之抗CD98抗體或其抗原結合片段的治療劑或診斷劑投予至對象的腦部導致Fc介導之效應功能降低且/或不誘導快速網狀紅血球耗盡，如相較於投予未偶合至抗CD98抗體或其抗原結合片段之治療劑或診斷劑。

【0030】 本發明之又另一大致態樣關於一種在有需要之對象中誘導抗體依賴性吞噬作用(ADP)而不刺激促發炎細胞介素的分泌之方法，其包含向該對象投予複合體，該複合體包含偶合至、較佳地共價接合至根據本發明之一實施例之其抗原結合片段的治療性抗體或其抗原結合片段，其中該治療性抗體或其抗原結合片段不具有效應功能，例如該治療性抗體或其抗原結合片段在位置L234、L235、D270、N297、E318、K320、K322、P331、及P329包含一或多個胺基酸修飾，諸如L234A、L235A、及P331S中之一、二、或三個突變，其中胺基酸殘基之編號係根據如Kabat中所陳述之EU索引。較佳地，治療性抗體或其抗原結合片段特異性結合至tau聚集物(tau aggregate)。

【0031】 本發明之其他態樣、特徵、及優點將由於下列揭露（包括本發明之實施方式及其較佳實施例、及隨附之申請專利範圍）而為顯而易見的。

【圖式簡單說明】

【0032】 前述發明內容以及下文實施方式在結合附圖閱讀時可更有利理解。出於說明本發明之目的，圖式中顯示目前較佳的實施例。然而應理解的是，本發明並不限於圖式中所示之確切實施例。

【0033】 本專利或申請文件至少含有一個以彩色製成的圖式。在提出申請並支付必要費用後，專利局會提供具有彩色圖式的本專利或專利申請公開案副本。

〔圖1〕係用於腦部遞送平台之三腳架(tripod) mAb格式的圖示。

〔圖2〕係顯示抗CD98hc Zymeworks三腳架抗體對^{3}H-白胺酸吸收之影響的長條圖。數據係四重複之平均值± SEM。虛線表示Zymeworks三腳架同型對照組(B624)的± (3 × SD)。

〔圖3〕係顯示三腳架mAb在人類腦部內皮細胞中之內化(internalization)的影像。三腳架mAb係染成紅色，核係染成藍色，且肌動蛋白係染成綠色。所顯示之影像係針對BBBB449。

〔圖4〕係顯示pH依賴性結合之圖，該結合係藉由將在pH 7.4下之解離速率與當將pH降低至6.5及6.0時之解離速率進行比較來評估。如果解離速率隨著pH降低而變快，則三腳架mAb得分為正。數據係針對BBBB578。

〔圖5〕係顯示三腳架mAb BBBB1067在人類腦部內皮細胞中之內化的影像。三腳架mAb係染成紅色，且肌動蛋白係染成綠色。

〔圖6〕係顯示*i.v*藥之mAb之大腦濃度的圖。所有腦部穿梭劑mAb均具有比非腦部穿梭劑mAb增加的暴露。個別的點代表各個動物(n=3)。

〔圖7〕係顯示mAb介導之吸收進入小神經膠細胞吞噬體的圖。相較於非腦部穿梭劑mAb (PT1B844)，所有腦部穿梭劑mAb均促進相似之吸收進入吞噬體。

【實施方式】

【0034】　各篇公開案、論文、及專利已於先前技術及整份說明書引用或描述；此等參考文獻之各者全文係以引用方式併入本文中。本說明書中所包括之對於文件、行動、材料、裝置、物品、或類似者的論述，其目的在於提供關於本發明的脈絡。此等論述並非承認，任一或所有此等情事形成了關於任何所揭示或請求之發明的先前技術部分。

【0035】　除非另有定義，否則本文中所使用之所有技術及科學用語，均與本發明有關技術領域中具有通常知識者所通常了解之意義相同。在其他方面，在本文中所使用的某些用語具有如本說明書所定之意義。在本文中所引用的所有專利、已公開專利申請案及公開案係以引用方式併入，猶如全文說明於本文中。必須注意的是，本文及附加之申請專利範圍中所使用之單數形式「一(a/an)」及「該(the)」皆包括複數指稱，除非上下文另有明確說明。

【0036】　除非另有說明，在本文中描述之任何數值（諸如濃度或濃度範圍）應理解為在所有情況下皆受到用語「約(about)」之修飾。因此，數值一般包括

記載值之± 10%。例如，10 mg之劑量包括9 mg至11 mg。如本文中所使用，數值範圍之使用明確包括所有可能的子範圍、在該範圍內之所有個別數值，包括在此類範圍內之整數及該等值之分數，除非上下文另有明確指示。

【0037】 如本文中所使用，多個所述元件之間的聯合用語「及/或(and/or)」係理解為涵蓋個別及組合選項兩者。例如，其中兩個元件係藉由「及/或」結合，第一選項係指第一元件在沒有第二元件的情況下之適用性。第二選項係指第二元件在沒有第一元件的情況下之適用性。第三選項係指第一及第二元件一起的適用性。這些選項之任一者應理解為落入該含義內，並因此滿足如本文中所使用之用語「及/或」之要求。該等選項之多於一者的並行適用性亦應理解為落入該含義內，並因此滿足用語「及/或」之要求。

【0038】 在整份說明書及隨附之申請專利範圍中，除非上下文另有規定，否則詞語「包含(comprise)」及諸如「包含(comprises/comprising)」的變化形式，將被理解為暗示包括所述整數或步驟或整數或步驟之群組，但不排除任何其他整數或步驟或整數或步驟之群組。當用於本文中時，用語「包含(comprising)」可用用語「含有(containing)」或「包括(including)」取代，或有時候當用於本文中時可用用語「具有(having)」取代。

【0039】 當用於本文時，「由...組成(consisting of)」排除所請之元件中未指定之任何元件、步驟、或成分。當用於本文時，「基本上由...組成(consisting essentially of)」不排除不會實質影響申請專利範圍之基本及新穎特徵的材料或步驟。當任何前述用語「包含(comprising)」、「含有(containing)」、「包括(including)」、及「具有(having)」在本文中用於本發明之態樣或實施例的上下文時，可用用語「由...所組成(consisting of)」或「基本上由...所組成(consisting essentially of)」置換，以改變本揭露之範疇。

【0040】 用語「抗體(antibody)」在本文中係以最廣泛的意義使用，且具體包括全長單株抗體、多株抗體、及（除非上下文中另有說明或牴觸）其抗原結合片段、抗體變體、及多特異性分子，只要其等展現所欲之生物活性。通常而言，全長抗體係一種醣蛋白，其包含由雙硫鍵互連之至少兩個重(H)鏈及兩個輕

(L)鏈，或其抗原結合部分。各重鏈包含重鏈可變區（在本文中縮寫為VH）及重鏈恆定區。重鏈恆定區包含三個域，即CH1、CH2、及CH3。各輕鏈包含輕鏈可變區（在本文中縮寫為VL）及輕鏈恆定區。輕鏈恆定區包含一個域，即CL。VH區及VL區可進一步細分成多個高度變異區（稱為互補決定區(CDR)），其間穿插多個更加保守之區（稱為架構區(FR)）。各VH及VL係由三個CDR及四個FR構成，按照下列順序從胺基端到羧基端排列：FR1、CDR1、FR2、CDR2、FR3、CDR3、FR4。重鏈及輕鏈之可變區含有與抗原交互作用之結合域。與抗體生產相關之抗體分子結構及各種技術的一般原理係提供於例如Harlow and Lane, ANTIBODIES: A LABORATORY MANUAL, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y., (1988)。

【0041】 取決於其重鏈之恆定域的胺基酸序列，全長抗體可被指派至不同的「類別」。全長抗體有五大類：IgA、IgD、IgE、IgG、及IgM，且這些類別中的數種可進一步分成「子類別」（同型），例如IgG1、IgG2、IgG3、IgG4、IgA、及IgA2。對應於不同抗體類別之重鏈恆定域分別稱為α (alpha)、δ (delta)、ε (epsilon)、γ (gamma)、及μ (mu)。不同類別免疫球蛋白之次單元結構及三維構形係熟知的。

【0042】 「抗體」亦可為重鏈(VHH)抗體上之單可變域，亦稱為僅重鏈抗體(HcAb)，其沒有輕鏈且可由駱駝科動物或鯊魚自然生產。HcAb之抗原結合部分包含VHH片段。

【0043】 如本文中所使用，用語「重組抗體(recombinant antibody)」係指一種抗體（例如，嵌合、人源化、或人類抗體或其抗原結合片段），其係由包含編碼該抗體之核酸的重組宿主細胞表現。用於生產重組抗體之「宿主細胞」的實例包括：(1)哺乳動物細胞，例如中國倉鼠卵巢(CHO)、COS、骨髓瘤細胞（包括YO及NSO細胞）、幼倉鼠腎臟(BHK)、Hela、及Vero細胞；(2)昆蟲細胞，例如sf9、sf21、及Tn5；(3)植物細胞，例如屬於菸草(*Nicotiana*)屬之植物（例如，菸草(*Nicotiana tabacum*)）；(4)酵母細胞，例如屬於酵母菌(*Saccharomyces*)屬者（例如，釀酒酵母菌(*Saccharomyces cerevisiae*)）或屬於麴菌(*Aspergillus*)屬者

（例如，黑麴菌(*Aspergillus niger*)）；(5)細菌細胞，例如大腸桿菌(*Escherichia. coli*)細胞或枯草桿菌(*Bacillus subtilis*)細胞等。

【0044】 抗體之「抗原結合片段」係一種分子，其包含全長抗體能夠可檢測地結合至抗原的部分，一般包含至少VH區之一或多個部分。抗原結合片段包括多價分子（包含抗體之一、二、三、或更多個抗原結合部分）及單鏈建構體，其中VL區及VH區（或其所選部分）係藉由合成連接子或藉由重組方法連接，以形成功能性、抗原結合分子。抗原結合片段亦可係單域抗體(sdAb)（亦稱為奈米抗體(nanobody)），其係由單一單體可變抗體域(VHH)所組成之抗體片段。雖然抗體之一些抗原結合片段可藉由使較大抗體分子實際斷裂（例如，酶切割）來獲得，但大多數一般係藉由重組技術生產。本發明之抗體可製備為全長抗體或其抗原結合片段。抗原結合片段之實例包括Fab、Fab′、$F(ab)_2$、$F(ab')_2$、$F(ab)_3$、Fv（一般為抗體之單臂的VL域及VH域）、單鏈Fv（scFv，請參見例如Bird et al., Science 1988; 242:423-426；及Huston et al. PNAS 1988; 85:5879-5883）、dsFv、Fd（一般為VH域及CH1域）、及dAb（一般為VH域）片段；VH域、VL域、VHH域、及V-NAR域；包含單一VH及單一VL鏈之單價分子；微抗體(minibody)、雙鏈抗體(diabody)、三鏈抗體(triabody)、四鏈抗體(tetrabody)、及κ抗體(kappa body)（請參見例如，Ill et al., Protein Eng 1997; 10:949-57）；駱駝IgG；IgNAR；以及一或多種經單離CDR或功能性互補位(paratope)，其中可將經單離CDR或抗原結合殘基或多肽聯結或連接在一起，以形成功能性抗體片段。各種類型的抗體片段已描述或綜述於例如Holliger and Hudson, Nat Biotechnol 2005; 23:1126-1136；WO2005040219、及已公開之美國專利申請案20050238646及20020161201。抗體片段可使用習知重組或蛋白質工程改造技術獲得，且該等片段可以與完整抗體相同之方式針對抗原結合或其他功能進行篩選。

【0045】 已針對抗體片段之生產開發出各種技術。傳統上，這些片段係經由全長抗體之蛋白水解消化得到（請參見例如Morimoto et al., Journal of Biochemical and Biophysical Methods, 24:107-117 (1992)；及Brennan et al.,

Science, 229:81 (1985))。然而，這些片段現在可直接由重組宿主細胞生產。替代地，Fab′-SH片段可直接自大腸桿菌(*E. coli*)回收並經化學偶合，以形成F(ab′)2片段(Carter et al., Bio/Technology, 10:163-167 (1992))。根據另一方法，F(ab′)2片段可直接自重組宿主細胞培養物中單離出來。在其他實施例中，選用之抗體係單鏈Fv片段(scFv)。參見WO 1993/16185；美國專利第5,571,894號；及美國專利第5,587,458號。例如，抗體片段亦可係「線性抗體」，例如美國專利第5,641,870號中所述。此類線性抗體片段可係單特異性或雙特異性的。

【0046】 如本文中所使用，用語「抗體衍生物(antibody derivative)」係指包含全長抗體或其抗原結合片段之分子，其中一或多個胺基酸經化學修飾或取代。可用於抗體衍生物之化學修飾包括例如烷化、聚乙二醇化(PEGylation)、醯化、酯形成或醯胺形成、或類似者，例如用於將抗體連接至第二分子。例示性修飾包括聚乙二醇化（例如，半胱胺酸聚乙二醇化）、生物素化、放射性標示、及與第二劑（諸如細胞毒性劑）之接合。

【0047】 本文中之抗體包括抗原結合或生物活性經改變之「胺基酸序列變體」。此類胺基酸改變之實例包括對於抗原之親和力增強的抗體（例如，「親和力成熟」抗體）及Fc區（如果存在）經改變（例如，抗體依賴性細胞毒性(ADCC)及/或補體依賴性細胞毒性(CDC)經改變（增加或減少）（請參見例如，Presta, L.之WO 00/42072及Iduosogie等人之WO 99/51642）；及/或血清半衰期經增加或減少（請參見例如，Presta, L.之WO00/42072））之抗體。

【0048】 「多特異性分子」包含一種抗體或其抗原結合片段，其係聯結或連接至至少一個其他功能性分子（例如，另一個肽或蛋白質，諸如另一個抗體或受體之配體），藉以形成結合至至少兩種不同結合部位或目標分子之分子。例示性多特異性分子包括雙特異性抗體及連接至可溶受體片段或配體之抗體。

【0049】 如本文中所使用，用語「人類抗體(human antibody)」意欲包括具有架構區及CDR區兩者均衍生自（即，同一於或基本上同一於）人類生殖系免疫球蛋白序列之可變區的抗體。此外，如果抗體含有恆定區，則恆定區亦「衍生自」人類生殖系免疫球蛋白序列。本發明之人類抗體可包括非由人類生殖系免

疫球蛋白序列編碼的胺基酸殘基（例如，藉由體外隨機或位點特異性誘變或藉由體內體細胞突變引入之突變）。然而，如本文中所使用，用語「人類抗體」不意欲包括衍生自另一哺乳動物物種（諸如小鼠）之生殖系的CDR序列已移植至人類架構序列的抗體。

【0050】 「人源化(humanized)」抗體係含有衍生自非人類免疫球蛋白之最小序列的人類/非人類嵌合抗體。在大多數情況下，人源化抗體係人類免疫球蛋白（受體抗體(recipient antibody)），其中來自受體之高度變異區的殘基經來自具有所欲特異性、親和力、及能力之非人類物種（諸如小鼠、大鼠、兔、或非人類靈長類）（供體抗體）之高度變異區的殘基置換。在一些情況下，人類免疫球蛋白之FR殘基經對應之非人類殘基置換。此外，人源化抗體可包含在接受者抗體中或在供體抗體中未發現的殘基。進行這些修飾以進一步精進抗體性能。通常而言，人源化抗體將包含實質上所有至少一個（且一般而言兩個）可變域，其中所有或實質上所有高度變異環對應於非人類免疫球蛋白之高度變異環，且所有或實質上所有FR殘基係人類免疫球蛋白序列之FR殘基。人源化抗體可選地亦可包含免疫球蛋白恆定區(Fc)之至少一部分，一般為人類免疫球蛋白之恆定區。關於進一步細節，請參見例如Jones et al., Nature 321:522-525 (1986)；Riechmann et al., Nature 332:323-329 (1988)；及Presta, Curr. Op. Struct. Biol. 2:593-596 (1992)、WO 92/02190、美國專利申請案20060073137、及美國專利第6,750,325、6,632,927、6,639,055、6,548,640、6,407,213、6,180,370、6,054,297、5,929,212、5,895,205、5,886,152、5,877,293、5,869,619、5,821,337、5,821,123、5,770,196、5,777,085、5,766,886、5,714,350、5,693,762、5,693,761、5,530,101、5,585,089、及5,225,539號。

【0051】 當用於本文中時，用語「高度變異區(hypervariable region)」係指抗體負責抗原結合之胺基酸殘基。高度變異區通常包含來自「互補決定區」或「CDR」之胺基酸殘基（輕鏈可變域中之殘基24-34 (L1)、50-56 (L2)、及89-97 (L3)，及重鏈可變域中之殘基31-35 (H1)、50-65 (H2)、及95-102 (H3)；(Kabat et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S.

Department of Health and Human Services, NIH Publication No. 91-3242)）及/或來自「高度變異環」之殘基（輕鏈可變域中之殘基26-32 (L1)、50-52 (L2)、及91-96 (L3)，及重鏈可變域中之殘基26-32 (H1)、53-55 (H2)、及96-101 (H3)；Chothia and Lesk, J. Mol. Biol. 1987; 196:901-917)。一般而言，此區中之胺基酸殘基的編號係藉由上述Kabat et al.中所述之方法執行。諸如「Kabat位置」、「如Kabat中之可變域殘基編號」、及「根據Kabat」之片語在本文中係指用於重鏈可變域或輕鏈可變域之此編號系統。使用Kabat編號系統，肽之實際線性胺基酸序列可含有較少或額外的對應於可變域之FR或CDR的縮短或插入之胺基酸。例如，重鏈可變域可包括CDR H2之殘基52後的單一胺基酸插入（根據Kabat之殘基52a）及重鏈FR殘基82後的插入殘基（例如，根據Kabat之殘基82a、82b、及82c等）。給定抗體之Kabat殘基編號可藉由比對抗體序列之同源性區與「標準」Kabat編號序列來判定。

【0052】 「架構區」或「FR」殘基係本文中所定義之CDR以外的VH或VL殘基。

【0053】 「表位」或「結合部位」係抗原上的區域或區，抗原結合肽（諸如抗體）特異性結合至這些區域或區。蛋白質表位可包含直接涉及結合之胺基酸殘基（亦稱為表位之免疫優勢(immunodominant)組分）及其他非直接涉及結合之胺基酸殘基，諸如被特異性抗原結合肽有效阻斷之胺基酸殘基（換言之，該胺基酸殘基係在特異性抗原結合肽之「溶劑排除表面(solvent-excluded surface)」及/或「足跡」內）。

【0054】 「互補位」係抗體之抗原結合部分特異性結合抗原的區域或區。除非上下文中另有說明或明顯抵觸，互補位可包含直接涉及表位結合之胺基酸殘基（其中數個一般位於CDR中）及其他非直接涉及結合之胺基酸殘基，諸如被特異性結合抗原有效阻斷之胺基酸殘基（換言之，該胺基酸殘基係在特異性結合抗原之「溶劑排除表面」及/或「足跡」內）。

【0055】 作為參考抗體之「結合至相同表位之抗體」係指在競爭檢定中阻斷參考抗體與其抗原之結合達50%或更多的抗體，且相反地，參考抗體在競爭檢定中阻斷抗體與其抗原之結合達50%或更多。

【0056】 「經單離」抗體係已與其自然環境之組分分離者。在一些實施例中，抗體經純化至大於95%或99%純度，如藉由例如電泳（例如，SDS-PAGE、等電聚焦(IEF)、毛細管電泳）或層析（例如，離子交換或逆相HPLC）所判定。關於抗體純度評估方法之綜述，請參見例如Flatman et al, J. Chromatogr. B 848:79-87 (2007)。

【0057】 與本發明之方法有關的用語「投予(administering)」，意指藉由使用本發明之接合物或其形式、組成物、或藥劑來治療性地或疾病預防性地預防、治療、或改善如本文所述之症候群、病症、或疾病的方法。此類方法包括在療程期間的不同時間投予有效量的該抗體、其抗原結合片段、或接合物、或其形式、組成物、或藥劑，或者以組合形式並行投予有效量的該抗體、其抗原結合片段、或接合物、或其形式、組成物、或藥劑。本發明之方法應被理解為包括所有習知的治療性治療方案。

【0058】 目標抗體「阻斷」目標分子與天然目標配體之結合的能力，意指該抗體（在使用可溶或細胞-表面相關目標及配體分子之檢定中）可以劑量依賴性方式可檢測地降低目標分子與配體之結合，其中目標分子於該抗體不存在下會可檢測地結合至配體。

【0059】 「血腦障壁」或「BBB」係指末梢循環與腦部及脊髓之間的生理障壁，其係由腦部微血管內皮質膜內之緊密連接形成，從而產生限制分子輸送進入腦部的緊密障壁。BBB可限制甚至極小分子（諸如脲，60道耳頓）輸送進入腦部。BBB之實例包括腦內之BBB、脊髓內之血脊髓障壁、及視網膜內之血視網膜障壁，這些全都是CNS內之鄰近微血管障壁。BBB亦涵蓋血CSF障壁（脈絡叢），其中障壁係由室管膜細胞構成而非微血管內皮細胞。

【0060】 「血腦障壁受體」（在本文中縮寫為「R/BBB」）係表現在腦部內皮細胞上之胞外膜連接受體蛋白，其能夠將分子輸送跨過BBB或用於輸送外源

投予之分子。R/BBB之實例包括但不限於大型中性胺基酸輸送蛋白(LAT)複合物（包括CD98成分）轉鐵蛋白受體(TfR)、胰島素受體、類胰島素生長因子受體(IGF-R)、低密度脂蛋白受體（包括但不限於低密度脂蛋白受體相關蛋白1(LRP1)及低密度脂蛋白受體相關蛋白8 (LRP8)）、及肝素結合表皮生長因子樣生長因子(HB-EGF)。本文中的例示性R/BBB係CD98hc。

【0061】 「中樞神經系統」或「CNS」係指控制身體機能之神經組織複合體，且包括腦部及脊髓。

【0062】 如本文中所使用，「接合物(conjugate)」係指共價連接至一或多個異源分子（包括但不限於治療性肽或蛋白質、抗體、標示、或神經病症藥物）之蛋白質。

【0063】 如本文中所使用，用語「偶合(coupled)」係指將二或更多個物件接合或連接在一起。當用於化學或生物化合物時，偶合可指二或更多個化學或生物化合物之間的共價連接。舉非限制性實例來說，本發明之抗體可與受到關注的肽偶合以形成抗體偶合肽。抗體偶合肽可經由經設計以將抗體接合至肽的特定化學反應形成。在某些實施例中，本發明之抗體可與本發明之肽經由連接子共價偶合。連接子可例如先共價連接至抗體或肽，接著再共價連接至肽或抗體。

【0064】 劑（例如醫藥配方）之「有效量(effective amount)」或「治療有效量(therapeutically effective amount)」係指有效達到所欲治療或疾病預防結果所需之劑量及時間段的量。

【0065】 如本文中所使用，「連接子(linker)」係指共價連接兩個不同實體之化學連接子或單鏈肽連接子。連接子可用於連接本發明之抗體或其片段、血腦障壁穿梭劑、融合蛋白、及接合物中的任兩者。連接子可連接例如scFv中之VH及VL、或單株抗體或其抗原結合片段與治療性分子（諸如第二抗體）。在一些實施例中，如果單價結合實體包含針對CD98（較佳地人類CD98）之scFv，且治療性分子包含針對CNS目標（諸如Tau）之抗體，則連接子可將scFv連接至針對Tau之抗體。可使用包含由肽鍵連接之1至25個胺基酸（諸如1、2、3、4、

5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、或25個胺基酸）的單鏈肽連接子。在某些實施例中，胺基酸係選自二十個天然存在的胺基酸。在某些其他實施例中，胺基酸之一或多者係選自甘胺酸、丙胺酸、脯胺酸、天冬醯胺酸、麩醯胺酸、及離胺酸。亦可使用化學連接子，諸如烴連接子、聚乙二醇(PEG)連接子、聚丙二醇(PPG)連接子、多醣連接子、聚酯連接子、由PEG及嵌入式雜環所組成之混成連接子、及烴鏈。

【0066】 如本文中所使用，「神經病症(neurological disorder)」係指影響CNS及/或具有CNS中之病因的疾病或病症。例示性CNS疾病或病症包括但不限於神經病變、類澱粉變性、癌症、眼部疾病或病症、病毒或微生物感染、發炎、缺血、神經退化性疾病、癲癇、行為障礙、及溶體儲積症。為了本申請案之目的，CNS將理解為包括眼睛，其正常係由血視網膜障壁而與身體其他地方隔離。神經病症之具體實例包括但不限於神經退化性疾病（包括但不限於路易氏體病、脊髓灰質炎後症候群、Shy-Draeger症候群、橄欖體橋腦小腦萎縮、巴金森氏症、多系統萎縮、紋狀體與黑質體退化症、脊髓小腦性失調症、脊髓性肌萎縮）、tau蛋白病（包括但不限於阿茲海默症及核上神經麻痺症）、普里昂疾病（包括但不限於牛海綿狀腦病、羊搔癢症、庫賈氏症候群、庫魯病、吉斯曼-史特斯勤-先克病、慢性消耗病、及致死性家族性失眠症）、延髓性麻痺、運動神經元疾病、及神經系統異退化性病症（包括但不限於Canavan病、亨丁頓舞蹈症、神經元蠟樣脂褐質儲積症、亞歷山大氏病、妥瑞氏症候群、Menkes氏捲髮症候群、柯凱因氏症候群、Halervorden-Spatz氏症候群、拉弗拉病、雷特氏症候群、肝豆狀核變性、Lesch-Nyhan氏症候群、及Unverricht-Lundborg氏症候群）、失智症（包括但不限於匹克症及脊髓小腦性失調症）、癌症（例如，CNS及/或腦部之癌症，包括身體其他地方之癌症所致的腦部轉移）。

【0067】 「神經病症藥物」係一種藥物或治療劑，其可用於治療或改善一或多種神經病症之影響。本發明之神經病症藥物包括但不限於小分子化合物、抗體、肽、蛋白質、一或多種CNS目標之天然配體、一或多種CNS目標之天然配體的經修飾版本、適體(aptamer)、抑制性核酸（即，小型抑制性RNA (siRNA)

及短髮夾RNA (shRNA)）、核酶(ribozyme)、或任何前述者之活性片段。本發明之例示性神經病症藥物係描述於本文中且包括但不限於：抗體、適體、蛋白質、肽、抑制性核酸及小分子、及本身係CNS抗原或目標分子或特異性辨識且/或作用於（即，抑制、活化、或檢測）CNS抗原或目標分子的任何前述者之活性片段，諸如但不限於類澱粉蛋白前驅蛋白或其部分、β類澱粉蛋白、β-分泌酶、γ-分泌酶、tau、α-突觸核蛋白、parkin、亨丁頓蛋白、DR6、早老素、ApoE、神經膠質瘤或其他CNS癌症標記、及神經營養因子。神經病症藥物及其等可用於治療之對應病症的非限制性實例：腦部衍生神經營養因子(BDNF)、慢性腦部傷害（神經生成）、纖維母細胞生長因子2 (FGF-2)、抗表皮生長因子受體腦部癌症、(EGFR)-抗體、神經膠細胞系衍生神經因子巴金森氏症、(GDNF)、腦部衍生神經營養因子(BDNF)肌萎縮性脊髓側索硬化症、憂鬱、腦部之溶體酶溶體儲積症、睫狀神經營養因子(CNTF)肌萎縮性脊髓側索硬化症、神經調節蛋白1思覺失調症、抗HER2抗體（例如，曲妥珠單抗）自HER2陽性癌症之腦部轉移。

【0068】 用語「醫藥配方(pharmaceutical formulation)」係指一種製劑，其呈允許其中所含有之活性成分的生物活物具備有效性之形式，且該製劑不含有對該配方所投予之對象具有不可接受之毒性的額外組分。

【0069】 如本文中所使用，「醫藥上可接受之載劑或稀釋劑(pharmaceutically accep表carrier or diluent)」意指任何適用於投予至個體之物質。例如，醫藥上可接受之載劑可係無菌水溶液，諸如磷酸鹽緩衝鹽水(PBS)或注射用水。

【0070】 如本文中所使用，「醫藥上可接受之鹽(pharmaceutically acceptable salt)」意指化合物（諸如寡聚化合物或寡核苷酸）的生理上及醫藥上可接受之鹽，即保留母化合物之所欲生物活性且不會對其產生非所欲之毒理效應的鹽。

【0071】 用於本發明中之醫藥上可接受之酸性/陰離子性鹽包括但不限於：乙酸鹽、苯磺酸鹽、苯甲酸鹽、碳酸氫鹽、酒石酸氫鹽、溴化物、依地酸鈣(calcium edetate)、樟腦磺酸鹽(camsylate)、碳酸鹽、氯化物、檸檬酸鹽、二氫氯化物、依地酸鹽(edetate)、乙二磺酸鹽(edisylate)、丙酸酯十二烷硫酸鹽(estolate)、乙磺酸鹽(esylate)、反丁烯二酸鹽、葡庚糖酸鹽(glyceptate)、葡萄糖

酸鹽(gluconate)、麩胺酸鹽(glutamate)、羥乙醯胺基苯砷酸鹽(glycollylarsanilate)、己基間苯二酚鹽(hexylresorcinate)、海巴明(hydrabamine)、氫溴酸鹽、氫氯酸鹽、羥基萘甲酸鹽(hydroxynaphthoate)、碘化物、2-羥乙磺酸鹽(isethionate)、乳酸鹽、乳糖酸鹽、蘋果酸鹽、順丁烯二酸鹽、苯乙醇酸鹽、甲磺酸鹽、甲基溴化物、甲基硝酸鹽、甲基硫酸鹽、黏酸鹽(mucate)、萘磺酸鹽(napsylate)、硝酸鹽、巴摩酸鹽(pamoate)、泛酸鹽、磷酸鹽/二磷酸鹽、聚半乳糖醛酸鹽、水楊酸鹽、硬脂酸鹽、次乙酸鹽、琥珀酸鹽、硫酸鹽、單寧酸鹽、酒石酸鹽、茶氯酸鹽(teoclate)、甲苯磺酸鹽以及三碘化物。有機或無機酸亦包括且不限於：氫碘酸、過氯酸、硫酸、磷酸、丙酸、乙醇酸、甲磺酸、羥乙基磺酸、草酸、2-萘磺酸、對甲苯磺酸、環己磺醯胺酸、醣酸或三氟乙酸。醫藥上可接受之鹼性/陽離子性鹽包括且不限於鋁、2-胺基-2-羥甲基-丙烷-1,3-二醇（亦稱為參(羥基甲基)胺基甲烷、托美滇(tromethane)或「TRIS」）、氨、苯札辛(benzathine)、三級丁胺、鈣、氯普魯卡因(chloroprocaine)、膽鹼、環己胺、二乙醇胺、乙二胺、鋰、L-離胺酸、鎂、美古明(meglumine)、N-甲基-D-還原葡糖胺、哌啶、鉀、普魯卡因(procaine)、奎寧、鈉、三乙醇胺、或鋅。

【0072】 「多肽(polypeptide)」或「蛋白質(protein)」意指包含至少二個以肽鍵連接之胺基酸殘基以形成多肽的分子。少於50個胺基酸的小型多肽可稱為「肽(peptide)」。

【0073】 當用於指稱胺基酸序列時，用語「序列同一性(sequence identity)」、或「)序列同一性百分比(%) (percent (%) sequence identity)」、或「同一性% (% identity)」、或「與...%同一(% identical to)」描述相較於構成胺基酸序列總長度的胺基酸殘基數目，二或更多個經比對胺基酸序列之同一胺基酸的匹配（「命中(hit)」）數目。換言之，使用比對，針對二或更多個序列，當比較該等序列並對其進行比對以獲得最大對應性（如使用所屬技術領域中已知的序列比較演算法所測得）時，或者當手動比對且目視檢查時，可判定胺基酸殘基相同之百分比（例如，在胺基酸序列之全長上有90%、91%、92%、93%、94%、95%、97%、98%、99%、或100%同一性）。判定序列同一性所比

較的序列可能因胺基酸的（多個）取代、（多個）添加、或（多個）缺失而不同。用於比對蛋白質序列之合適程式係所屬技術領域中具有通常知識者所習知。例如，蛋白質序列的序列同一性百分比可用諸如CLUSTALW、Clustal Omega、FASTA、或BLAST之程式，例如使用NCBI BLAST演算法判定(Altschul SF, et al (1997), *Nucleic Acids Res*. 25:3389-3402)。

【0074】 「特異性結合(specific binding/specifically bind)」或「結合(bind)」係指抗體以比對其他抗原更大的親和力結合至抗原或抗原內之表位。一般而言，抗體以下列解離常數(K_D)結合至抗原或抗原內之表位：約1×10^{-8} M或更小，例如約1×10^{-9} M或更小、約1×10^{-10} M或更小、約1×10^{-11} M或更小、或約1×10^{-12} M或更小，一般以比其結合至非特異性抗原（例如，BSA、酪蛋白）之K_D小至少一百倍的K_D。K_D係平衡解離常數，即抗體與其抗原之間的k_{off}/k_{on}比率。K_D與親和力是負相關的。「結合速率(on-rate)」(k_{on})係用於表徵抗體多快結合至其目標的常數。「解離速率(off-rate)」(k_{off})係用於表徵抗體多快與其目標解離的常數。解離常數K_D可使用標準程序測量。例如，抗體之K_D可藉由使用表面電漿共振（諸如藉由使用生物感測器系統，例如Biacore®系統）、或藉由使用生物層干涉技術（諸如Octet RED96系統）判定。抗體之K_D值越小，抗體結合至目標抗原的親和力越高。然而，特異性結合至抗原或抗原內之表位的抗體可能對於其他相關抗原具有交叉反應性，例如對於來自其他物種（諸如人類或猴）的相同抗原（同源物(homolog)）具有交叉反應性，例如食蟹獼猴(*Macaca fascicularis*, cynomolgus, cyno)、黑猩猩(*Pan troglodytes*, chimpanzee, chimp)、或狨(*Callithrix jacchus*, common marmoset, marmoset)。當單特異性抗體特異性結合一種抗原或一種表位時，雙特異性抗體特異性結合二種不同的抗原或二種不同的表位。

【0075】 如本文中所使用，用語「對象(subject)」係指哺乳動物。哺乳動物包括但不限於馴養動物（例如，牛、綿羊、貓、狗、及馬）、靈長類（例如，人類及非人類靈長類，諸如猴）、兔、及嚙齒動物（例如，小鼠及大鼠）。在某些實施例中，個體或對象係人類。當對象係人類時，其亦可稱為「患者」。

【0076】 在兩個胺基酸序列之上下文中，用語「實質上同一(substantially identical)」意指該等序列當經最佳比對（諸如藉由GAP或BESTFIT程式使用預設缺口權重(gap weight)）時共有至少約50百分比之序列同一性。一般而言，實質上同一之序列將展現至少約60、至少約70、至少約80、至少約90、至少約95、至少約98、或至少約99百分比之序列同一性。

【0077】 本文中所使用之用語「CD98」或「CD98hc」係指由分化簇98重鏈(CD98hc)所組成的整體膜蛋白，該分化簇98重鏈(CD98hc)藉由二硫鍵與多個輕鏈中的任一者相連。當與LAT1或LAT2相關聯時，該異二聚物輸送蛋白複合物表現為必要胺基酸交換器。CD98hc具有約80 kDa之分子量。較佳的是，CD98hc係人類CD98hc (huCD98hc)。huCD98hc係由SLC3A2基因編碼。

【0078】 如本文中所使用，「目標抗原(target antige)」或「腦部目標(brain target)」係指表現於CNS（包括腦部）中之抗原及/或分子，其可用抗體或小分子加以靶向。此類抗原及/或分子之實例包括但不限於：β-分泌酶1 (BACE1)、β類澱粉蛋白(Aβ)、表皮生長因子受體(EGFR)、人類表皮生長因子受體2 (HER2)、Tau、載脂蛋白E4 (ApoE4)、α-突觸核蛋白、CD20、亨丁頓蛋白、普里昂蛋白(PrP)、富白胺酸重複激酶2 (LRRK2)、parkin、早老素1、早老素2、γ分泌酶、死亡受體6 (DR6)、類澱粉蛋白前驅蛋白(APP)、p75神經營養因子受體(p75NTR)、及凋亡蛋白酶6。在一些實施例中，目標抗原係BACE1。在一些實施例中，目標抗原係Tau。

【0079】 如本文中所使用，「治療(treatment)」（及其英文文法變化型，諸如「treat」或「treating」）係指試圖改變受治療個體之自然病程的臨床介入，且可出於疾病預防或在臨床病理病程期間執行。所欲治療效果包括但不限於預防疾病發生或再發、減輕症狀、減少疾病之任何直接或間接病理後果、預防轉移、降低疾病進展速率、改善或緩和疾病狀態、及緩解或改善預後。在一些實施例中，本發明之抗體係用於延緩疾病發展或減慢疾病進展。

【0080】 抗體或免疫球蛋白可分為五大類，即IgA、IgD、IgE、IgG、及IgM，取決於重鏈恆定域胺基酸序列。IgG係五種免疫球蛋白中最穩定的一種，

在人類的血清半衰期約為23天。IgA及IgG係進一步次分為下列同型(isotype)：IgA_1、IgA_2、IgG_1、IgG_2、IgG_3及IgG_4。四種IgG亞型各具有不同的生物功能稱為效應功能。這些效應功能通常透過與Fc受體(FcγR)交互作用且/或藉由結合C1q及固定補體介導。結合至FcγR可導致抗體依賴性細胞介導之細胞裂解或抗體依賴性細胞毒性(ADCC)，而結合至補體因子可導致補體介導之細胞裂解或補體依賴性細胞毒性(CDC)。本發明之抗CD98抗體（或待接合或融合至抗CD98抗體之治療性或診斷性抗體）可不具有或具有極少的效應功能，但仍保留其結合FcRn之能力，此結合可為抗體藉以具有延長之體內半衰期的主要手段。

【0081】 FcγR或補體（例如，C1q）與抗體之結合係由所謂Fc部分結合部位處之已界定蛋白質-蛋白質交互作用造成。此類Fc部分結合部位在所屬技術領域中係已知的。此類Fc部分結合部位包括例如特徵在於胺基酸L234、L235、D270、N297、E318、K320、K322、P331、及P329（編號根據Kabat之EU索引）者。在一些實施例中，本發明之抗CD98抗體（或待接合或融合至抗CD98抗體之治療性或診斷性抗體）在一或多個Fc部分結合部位含有一或多個取代，以消除效應功能。例如，本發明之抗CD98抗體（或待接合或融合至抗CD98抗體之治療性或診斷性抗體）可含有含一或多個下列取代之Fc區：以脯胺酸取代殘基233處之麩胺酸、以丙胺酸或纈胺酸取代殘基234處之苯丙胺酸、及以丙胺酸或麩胺酸取代殘基235處之白胺酸（EU編號，Kabat, E. A. et al. (1991) Sequences of Proteins of Immunological Interest, 5th Ed. U.S. Dept. of Health and Human Services, Bethesda, Md., NIH Publication no. 91-3242）。較佳地，所關注之抗體含有L234A、L235A、及P331S中之一、二、或三個突變（EU編號，Kabat）。

【0082】 子類別IgG1、IgG2、及IgG3之抗體通常會顯示補體活化（包括C1q及C3結合），而IgG4不會活化補體系統且不會結合C1q及/或C3。人類IgG4 Fc區相較於其他IgG亞型具有減少之結合FcγR及補體因子的能力。較佳地，本發明之抗CD98抗體（或待接合或融合至抗CD98抗體之治療性或診斷性抗體）包含衍生自人類IgG4 Fc區之Fc區。更佳地，Fc區含有具有消除效應功能之取代的

人類IgG4 Fc區。例如，藉由以Ala取代殘基297處（EU編號）之Asn來移除IgG4 Fc區中之N-連接醣基化部位係另一種確保消除殘餘效應活性之方法。

抗 CD98 抗體及其抗原結合片段

【0083】 在一個大致態樣中，本申請案關於一種結合至靈長類CD98（諸如人類CD98或猴CD98）之抗體或其抗原結合片段，且該抗體或其抗原結合片段針對將劑遞送至有需要之對象的腦部經最佳化。本發明之發明人驚訝地發現，在結合速率及解離速率兩者均會影響腦部濃度的作用下，親和力與胞吞轉送效率之間有比先前已描述者更細微的關係。具體而言，必須有不會太快或太慢的中性解離速率才能獲得劑（諸如mAb）的最佳腦部PK及PD，以讓抗CD98抗體或其抗原結合片段有效率遞送。

【0084】 較佳地，本申請案之抗CD98抗體或其抗原結合片段係pH敏感的，例如其在不同pH下具有不同之CD98結合親和力。例如，本申請案之抗CD98抗體在中性pH（諸如生理pH（例如pH 7.4））下可以高親和力結合至CD98，但在內化至內體隔室中之後，其在酸性pH（諸如相對較低之pH（pH 5至6.0））下會自CD98解離。親和力係兩個部份（例如，抗體及抗原）之間的結合強度之量度。親和力可以數種方式表示。一種方式是以交互作用之解離常數(K_D)表示。K_D可藉由常規方法（包括平衡透析）測量，或藉由分別直接測量抗原-抗體解離及締合之速率，即k_{off}（kd或k_{dis}）及k_{on}（或ka）速率（請參見例如*Nature,* 1993 361:186-87）。k_{off}/k_{on}之比率消去所有與親和力無關之參數，且等於解離常數K_D（大致上請參見Davies et al., *Annual Rev Biochem,* 1990 59:439-473）。因此，較小的K_D意指較高的親和力。親和力的另一種表示方式是K_a，其為K_D之倒數、或k_{on}/k_{off}。因此，較高的K_a意指較高的親和力。例如，用於本申請案之組成物及/或方法的抗體或其抗原結合片段可係在中性pH（例如，pH 6.8至7.8）、諸如生理pH（例如，pH 7.4）下以1奈莫耳(nM, 10^{-9} M)或更大之K_D結合至CD98且在酸性pH（例如，pH 4.5至6.5，諸如pH 5.0）下以10^{-4} sec^{-1}或更大之k_{dis}自CD98解離的抗體或其片段。

【0085】 因此，本申請案之一個大致態樣關於一種抗CD98抗體或其抗原結合片段，其用於將劑遞送至有需要之對象的腦部，其中該抗CD98抗體或其抗原結合片段在中性pH下以至少1 nM、較佳地1 nM至500 nM之解離常數K_D且在酸性pH、較佳地pH 5下以至少10^{-4} sec^{-1}、較佳地10^{-4}至10^{-1} sec^{-1}之解離速率常數k_d結合至CD98、較佳地人類CD98hc、更佳地CD98hc。

【0086】 在一個實施例中，本申請案之抗CD98抗體或其抗原結合片段在中性pH下具有2×10^{-2}至2×10^{-4} sec^{-1}、諸如2×10^{-2}、1×10^{-2}、9×10^{-3}、8×10^{-3}、7×10^{-3}、6×10^{-3}、5×10^{-3}、4×10^{-3}、3×10^{-3}、2×10^{-3}、1×10^{-3}、9×10^{-4}、8×10^{-4}、7×10^{-4}、6×10^{-4}、5×10^{-4}、4×10^{-4}、3×10^{-4}、2×10^{-4} sec^{-1}、或任何其間之值的解離速率常數k_d。

【0087】 在某些實施例中，結合至人類CD98之抗體或其抗原結合片段係重鏈(VHH)抗體上之單可變域，其包含具有下列之胺基酸序列的重鏈互補決定區(HCDR) HCDR1、HCDR2、及HCDR3：

(i) 分別為 SEQ ID NO: 29、30、及 31；

(ii) 分別為 SEQ ID NO: 48、49、及 50；或

(iii) 分別為 SEQ ID NO: 143、144、及 145。

【0088】 較佳地，其係包含與SEQ ID NO: 28、SEQ ID NO: 47、或SEQ ID NO: 142具有至少80%、諸如至少85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、或100%序列同一性之胺基酸序列的VHH片段。

【0089】 在其他實施例中，結合至人類CD98之抗體或其抗原結合片段包含重鏈可變區及輕鏈可變區，該重鏈可變區包含重鏈互補決定區(HCDR) HCDR1、HCDR2、及HCDR3，該輕鏈可變區包含輕鏈互補決定區(LCDR) LCDR1、LCDR2、及LCDR3，其中該HCDR1、HCDR2、HCDR3、LCDR1、LCDR2、及LCDR3具有下列之胺基酸序列：

i) 分別為 SEQ ID NO: 7、8、9、10、11、及 12；

(ii) 分別為 SEQ ID NO: 67、68、69、70、71、及 72；

(iii) 分別為 SEQ ID NO: 89、90、91、92、93、及 94；

(iv) 分別為 SEQ ID NO: 113、114、115、116、117、及 118；

(v) 分別為 SEQ ID NO: 123、124、125、126、127、及 128；

(vi) 分別為 SEQ ID NO: 133、134、135、136、137、及 138；

(vii) 分別為 SEQ ID NO: 150、151、152、153、154、及 155；

(viii) 分別為 SEQ ID NO: 160、161、162、163、164、及 165；

(ix) 分別為 SEQ ID NO: 170、171、172、173、174、及 175；

(x) 分別為 SEQ ID NO: 180、181、182、183、184、及 185；

(xi) 分別為 SEQ ID NO: 194、195、196、197、198、及 199；或

(xii) 分別為 SEQ ID NO: 204、205、206、207、208、及 209。

【0090】 在其他實施例中，本申請案之抗體或其抗原結合片段與本文中所例示之抗體或抗原結合片段競爭。抗體或抗原之結合部位可藉由已知方法（諸如ELISA、西方墨點法等）判定。在某些實施例中，此一競爭抗體結合至例示抗體或其抗原結合片段所結合之相同表位（例如，線性或構象表位(conformational epitope)）。用於定位(mapping)抗體所結合之表位的詳細例示性方法係提供於Morris, G. E., (ed.)，「Epitope Mapping Protocols，」In: Methods in Molecular Biology, Vol. 66, Humana Press, Totowa, N.J.(1996)。作為參考抗體之「結合至相同表位之抗體」係指在競爭檢定中阻斷參考抗體與其抗原之結合達50%或更多的抗體，且相反地，參考抗體在競爭檢定中阻斷抗體與其抗原之結合達50%或更多。

【0091】 較佳地，抗體或其抗原結合片段係單鏈可變片段(scFv)，其包含經由可撓性連接子共價連接至輕鏈可變區(LV)之重鏈可變區(HV)。儘管移除了恆定區並引入了連接子，scFv仍可保留原始免疫球蛋白之特異性。在scFv中，域之順序可為H_V-連接子- L_V、或L_V-連接子- H_V。連接子可從頭(*de novo*)設計或衍生自已知蛋白質結構，以在橋聯scFv之可變域時提供相容之長度及構形而不會有嚴重之立體干擾。連接子可具有10至約25個胺基酸的長度。較佳地，連接子係在可變域之羧基端與其他域之胺基端之間橫跨約3.5 nm (35 Å)而不會影響該等域摺疊及形成完整抗原結合部位之能力的肽連接子（Huston et al., *Methods in*

Enzymology, vol. 203, pp. 46–88, 1991，其全文以引用方式併入本文中）。連接子較佳地包含親水性序列，以避免肽在整個蛋白摺疊過程中嵌入(intercalation)可變域內或可變域之間(Argos, *Journal of Molecular Biology*, vol. 211, no. 4, pp. 943–958, 1990)。例如，連接子可包含Gly及Ser殘基及/或連同穿插之帶電荷殘基（諸如Glu、Thr、及Lys）以增強溶解度。在一個實施例中，連接子具有SEQ ID NO: 189 (GTEGKSSGSGSESKST)之胺基酸序列。亦可鑑於本揭露而使用任何其他合適的連接子。

【0092】 在一些實施例中，scFv包含與下列之胺基酸序列具有至少80%、諸如至少85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、或100%序列同一性的胺基酸序列：SEQ ID NO: 6、SEQ ID NO: 66、SEQ ID NO: 88、SEQ ID NO: 112、SEQ ID NO: 122、SEQ ID NO: 132、SEQ ID NO: 149、SEQ ID NO: 159、SEQ ID NO: 169、SEQ ID NO: 179、SEQ ID NO: 193、或SEQ ID NO: 203。

【0093】 在一較佳實施例中，結合至CD98（較佳地CD98hc、更佳地人類CD98hc）之抗體或其抗原結合片段不含有游離半胱胺酸。

【0094】 抗CD98抗體或其抗原結合片段（諸如VHH或scFv片段）可鑑於本揭露而使用所屬技術領域中之合適方法生產。例如，VHH或scFv片段可藉由使重組宿主細胞（諸如細菌、酵母菌、或哺乳動物細胞）在適於生產抗體片段之條件下生長，且自細胞培養物回收該片段而重組生產。

腦部穿梭劑建構體

【0095】 經最佳化之RMT腦部遞送平台係使用CD98藉由下列方式開發：提升內在胞吞轉送效率，擴展末梢藥物動力學，且針對可接受之安全性概況進行工程改造同時維持治療性mAb之效力。對食蟹獼猴中胞吞轉送受體親和力與腦部濃度之間的相互作用進行研究。結合動力學之徹底研究展示，為了獲得mAb之最佳腦部PK及PD，需要不會太快或太慢的中性解離速率。

【0096】 亦發現，與新生兒Fc受體(FcRn)之結合增加的經工程改造抗體恆定區會導致末梢清除降低及腦部濃度提升。

【0097】 將額外Fc突變引入，以除去與Fcγ受體(FcγR)之結合並避免效應功能介導之毒性。當與高親和力抗Tau結合mAb偶合時，這些突變會透過針對小神經膠細胞吸收及目標降解之新穎、非FcγR機制來防止末梢中的效應功能介導之毒性，同時仍維持抗體依賴性吞噬作用(ADP)。此機制係依賴於透過CD98之內化，且在促進目標降解上比傳統FcγR介導之ADP更有效率，而不會刺激促發炎細胞介素之分泌。就發明人所知，此為非FcγR介導之ADP的首次報導，代表針對吞噬作用之新穎、有效率、非發炎性機制，其可用於各種治療應用。

【0098】 因此，在一個大致態樣中，本申請案關於一種抗體靶向之腦部遞送系統，其包含本申請案之抗CD98抗體或其抗原結合片段。抗CD98抗體或其抗原結合片段可用於將治療劑或診斷劑遞送至細胞（例如，癌細胞）或BBB系統中。可遞送之劑包括任何神經病症藥物或可用於檢測或分析神經病症藥物之劑。例如，此類劑可係神經營養因子，包括但不限於神經生長因子(NGF)、腦部衍生神經營養因子(BDNF)、睫狀神經營養因子(CNTF)、神經膠細胞系神經營養因子(GDNF)、及類胰島素生長因子(IGF)；神經肽，包括但不限於P物質、神經肽Y、血管活性腸肽(vasoactive intestinal peptide, VIP)、γ-胺基丁酸(GABA)、多巴胺、膽囊收縮素(CCK)、腦內啡(endorphin)、腦啡肽(enkephalin)、及促甲狀腺素釋放激素(TRH)；細胞介素；抗焦慮劑；抗驚厥劑；多核苷酸及轉殖基因，包括例如小干擾RNA及/或反義寡核苷酸；或結合至腦部目標之抗體或其抗原結合片段。本申請案之抗CD98抗體或其抗原結合片段可係增強所關注之劑自血液遞送至腦部中並在腦部中發揮功能的有效手段。

【0099】 具體而言，所關注之劑可呈組合形式或連接至本申請案之抗CD98抗體或其抗原結合片段經腸胃外（例如，靜脈內）遞送。例如，劑可非共價附接至抗CD98抗體或其抗原結合片段。劑亦可共價附接至抗CD98抗體或其抗原結合片段以形成接合物。在某些實施例中，接合係藉由蛋白質融合之建構（即，藉由基因融合兩個編碼抗CD98抗體或其抗原結合片段之基因與神經病症藥物並

表現為單一蛋白質）。可鑑於本揭露而使用已知方法來將劑連接至抗體或其抗原結合片段。請參見例如Wu et al., *Nat Biotechnol*., 23(9):1137-46, 2005；Trail et al., *Cancer Immunol Immunother*., 52(5):328-37, 2003；Saito et al., *Adv Drug Deliv Rev*., 55(2):199-215, 2003；Jones et al., *Pharmaceutical Research*, 24(9):1759-1771, 2007。

【0100】 在一些實施例中，待遞送至腦部之治療劑或診斷劑及抗CD98抗體或其抗原結合片段可經由非肽連接子或肽連接子共價連接在一起（或接合）。非肽連接子之實例包括但不限於聚乙二醇、聚丙二醇、乙二醇與丙二醇之共聚物、聚氧乙基化多元醇、聚乙烯醇、多醣、右旋糖酐、聚乙烯醚、可生物降解聚合物、經聚合脂質、幾丁質、及玻尿酸、或其衍生物、或其組合。肽連接子可係由1至50個由肽鍵連接之胺基酸所組成的肽鏈或其衍生物，其N端及C端可共價連接至抗CD98抗體或其抗原結合片段。

【0101】 在某些實施例中，本申請案之接合物係多特異性抗體，其包含結合CD98之第一抗原結合區及結合腦部抗原（諸如β-分泌酶1 (BACE1)、tau、及本文所揭示之其他腦部抗原）之第二抗原結合區。用於製造多特異性抗體之技術包括但不限於兩個具有不同特異性之免疫球蛋白重鏈-輕鏈對的重組共表現（請參見Milstein and Cuello, *Nature* 305: 537, 1983、WO 93/08829、及Traunecker et al, *EMBO J*. 10: 3655, 1991）、及「鈕扣(knob-in-hole)」工程改造（請參見例如美國專利第5,731,168號）。多特異性抗體亦可藉由下列方式製造：工程改造靜電操縱(electrostatic steering)效應(WO 2009/089004A1)；交聯二或更多個抗體或片段（請參見例如美國專利第4,676,980號及Brennan et al, *Science*, 229: 81, 1985）；使用白胺酸拉鏈（請參見例如Kostelny et al, *J. Immunol*., 148(5): 1547-1553,1992）；使用「雙鏈抗體」技術（請參見例如Hollinger et al, *Proc. Natl. Acad. Sci. USA*, 90:6444-6448, 1993）；使用單鏈Fv (sFv)二聚體（請參見例如Gruber et al, *J. Immunol*, 152:5368 (1994)）；及製備三特異性抗體，如例如Tutt et al. *J. Immunol*. 147: 60, 1991中所述。本申請案之多特異性抗體亦涵蓋具有三或更多個功能性抗原結合部位之抗體，包括「章魚狀抗體(Octopus antibody)」

或「雙可變域免疫球蛋白」(DVD)（請參見例如US 2006/0025576A1及Wu et al. *Nature Biotechnology*, 25(11):1290-7, 2007）。本申請案之多特異性抗體亦涵蓋「雙作用Fab (Dual Acting Fab)」或「DAF」，其包含結合至CD98以及腦部抗原（例如，BACE1或Tau）之抗原結合區（例如，請參見US 2008/0069820）。在一個實施例中，抗體係抗體片段，各種此類片段已揭示在本文中。

【0102】 在一個實施例中，本申請案之多特異性抗體係融合建構體，其包含共價連接（或融合）至第二抗體或其抗原結合片段的本申請案之抗CD98抗體或其抗原結合片段。較佳地，第二抗體或其抗原結合片段結合至腦部目標，諸如BACE、tau、或其他腦部抗原，諸如本文所述者。抗CD98抗體或其抗原結合片段可直接或經由連接子融合至第二抗體或其抗原結合片段之輕鏈及/或重鏈的羧基端及/或胺基端。

【0103】 在一個實施例中，抗CD98抗體或其抗原結合片段係直接或經由連接子融合至第二抗體或其抗原結合片段之輕鏈的羧基端。

【0104】 在另一實施例中，抗CD98抗體或其抗原結合片段係直接或經由連接子融合至第二抗體或其抗原結合片段之輕鏈的胺基端。

【0105】 在另一實施例中，抗CD98抗體或其抗原結合片段係直接或經由連接子融合至第二抗體或其抗原結合片段之重鏈的羧基端。

【0106】 在另一實施例中，抗CD98抗體或其抗原結合片段係直接或經由連接子融合至第二抗體或其抗原結合片段之重鏈的胺基端。

【0107】 在一較佳實施例中，本申請案之融合建構體包含本申請案之抗CD98抗體或其抗原結合片段、較佳地抗huCD98hc VHH或scFv片段，該抗CD98抗體或其抗原結合片段經由連接子共價連接至結合至腦部目標之第二抗體或其抗原結合片段之兩個重鏈中僅一者之羧基端。較佳地，連接子具有SEQ ID NO: 312或SEQ ID NO: 313之胺基酸序列。

【0108】 為了促進在兩個重鏈（例如，一個具有與抗CD98抗體或其抗原結合片段之融合而一個則沒有，或者一個含有針對抗CD98臂之Fc而一個則針對抗腦部目標臂）之間形成異二聚體，將異二聚體突變引入這兩個重鏈之Fc中。此類

Fc突變之實例包括但不限於Zymework突變（請參見例如US10,457,742）及「鈕扣(knob in hole)」突變（請參見例如Ridgway et al., Protein Eng., 9(7): 617-621, 1996）。其他異二聚體突變亦可用於本發明中。在一些實施例中，使用如本文所述之經修飾CH3，以促進在兩個重鏈之間形成異二聚體。

【0109】 除了異二聚體突變以外，亦可引入其他突變。在一些實施例中，融合建構體或雙特異性抗體之Fc區進一步包含改變（增加或減少）、較佳地消除ADCC/CDC的一或多個突變（諸如本文所述之AAS突變）、及/或改變（增加或減少，較佳地增加）融合建構體或雙特異性抗體與FcRn之結合的一或多個突變（諸如本文所述之YTE突變）。在一些實施例中，將融合建構體或雙特異性抗體中之一或多個半胱胺酸殘基用其他胺基酸取代，諸如絲胺酸。

【0110】 在某些實施例中，本申請案之融合建構體包含：

(1) 第一重鏈，其具有與選自由下列所組成之群組的胺基酸序列至少80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 13、16、19、22、25、32、35、38、41、44、51、54、57、60、63、73、76、79、82、85、95、98、101、104、107、119、129、139、146、156、166、176、186、200、210、及 219；

(2) 兩個輕鏈，其等各獨立地具有分別與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 14、17、20、23、26、33、36、42、45、52、55、58、61、64、74、77、80、83、86、96、99、102、105、108、120、130、140、147、157、167、177、187、201、211、及 220；及

(3) 第二重鏈，其具有分別與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 15、18、21、24、27、34、37、43、46、53、56、59、62、65、75、78、81、84、87、97、100、103、106、109、121、131、141、148、158、168、178、188、202、212、及 221。

【0111】 本申請案之接合物（諸如多特異性抗體或融合建構體）可鑑於本揭露而藉由任何所屬技術領域中已知之數種技術生產。例如，其可表現自重組宿主細胞，其中藉由標準技術將編碼融合建構體或多特異性抗體之重鏈及輕鏈的（多個）表現載體轉染至宿主細胞中。宿主細胞可係原核或真核宿主細胞。

【0112】 在一例示性系統中，藉由轉染或電穿孔將編碼本申請案之融合建構體的異二聚體兩個重鏈及輕鏈之一或多個重組表現載體引入宿主細胞中。培養所選之轉化體(transformant)宿主細胞，以允許重鏈及輕鏈在足以生產融合建構體之條件下表現，並自培養基中回收融合建構體。使用標準分子生物學技術製備重組表現載體，轉染宿主細胞，選擇轉化體，培養宿主細胞，並自培養基中回收蛋白質建構體。

【0113】 本申請案提供一種經單離之核酸，其編碼抗CD98抗體或其抗原結合片段（單獨或作為本文所述之任何實施例中或任何請求項中之融合建構體或多特異性抗體的一部分）之胺基酸序列。經單離之核酸可係載體（較佳地表現載體）之一部分。

【0114】 在另一態樣中，本申請案關於一種宿主細胞，其經本文所揭示之載體轉化。在一實施例中，宿主細胞係原核細胞，例如大腸桿菌。在另一實施例中，宿主細胞係真核細胞，例如原生生物細胞、動物細胞、植物細胞、或真菌細胞。在一實施例中，宿主細胞係哺乳動物細胞，包括但不限於CHO、COS、NS0、SP2、PER.C6、或真菌細胞（諸如釀酒酵母菌）、或昆蟲細胞（諸如Sf9）。

醫藥組成物及相關方法

【0115】 本發明亦關於醫藥組成物、其製備方法及使用其之方法。

【0116】 在另一大致態樣中，本發明關於一種醫藥組成物，其包含本發明之抗CD98抗體或其抗原結合片段或其接合物及醫藥上可接受之載劑。本發明之抗CD98抗體或其抗原結合片段或接合物（諸如多特異性抗體或融合建構體）亦可用於製造用於本文提及之治療應用的藥劑。醫藥上可接受之載劑可係任何合適

的賦形劑、稀釋劑、填料、鹽、緩衝劑、穩定劑、助溶劑、油、脂質、含脂質囊泡、微球、脂質體包封(liposomal encapsulation)、或其他所屬技術領域中熟知用於醫藥配方之材料。將理解載劑、賦形劑或稀釋劑之特徵將取決於特定應用之投予途徑而定。

【0117】 因此，在一個實施例中，本申請案關於一種將治療劑或診斷劑輸送跨過血腦障壁(BBB)之方法，其包含使偶合至該治療劑或診斷劑之抗CD98抗體或其抗原結合片段暴露於血腦障壁，使得該抗體或其抗原結合片段將偶合至其之該劑輸送跨過血腦障壁。在一個實施例中，劑係神經病症藥物。在另一實施例中，劑係顯影劑或用於檢測神經病症之劑。較佳的是，抗CD98抗體或其抗原結合片段或其接合物不干擾胺基酸輸送。抗體以不干擾胺基酸輸送的方式特異性結合CD98。在一些實施例中，BBB係在哺乳動物（較佳地靈長類，諸如人類，更佳地患有神經病症之人類）中。在一個實施例中，神經病症係選自由下列所組成之群組：阿茲海默症(AD)、中風、失智症、肌肉失養症(MD)、多發性硬化症(MS)、肌萎縮性脊髓側索硬化症(ALS)、囊腫纖維化、Angelman氏症候群、Liddle氏症候群、巴金森氏症、匹克症、柏哲德氏症(Paget' s disease)、癌症、及創傷性腦部傷害。

【0118】 在一個實施例中，本申請案之抗CD98抗體或其抗原結合片段、或其接合物係用於在症狀發作之前檢測神經病症及/或評估疾病或病症之嚴重性或持續時間。抗體、其抗原結合片段或接合物允許神經病症之檢測及/或造影，包括藉由放射線攝影術、斷層造影、或磁振造影(MRI)進行造影。

【0119】 在另一實施例中，抗CD98抗體或其抗原結合片段、或其接合物係用於治療神經病症（例如，阿茲海默症），其包含向需要該治療之對象投予有效量的抗CD98抗體或其抗原結合片段、或其接合物。在一些實施例中，該方法進一步包含向對象投予有效量的至少一種額外治療劑。

【0120】 在另一實施例中，本申請案關於一種本申請案之抗CD98抗體或其抗原結合片段或接合物在製造或製備藥劑中之用途。在一個實施例中，藥劑係用

於治療神經疾病或病症。在一進一步實施例中，藥劑係用於治療神經疾病或病症之方法中，該方法包含向患有神經疾病或病症之個體投予有效量的該藥劑。

【0121】 本申請案之另一大致態樣關於一種在有需要之對象中誘導抗體依賴性吞噬作用(ADP)而不刺激促發炎細胞介素的分泌之方法，其包含向該對象投予複合體，該複合體包含偶合至、較佳地共價接合至根據本申請案之一實施例的抗CD98抗體結合片段之其抗原結合片段的治療性抗體或其抗原結合片段，其中該治療性抗體或其抗原結合片段不具有效應功能。例如，治療性抗體或其抗原結合片段可包含降低或消除效應功能（諸如ADCC或CDC）之一或多個胺基酸修飾，諸如降低或除去與Fcγ受體之結合的突變。此類突變可在位置L234、L235、D270、N297、E318、K320、K322、P331、及P329，諸如L234A、L235A、及P331S中之一、二、或三個突變，其中胺基酸殘基之編號係根據如Kabat中所陳述之EU索引。在一個實施例中，治療性抗體或其抗原結合片段特異性結合至tau聚集物。

【0122】 在一些實施例中，該方法進一步包含向對象投予有效量的至少一種額外治療劑。在某些實施例中，額外治療劑係有效治療與抗CD98抗體或其抗原結合片段或接合物所用來治療之神經病症相同或不同的神經病症之治療劑。例示性額外治療劑包括但不限於：各種上述神經藥物、膽鹼酯酶抑制劑（諸如多奈派齊(donepezil)、加蘭他敏(galantamine)、卡巴拉汀(rovastigmine)、及塔克寧(tacrine)）、NMDA受體拮抗劑（諸如美金剛(memantine)）、β類澱粉蛋白肽聚集抑制劑、抗氧化劑、γ-分泌酶調節劑、神經生長因子(NGF)模擬物或NGF基因療法、PPARγ促效劑、HMS-CoA還原酶抑制劑（斯他汀(statin)）、安帕金(ampakine)、鈣通道阻斷劑、GABA受體拮抗劑、肝醣合成酶激酶抑制劑、靜脈注射免疫球蛋白(intravenous immunoglobulin)、蕈毒鹼受體促效劑、菸鹼受體調節劑、主動或被動β類澱粉蛋白肽免疫、磷酸二酯酶抑制劑、血清素受體拮抗劑、及抗β類澱粉蛋白肽抗體。在某些實施例中，至少一種額外治療劑係針對其減輕神經藥物之一或多種副作用來加以選擇。額外治療劑可以相同或分開之配方投予，且與抗CD98抗體或其抗原結合片段或接合物一起或分開投予。本申

請案之抗CD98抗體或抗原結合片段或接合物可在投予額外治療劑及/或佐劑之前、同時、及/或之後投予。本申請案之抗CD98抗體或其抗原結合片段或接合物亦可與其他介入性療法（諸如但不限於放射療法、行為療法、或所屬技術領域中已知且適用於待治療或預防之神經病症的其他療法）組合使用。

【0123】 本申請案之抗CD98抗體或其抗原結合片段或接合物（及任何額外治療劑）可藉由任何合適手段投予，包括腸胃外、肺內、及鼻內，且如果需要局部治療則包括病灶內投予。腸胃外輸注包括肌內、靜脈內、動脈內、腹膜內、或皮下投予，部分取決於投予係短期或長期。本文中已設想到各種給藥排程，包括但不限於在各種時間點之單次或多次投予、推注(bolus)投予、及脈衝輸注。

【0124】 為了預防或治療疾病，本申請案之抗CD98抗體或其抗原結合片段或接合物（當單獨使用或與一或多種其他額外治療劑組合使用時）的適當劑量將取決於各種因素，諸如待治療之疾病的類型、抗體或接合物的類型、疾病之嚴重性及病程、抗體、其抗原結合片段或接合物是為了預防性或治療性目的而投予、先前療法、患者之臨床病史及對抗體之反應、對象之生理狀態（包括例如，年齡、體重、健康）、及主治醫師之判斷。治療劑量經最佳地滴定以最佳化安全性及療效。抗體、其抗原結合片段或接合物係一次性或經過一系列的治療而合適地投予至患者。

【0125】 根據具體實施例，治療有效量係指足以達成一、二、三、四、或更多個下列效應之療法之量：(i)減少或改善待治療之疾病、病症、或病況或與其相關之症狀的嚴重性；(ii)減少所欲治療之疾病、病症、或病況或與其相關之症狀的持續期間；(iii)預防所欲治療之疾病、病症或病況或與其相關之症狀的進展；(iv)造成所欲治療之疾病、病症或病況或與其相關之症狀的消退；(v)預防所欲治療之疾病、病症或病況或與其相關之症狀的發展或發生；(vi)預防所欲治療之疾病、病症或病況或與其相關之症狀的復發；(vii)減少具有所欲治療之疾病、病症或病況或與其相關之症狀的對象的住院；(viii)減少具有所欲治療之疾病、病症或病況或與其相關之症狀的對象的住院期長度；(ix)增加具有所欲

治療之疾病、病症或病況或與其相關之症狀的對象的存活；(xi)抑制或減少對象的所欲治療之疾病、病症或病況或與其相關之症狀；及/或(xii)增強或改善另一療法的（多種）疾病預防或治療效應。

【0126】 在另一態樣中，本申請案關於一種製品（諸如套組），其含有可用於治療、預防、及/或診斷上述病症之材料。製品包含容器及在該容器上或與該容器相關聯之標示或藥品仿單(package insert)。合適容器包括例如瓶子(bottle)、小瓶(vial)、注射器、IV溶液袋等。容器可形成自各種材料，諸如玻璃或塑膠。容器容納組成物（組成物本身或與其他有效用於治療、預防、及/或診斷病況之組成物組合），且可具有無菌出入孔（例如，容器可係靜脈內溶液袋或具有塞子的小瓶，塞子可被皮下注射針頭刺穿）。組成物中之至少一種活性劑係本申請案之抗體、其抗原結合片段、或接合物。標示或藥品仿單指示組成物係用於治療所選病況。此外，製品可包括(a)第一容器，其含有組成物於其中，其中該組成物包含本申請案之抗體、其抗原結合片段、或接合物；及(b)第二容器，其含有組成物於其中，其中該組成物包含額外細胞毒性劑或另外的治療劑。本發明之此實施例中的製品可進一步包括藥品仿單，其指示組成物可用於治療特定病況。可選地，製品可進一步包含第二（或第三）容器，其包含醫藥上可接受之緩衝劑，諸如注射用抑菌水(BWFI)、磷酸鹽緩衝鹽水、林格氏液(Ringer's solution)、及右旋糖溶液。其可進一步包括就商業及使用者觀點而言所欲之其他材料，包括其他緩衝劑、稀釋劑、過濾器、針頭、及注射器。

實施例

【0127】 本發明亦提供以下非限制性實施例。

1. 一種抗 CD98 抗體或其抗原結合片段，其用於將劑遞送至有需要之對象的腦部，其中該抗 CD98 抗體或其抗原結合片段在中性 pH 下以至少 1 nM 之解離常數 K_D 且在酸性 pH、較佳地 pH 5 下以至少 10^{-4} sec^{-1} 之解離速率常數 kd 結合至 CD98、較佳地人類 CD98 重鏈(huCD98hc)。

1a. 如實施例 1 之抗 CD98 抗體或其抗原結合片段，其在中性 pH 下具有 1 nM 至 500 nM、諸如 1 nM、10 nM、50 nM、100 nM、200 nM、300 nM、400 nM、500 nM、或任何其間之值的解離常數 KD。

1b. 如實施例 1 或 1a 之抗 CD98 抗體或其抗原結合片段，其在酸性 pH 下具有 10^{-4} sec^{-1} 至 10^{-1} sec^{-1}、諸如 10^{-4}、10^{-3}、10^{-2}、10^{-1} sec^{-1}、或任何其間之值的解離速率常數 kd。

2. 如實施例 1 至 1b 中任一者之抗 CD98 抗體或其抗原結合片段，其在中性 pH 下具有 2×10^{-2} 至 2×10^{-4} sec^{-1}、較佳地 8×10^{-3} sec^{-1} 之解離速率常數 kd。

2a.如實施例 2 之抗 CD98 抗體或其抗原結合片段，其中在中性 pH 下之該解離速率常數 kd 係 2×10^{-2} 至 2×10^{-4} sec^{-1}、諸如 2×10^{-2}、1×10^{-2}、9×10^{-3}、8×10^{-3}、7×10^{-3}、6×10^{-3}、5×10^{-3}、4×10^{-3}、3×10^{-3}、2×10^{-3}、1×10^{-3}、9×10^{-4}、8×10^{-4}、7×10^{-4}、6×10^{-4}、5×10^{-4}、4×10^{-4}、3×10^{-4}、2×10^{-4} sec^{-1}、或任何其間之值。

3.如實施例 1 至 2a 中任一者之抗 CD98 抗體或其抗原結合片段，其包含：

(1) 包含重鏈互補決定區(HCDR) HCDR1、HCDR2、及 HCDR3 之重鏈可變區及包含輕鏈互補決定區(LCDR) LCDR1、LCDR2、及 LCDR3 之輕鏈可變區，其中該 HCDR1、HCDR2、HCDR3、LCDR1、LCDR2、及 LCDR3 具有下列之胺基酸序列：

i. 分別為 SEQ ID NO: 7、8、9、10、11、及 12；

ii. 分別為 SEQ ID NO: 67、68、69、70、71、及 72；

iii. 分別為 SEQ ID NO: 89、90、91、92、93、及 94；

iv. 分別為 SEQ ID NO: 113、114、115、116、117、及 118；

v. 分別為 SEQ ID NO: 123、124、125、126、127、及 128；

vi. 分別為 SEQ ID NO: 133、134、135、136、137、及 138；

vii. 分別為 SEQ ID NO: 150、151、152、153、154、及 155；

viii.分別為 SEQ ID NO: 160、161、162、163、164、及 165；

ix. 分別為 SEQ ID No: 170、171、172、173、174、及 175；

x. 分別為 SEQ ID NO: 180、181、182、183、184、及 185；或

(2) 重鏈上之單可變域(VHH)，其包含具有下列之胺基酸序列的重鏈互補決定區(HCDR) HCDR1、HCDR2、及 HCDR3：

i. 分別為 SEQ ID NO: 29、30、及 31；

ii. 分別為 SEQ ID NO: 48、49、及 50；或

iii. 分別為 SEQ ID NO: 143、144、及 145。

4. 如實施例 3 之抗體或其抗原結合片段，其係 VHH 片段，該 VHH 片段包含與 SEQ ID NO: 28、SEQ ID NO: 47、或 SEQ ID NO: 142 具有至少 80%、諸如至少 85%、90%、95%、或 100%序列同一性之胺基酸序列。

4a. 如實施例 3 之抗體或其抗原結合片段，其中該 VHH 片段包含 SEQ ID NO: 28、SEQ ID NO: 47、或 SEQ ID NO: 142 之胺基酸序列。

5. 如實施例 3 之抗體或其抗原結合片段，其係單鏈可變片段(scFv)，該單鏈可變片段包含經由連接子、諸如長度為約 10 至約 25 個胺基酸之肽連接子共價連接至該輕鏈可變區(VL)的該重鏈可變區(VH)。

5a. 如實施例 5 之抗體或其抗原結合片段，其中該 VH 係經由該 scFv 中之該連接子連接至該 VL 之胺基端。

5b. 如實施例 5 之抗體或其抗原結合片段，其中該 VH 係經由該 scFv 中之該連接子連接至該 VL 之羧基端。

5c. 如實施例 5a 或 5b 之抗體或其抗原結合片段，其中該連接子包含 Gly 及 Ser 中之一或多者、及一或多個穿插之 Glu、Thr、及 Lys 殘基，較佳地該連接子具有 SEQ ID NO: 189 之胺基酸序列。

5d. 如實施例 5c 之抗體或其抗原結合片段，其中該 scFv 包含分別具有 SEQ ID NO: 279、280、281、282、283、及 284 之胺基酸序列、或分別具有 SEQ ID NO: 292、293、294、295、296、及 297 之胺基酸序列的 HCDR1、HCDR2、HCDR3、LCDR1、LCDR2、及 LCDR3；

5e. 如實施例 5c 或 5d 之抗體或其抗原結合片段，其中該 scFv 包含與下列之胺基酸序列具有至少 80%、諸如至少 85%、90%、95%、或 100%序列同一性之胺基酸序列：SEQ ID NO: 6、SEQ ID NO: 66、SEQ ID NO: 88、SEQ ID NO: 112、SEQ ID NO: 122、SEQ ID NO: 132、SEQ ID NO: 149、SEQ ID NO: 159、SEQ ID NO: 169、SEQ ID NO: 179、SEQ ID NO: 193、或 SEQ ID NO: 203。

5f. 如實施例 5e 之抗體或其抗原結合片段，其中該 scFv 包含下列之胺基酸序列：SEQ ID NO: 6、SEQ ID NO: 66、SEQ ID NO: 88、SEQ ID NO: 112、SEQ ID NO: 122、SEQ ID NO: 132、SEQ ID NO: 149、SEQ ID NO: 159、SEQ ID NO: 169、SEQ ID NO: 179、SEQ ID NO: 193、或 SEQ ID NO: 203。

5g. 如實施例 5e 之抗體或其抗原結合片段，其中該 scFv 包含 SEQ ID NO: 278、291、162、或 218 之胺基酸序列。

5h. 一種抗體或其抗原結合片段，其結合至如實施例 1 至 5g 中任一者之抗體或其抗原結合片段的相同表位。

5i. 一種抗體或其抗原結合片段，其與如實施例 1 至 5g 中任一者之抗體或其抗原結合片段競爭結合至該 CD98。

5j. 如實施例 3 至 5i 中任一者之抗體或其抗原結合片段，其在 pH7.4 下以 1 至 500 nM、諸如 1 nM、10 nM、50 nM、100 nM、200 nM、300 nM、400 nM、500 nM、或任何其間之值的解離常數 KD 結合至人類 CD98。

5k. 如實施例 1 至 5j 中任一者之抗體或其抗原結合片段，其在 pH5 下以 10^{-4} 至 10^{-1} sec^{-1}、諸如 10^{-4}、10^{-3}、10^{-2}、10^{-1} sec^{-1}、或任何其間之值的解離速率常數 kd 結合至人類 CD98。

6. 一種複合體，其包含偶合至治療劑或診斷劑的如實施例 1 至 5k 中任一者之抗體或其抗原結合片段。

6a. 如實施例 6 之複合體，其中該抗體或其抗原結合片段係非共價偶合至該治療劑或診斷劑。

6b. 如實施例 6 之複合體，其中該抗體或其抗原結合片段係共價偶合至該治療劑或診斷劑以形成接合物。

6c. 如實施例 6 之複合體，其中該抗體或其抗原結合片段係經由連接子共價連接至該治療劑或診斷劑。

6d. 如實施例 6c 之複合體，其中該連接子係非肽連接子，諸如聚乙二醇、聚丙二醇、乙二醇與丙二醇之共聚物、聚氧乙基化多元醇、聚乙烯醇、多醣、右旋糖酐、聚乙烯醚、可生物降解聚合物、經聚合脂質、幾丁質、及玻尿酸、或其衍生物、或其組合。

6e. 如實施例 6c 之複合體，其中該連接子係肽連接子，諸如由 1 至 50 個由肽鍵連接之胺基酸所組成的肽鏈或其衍生物。

6f. 如實施例 6 至 6e 中任一者之複合體，其中該抗體或其抗原結合片段係偶合至用於檢測神經病症之該診斷劑，較佳地該診斷劑係用於正子發射斷層造影(PET)之劑、或用於 IDK 之劑。

6g. 如實施例 6 至 6e 中任一者之複合體，其中該抗體或其抗原結合片段係偶合至治療劑、較佳地神經病症藥物。

6h. 如實施例 6g 之複合體，其中該神經病症藥物係選自由下列所組成之群組：小分子化合物、抗體、肽、蛋白質、一或多種 CNS 目標之天然配體、一或多種 CNS 目標之天然配體的經修飾版本、適體、抑制性核酸（即，小型抑制性 RNA (siRNA)及短髮夾 RNA (shRNA)）、核酶、及前述者之活性片段。

6i. 如實施例 6g 之複合體，其中該神經病症藥物係選自由下列所組成之群組：抗體、適體、蛋白質、肽、抑制性核酸及小分子、及本身係 CNS 抗原或目標分子或特異性辨識且/或作用於（即，抑制、活化、或檢測）CNS 抗原或目標分子的任何前述者之活性片段，諸如但不限於類澱粉蛋白前驅蛋白或其部分、β 類澱粉蛋白、β-分泌酶、γ-分泌酶、tau、α-突觸核蛋白、parkin、亨丁頓蛋白、DR6、早老素、ApoE、神經膠質瘤或其他 CNS 癌症標記、及神經營養因子。神經病症藥物及其等可用於治療之對應病症的非限制性實例：腦部衍生神經營養因子(BDNF)、慢性腦部傷害（神經生成）、纖維母細胞生長因子 2 (FGF-2)、抗表皮生長因子受體腦部癌症、(EGFR)-抗體、神經膠細胞系衍生神經因子巴金森氏症、(GDNF)、腦部衍生神經營養因子(BDNF)肌萎縮性脊髓

側索硬化症、憂鬱、腦部之溶體酶溶體儲積症、睫狀神經營養因子(CNTF)肌萎縮性脊髓側索硬化症、神經調節蛋白 1 思覺失調症、抗 HER2 抗體（例如，曲妥珠單抗）自 HER2 陽性癌症之腦部轉移。

7. 如實施例 6 之複合體，其係多特異性抗體，該多特異性抗體包含結合 CD98 之第一抗原結合區及結合腦部抗原（或腦部目標）之第二抗原結合區，其中該第一抗原結合區包含如實施例 1 至 5k 中任一者之其抗原結合片段。

7a. 如實施例 7 之多特異性抗體，其中該腦部目標係選自由下列所組成之群組：β-分泌酶 1 (BACE1)、β 類澱粉蛋白(Aβ)、表皮生長因子受體(EGFR)、人類表皮生長因子受體 2 (HER2)、Tau、載脂蛋白 E4 (ApoE4)、α-突觸核蛋白、CD20、亨丁頓蛋白、普里昂蛋白(PrP)、富白胺酸重複激酶 2 (LRRK2)、parkin、早老素 1、早老素 2、γ 分泌酶、死亡受體 6 (DR6)、類澱粉蛋白前驅蛋白(APP)、p75 神經營養因子受體(p75NTR)、及凋亡蛋白酶 6。

7b. 如實施例 7a 之多特異性抗體，其中該第二抗原結合區結合 BACE1 或 Tau。

7c. 如實施例 7 至 7b 中任一者之多特異性抗體，其中該第一抗原結合區係共價連接至第一 Fc，且該第二抗原結合區係共價連接至第二 Fc。

7d. 如實施例 7c 之多特異性抗體，其中該第一 Fc 與該第二 Fc 在一或多個胺基酸殘基上不同，以促進在該第一 Fc 與該第二 Fc 之間形成異二聚體。

8. 如實施例 7 至 7b 中任一者之多特異性抗體，其係融合建構體，該融合建構體包含共價連接結合該腦部抗原（或腦部目標）之第二抗體或其抗原結合片段的如實施例 1 至 5k 中任一者之抗體或其抗原結合片段。

8a. 如實施例 8 之融合建構體，其中如實施例 1 至 5k 中任一者之抗體或其抗原結合片段係共價連接、較佳地經由連接子連接至該第二抗體或其抗原結合片段之重鏈的胺基端。

8b. 如實施例 8 之融合建構體，其中如實施例 1 至 5k 中任一者之抗體或其抗原結合片段係共價連接、較佳地經由連接子連接至該第二抗體或其抗原結合片段之輕鏈的胺基端。

8c. 如實施例 8 之融合建構體，其中如實施例 1 至 5k 中任一者之抗體或其抗原結合片段係共價連接、較佳地經由連接子連接至該第二抗體或其抗原結合片段之輕鏈的羧基端。

8d. 如實施例 8 之融合建構體，其中如實施例 1 至 5k 中任一者之抗體或其抗原結合片段係共價連接、較佳地經由連接子連接至該第二抗體或其抗原結合片段之重鏈的羧基端。

9. 如實施例 8d 之融合建構體，其中如實施例 1 至 5k 中任一者之抗體或其抗原結合片段係經由連接子共價連接至該第二抗體或抗原結合片段之兩個重鏈中僅一者之羧基端。

9a. 如實施例 8a 至 9 中任一者之融合建構體，其中該連接子係包含 Gly 及 Ser 中之一或多者的肽連接子，較佳地該連接子具有 SEQ ID NO: 190 或 SEQ ID NO: 191 之胺基酸序列。

9b. 如實施例 8 至 9a 中任一者之融合建構體，其中該第二抗體或其抗原結合片段包含第一 Fc 在其第一重鏈及第二 Fc 在其第二重鏈，且該第一 Fc 與該第二 Fc 在一或多個胺基酸殘基上不同，以促進在該第一 Fc 與該第二 Fc 之間形成異二聚體。

9c. 如實施例 7d 之多特異性抗體或如實施例 9b 之融合建構體，其中該第一 Fc 含有一或多個「鈕(knob)」突變，且該第二 Fc 含有一或多個對應「孔(hole)」突變，或反之亦然（關於「鈕扣」突變，請參見例如美國專利第 5,731,168 號、Ridgway et al., Protein Eng., 9(7): 617-621, 1996，該等文獻之全文以引用方式併入本文中），較佳地 T366W 之鈕突變及 T366S、L368A、或 Y407V 之孔突變。

9d. 如實施例 7d 之多特異性抗體或如實施例 9b 之融合建構體，其中該第一 Fc 及該第二 Fc 之各者包含相較於野生型 CH3 域多肽之經修飾異二聚體 CH3 域，較佳地該經修飾異二聚體 CH3 域包含一或多個如 US10,457,742 中所述之突變。

9e. 如實施例 9d 之多特異性抗體或融合建構體，其中該第一 Fc 之該經修飾異二聚體 CH3 域在位置 T350、L351、F405、及 Y407 包含胺基酸修飾，且該第二 Fc 之該經修飾異二聚體 CH3 域在位置 T350、T366、K392、及 T394 包含胺基酸修飾。

9f. 如實施例 9e 之多特異性抗體或融合建構體，其中在位置 T350 之胺基酸修飾係 T350V、T350I、T350L、或 T350M；在位置 L351 之胺基酸修飾係 L351Y；在位置 F405 之胺基酸修飾係 F405A、F405V、F405T、或 F405S；在位置 Y407 之胺基酸修飾係 Y407V、Y407A、或 Y407I；在位置 T366 之胺基酸修飾係 T366L、T366I、T366V、或 T366M，在位置 K392 之胺基酸修飾係 K392F、K392L、或 K392M，且在位置 T394 之胺基酸修飾係 T394W。

9g. 如實施例 9e 之多特異性抗體或融合建構體，其中該第一 Fc 之該經修飾異二聚體 CH3 域包含突變 T350V、L351Y、F405A、及 Y407V，且該第二 Fc 之該經修飾異二聚體 CH3 域包含突變 T350V、T366L、K392L、及 T394W，或反之亦然。

10. 如實施例 7 至 9g 中任一者之多特異性抗體或融合建構體，其中該多特異性抗體或融合建構體之該 Fc 區進一步包含改變（增加或減少）、較佳地增加該第二抗體或其抗原結合片段與新生兒 Fc 受體(FcRn)之結合的取代。

10a. 如實施例 10 之多特異性抗體或融合建構體，其中該第二抗體或其抗原結合片段在該 Fc 域中包含增強該融合與該新生兒 Fc 受體(RcRn)之結合的一或多個突變。

10b. 如實施例 10 或 10a 之多特異性抗體或融合建構體，其中該一或多個突變增強在酸性 pH 下之該結合。

10c. 如實施例 10b 之多特異性抗體或融合建構體，其中該第二抗體之該 Fc 具有 M252Y/S254T/T256E (YTE)突變，其中胺基酸殘基之編號係根據如 Kabat 中所陳述之 EU 索引。

11. 如實施例 7 至 10c 中任一者之多特異性抗體或融合建構體，其中該多特異性抗體或融合建構體之該 Fc 區進一步包含改變（增加或減少）、較佳地降低或消除效應功能的取代。

11a. 如實施例 11 之多特異性抗體或融合建構體，其中該第二抗體或其抗原結合片段在該 Fc 域中包含降低或消除效應功能的一或多個突變，效應功能諸如抗體依賴性細胞毒性(ADCC)或補體依賴性細胞毒性(CDC)。

11b. 如實施例 11a 之多特異性抗體或融合建構體，其中該第二抗體之該 Fc 在位置 L234、L235、D270、N297、E318、K320、K322、P331、及 P329 具有一或多個胺基酸修飾，其中胺基酸殘基之編號係根據如 Kabat 中所陳述之 EU 索引。

11c. 如實施例 11b 之多特異性抗體或融合建構體，其中該第二抗體之該 Fc 具有 L234A、L235A、及 P331S（AAS 突變）中之一、二、或三個突變。

12. 如實施例 7 至 11c 中任一者之多特異性抗體或融合建構體，其中該第一抗原結合區或該抗體或其抗原結合片段不含有半胱胺酸。

13. 如實施例 7 至 12 之多特異性抗體或融合建構體，其中該第二抗原結合區或該第二抗體或其抗原結合片段結合 Tau，較佳地其包含分別具有 SEQ ID NO: 213 至 218 之胺基酸序列的 HCDR1、HCDR2、HCDR3、LCDR1、LCDR2、及 LCDR3，較佳地該第二抗體係單株抗體，該單株抗體包含具有 SEQ ID NO: 110 之胺基酸序列的重鏈及具有 SEQ ID NO: 111 之胺基酸序列的輕鏈。

14. 如實施例 9 之融合建構體，其包含：

(1) 第一重鏈，其具有與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 13、16、19、22、25、32、35、38、41、44、51、54、57、60、63、73、76、79、82、85、95、98、101、104、107、119、129、139、146、156、166、176、186、200、210、及 219；

(2) 兩個輕鏈，其等各獨立地具有分別與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 14、17、20、23、26、33、36、42、45、52、55、58、61、64、74、77、80、83、86、96、99、102、105、108、120、130、140、147、157、167、177、187、201、211、及 220；及

(3) 第二重鏈，其具有分別與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 15、18、21、24、27、34、37、43、46、53、56、59、62、65、75、78、81、84、87、97、100、103、106、109、121、131、141、148、158、168、178、188、202、212、及 221。

14a.如實施例 14 之融合建構體，其中該兩個輕鏈具有相同胺基酸序列。

14b.如實施例 14 之融合建構體，其中該兩個輕鏈具有不同胺基酸序列。

14c.如實施例 14 之融合建構體，其中：

(1) 第一重鏈，其具有選自由下列所組成之群組的胺基酸序列：SEQ ID NOs: 13、16、19、22、25、32、35、38、41、44、51、54、57、60、63、73、76、79、82、85、95、98、101、104、107、119、129、139、146、156、166、176、186、200、210、及 219；

(2)兩個輕鏈，其等各具有分別選自由下列所組成之群組的胺基酸序列：SEQ ID NOs: 14、17、20、23、26、33、36、42、45、52、55、58、61、64、74、77、80、83、86、96、99、102、105、108、120、130、140、147、157、167、177、187、201、211、及 220；及

(3) 第二重鏈，其具有分別選自由下列所組成之群組的胺基酸序列：SEQ ID NOs: 15、18、21、24、27、34、37、43、46、53、56、59、62、65、75、78、81、84、87、97、100、103、106、109、121、131、141、148、158、168、178、188、202、212、及 221。

15. 一種經單離之核酸，其編碼如實施例 1 至 5k 中任一者之抗體或抗原結合片段、或如實施例 7 至 14c 中任一者之融合建構體。

16. 一種載體，其包含如請求項 15 所述之經單離之核酸。

17. 一種宿主細胞，其包含如實施例 15 之核酸或如實施例 16 之載體。

18. 一種生產如實施例 1 至 5k 中任一者之抗體或抗原結合片段、或如實施例 7 至 14c 中任一者之融合建構體的方法，其包含在生產該抗體或抗原結合片段、該融合建構體之條件下，培養包含編碼該抗體或抗原結合片段、或該融合建構體之核酸的細胞；及自該細胞或細胞培養物回收該抗體或抗原結合片段、或該融合建構體。

19. 一種醫藥組成物，其包含如實施例 1 至 5k 中任一者之抗體或抗原結合片段、如實施例 6 至 6i 中任一者之複合體、或如實施例 7 至 14c 中任一者之多特異性抗體或融合建構體、及醫藥上可接受之載劑。

20. 一種治療或檢測有需要之對象的神經病症之方法，其包含向該對象投予有效量的如實施例 1 至 5k 中任一者之抗體或抗原結合片段、如實施例 6 至 6i 中任一者之複合體、或如實施例 7 至 14c 中任一者之多特異性抗體或融合建構體、或如實施例 19 之醫藥組成物。

21. 一種增加治療劑或診斷劑遞送至有需要之對象的腦部之方法，其包含向該對象投予接合物，該接合物包含偶合至如實施例 1 至 5k 中任一者之抗體或其抗原結合片段的該治療劑或診斷劑。

22. 一種將治療劑或診斷劑輸送跨過血腦障壁(BBB)之方法，其包含使偶合至該治療劑或診斷劑之如實施例 1 至 5k 中任一者之抗 CD98 抗體或其抗原結合片段暴露於該血腦障壁，使得該抗體或其抗原結合片段將偶合至其之該劑輸送跨過該血腦障壁。

23. 一種將治療劑或診斷劑遞送跨過有需要之對象的血腦障壁(BBB)之方法，其包含向該對象投予複合體，該複合體包含偶合至、較佳地共價接合至如實施例 1 至 5 中任一者之抗體或其抗原結合片段的該治療劑或診斷劑。

24. 一種在有需要之對象中誘導抗體依賴性吞噬作用(ADP)而不刺激促發炎細胞介素的分泌之方法，其包含向該對象投予複合體，該複合體包含偶合至、較佳地共價接合至如實施例 1 至 5 中任一者之其抗原結合片段的治療性

抗體或其抗原結合片段，其中該治療性抗體或其抗原結合片段在該 Fc 域中包含降低或消除效應功能的一或多個突變，該效應功能諸如抗體依賴性細胞毒性(ADCC)或補體依賴性細胞毒性(CDC)。

24a. 如實施例 24 之方法，其中該治療性抗體或其抗原結合片段在位置 L234、L235、D270、N297、E318、K320、K322、P331、及 P329 包含一或多個胺基酸修飾，其中胺基酸殘基之編號係根據如 Kabat 中所陳述之 EU 索引。

24b. 如實施例 24a 之方法，其中該治療性抗體或其抗原結合片段包含 L234A、L235A、及 P331S 中之一、二、或三個突變。

25. 如實施例 20 至 24b 中任一者之方法，其中該對象需要治療神經病症，較佳地該神經病症係選自由下列所組成之群組：神經退化性疾病（諸如路易氏體病、脊髓灰質炎後症候群、Shy-Draeger 症候群、橄欖體橋腦小腦萎縮、巴金森氏症、多系統萎縮、紋狀體與黑質體退化症、脊髓小腦性失調症、脊髓性肌萎縮）、tau 蛋白病（諸如阿茲海默症及核上神經麻痺症）、普里昂疾病（諸如牛海綿狀腦病、羊搔癢症、庫賈氏症候群、庫魯病、吉斯曼-史特斯勤-先克病、慢性消耗病、及致死性家族性失眠症）、延髓性麻痺、運動神經元疾病、及神經系統異退化性病症（諸如 Canavan 病、亨丁頓舞蹈症、神經元蠟樣脂褐質儲積症、亞歷山大氏病、妥瑞氏症候群、Menkes 氏捲髮症候群、柯凱因氏症候群、Halervorden-Spatz 氏症候群、拉弗拉病、雷特氏症候群、肝豆狀核變性、Lesch-Nyhan 氏症候群、及 Unverricht-Lundborg 氏症候群）、失智症（諸如匹克症及脊髓小腦性失調症）、及 CNS 及/或腦部之癌症（諸如身體其他地方之癌症所致的腦部轉移）。

26. 如實施例 20 至 25 中任一者之方法，其中該抗體或其抗原結合片段、該複合體、該多特異性抗體、該融合建構體、或該醫藥組成物經靜脈內投予。

27. 如實施例 20 至 26 中任一者之方法，其中該治療劑或治療性抗體或其抗原結合片段係神經病症藥物。

28. 如實施例 20 至 23 中任一者之方法，其中該劑係顯影劑或用於檢測神經病症之劑。

29. 如實施例 20 至 28 中任一者之方法，其中該抗 CD98 抗體或其抗原結合片段、其複合體或融合不會干擾胺基酸輸送。

30. 如實施例 20 至 29 中任一者之方法，其中該投予降低 Fc 介導之效應功能。

31. 如實施例 21 至 30 中任一項之方法，其中該投予不誘導快速網狀紅血球耗盡。

32. 如實施例 31 之方法，其中該治療性抗體或其抗原結合片段特異性結合至 tau 聚集物

33. 如實施例 20 至 32 中任一者之方法，其中該對象係靈長類，諸如人類，更佳地患有神經病症之人類。

34. 如實施例 33 之方法，其中該神經病症係選自由下列所組成之群組：：阿茲海默症(AD)、中風、失智症、肌肉失養症(MD)、多發性硬化症(MS)、肌萎縮性脊髓側索硬化症(ALS)、囊腫纖維化、Angelman 氏症候群、Liddle 氏症候群、巴金森氏症、匹克症、柏哲德氏症、癌症、及創傷性腦部傷害。

本發明的下列實例是要進一步說明本發明的本質。應了解的是，下列實例不會對本發明造成限制，且本發明之範疇係由隨附之申請專利範圍決定。

實例

實例 1

【0128】 雖然血腦障壁(BBB)防止有害物質進入腦部且對於腦內恆定(brain homeostasis)是不可或缺的，其也會對於將藥物有效率遞送至腦部造成難以克服的障礙。為此目的，開發了穿透BBB並導致明顯比單獨mAb高之腦部濃度的單株抗體(mAb)腦部穿梭劑平台。

抗體產生（*OMT* 大鼠及 *Ablexis* 小鼠）

【0129】 將OMT大鼠（OmniRat®，來自Ligand Pharmaceuticals）及Ablexis小鼠(Ablexis, LLC, San Diego, CA)用人類CD98hc (SEQ ID NO: 1)、或人類CD98hc、食蟹獼猴CD98hc (SEQ ID NO: 2)、及狨CD98hc (SEQ ID NO: 3)進行免疫。使用兩種規程進行OMT免疫，短時間（28天）及長規程（48天），各規程用於5隻OMT大鼠的免疫。使用具有Sigma/CFA佐劑的重複免疫多部位(RIMMS)規程對Ablexis小鼠進行免疫20或51天。簡言之，在鄰近區域引流淋巴結之多個皮下部位將動物重複免疫。使用huCD98hc ECD塗佈之盤(OMT)或huCD98hc過度表現性CHO-S細胞(Ablexis)，藉由ELISA對於長規程在第31天進行血清滴定，對於短規程在第14天進行血清滴定。自血清陽性動物中採集淋巴結並將其融合以產生融合瘤或篩選為單一B細胞。

【0130】 首先針對與huCD98hc塗佈之盤之結合，藉由ELISA篩選融合瘤。在確認篩選中對抗人類、食蟹獼猴(SEQ ID NO:2)、狨(SEQ ID NO:3)、小鼠(SEQ ID NO:4)、及大鼠(SEQ ID NO:5) CD98hc塗佈之ELISA盤測試命中者。然後，使用CHO-S細胞過度表現性huCD98hc或cyCD98hc、pBECS（一級人類腦部內皮質細胞，內源性CD98hc表現）、及CHO親本細胞作為陰性細胞系，完成基於細胞之檢定。在確認ELISA後，選擇94個命中者（62個命中者來自融合1、及32個命中者來自融合2）。在FACS分析中，可以確認31種細胞結合物，其中20種在ELISA中未確認為陽性。

【0131】 重新排列在至少一者檢定中被檢定並發現為陽性的所有殖株（94個殖株），並在ELISA及細胞結合(FACS)中重新測量。第一次確認篩選的數據在第二次確認篩選中得到確認。然後評估mAb在pBEC中的內化。然後獲得內化的mAb的V區定序數據。使用定序數據來建構三腳架mAb（圖1）。

抗體產生*(Llama)*

【0132】 為了產生對抗人類CD98hc的單域抗體(VHH)，在Abcore使用兩隻駱馬進行免疫。抗體效價係藉由ELISA使用人類CD98蛋白(1 μg/ml)判定。對來自這兩隻動物的三次採血進行測試，且兩隻動物均顯示良好的早期效價。

【0133】 噬菌體展示係在Abcore使用其標準規程完成。製作出兩個庫：來自兩隻動物的第二次採血之庫1及來自第二次及第三次採血之庫2。對來自12個隨機個別殖株之質體DNA進行定序，且>80%含有具有正確讀框之VHH插入。對兩個噬菌體展示庫以人類CD98使用標準Abcore淘選程序進行篩選。以人類CD98hc在10 μg/ml下進行三輪淘選。在淘選之後，對94個個別殖株藉由噬菌體ELISA針對與蛋白酶活化受體1 (Par1) N端域之特異性結合及與BSA（牛血清白蛋白）之非特異性結合進行篩選。測量與食蟹獼猴、小鼠、及大鼠CD98hc之交叉反應性。選出94個展示結合的殖株在重鍊及輕鏈可變區中進行序列分析。使用序列來建構三腳架mAb（圖1）。

【0134】 本發明之CD98hc抗體或抗原結合片段的實例係彙總於表1中：

表 1

名稱	序列	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
CD98hc 1	SEQ ID NO: 6	SEQ ID NO: 7 GGSISSGAYYW	SEQ ID NO: 8 IYYSGST	SEQ ID NO: 9 ARAGPKWELWFDY	SEQ ID NO: 10 SSDVDNYNY	SEQ ID NO: 11 DVSNRPS	SEQ ID NO: 12 SSFTSSSTWV
CD98hc 2	SEQ ID NO: 28	SEQ ID NO: 29 GRAFSSNG	SEQ ID NO: 30 ISCSGTST	SEQ ID NO: 31 AADTRHCMGYTKDEGYAY			
CD98hc 3	SEQ ID NO: 47	SEQ ID NO: 48 GRTISTYG	SEQ ID NO: 49 SCSGTST	SEQ ID NO: 50 AADTRHCMGYTKHGGYDY			
CD98hc 4	SEQ ID NO: 66	SEQ ID NO: 67 GFTFSSYG	SEQ ID NO: 68 ISYDGSNK	SEQ ID NO: 69 ARAPSSFYFDY	SEQ ID NO: 70 QSVLFSSNNKNY	SEQ ID NO: 71 WAS	SEQ ID NO: 72 QQYYSTPPT
CD98hc 5	SEQ ID NO: 88	SEQ ID NO: 89 GGSISSSY	SEQ ID NO: 90 IYNSGST	SEQ ID NO: 91 ARETYYFDY	SEQ ID NO: 92 QNVGIN	SEQ ID NO: 93 SAA	SEQ ID NO: 94 QQYNSYPLT
CD98hc 6	SEQ ID NO: 112	SEQ ID NO: 113 GYTFTSYY	SEQ ID NO: 114 INPSGGTT	SEQ ID NO: 115 ARDPNDYGGPKYFPH	SEQ ID NO: 116 QSVLYRSNNKNY	SEQ ID NO: 117 WAS	SEQ ID NO: 118 HQYYSTPLT
CD98hc 7	SEQ ID NO: 122	SEQ ID NO: 123 EYTFTSYY	SEQ ID NO: 124 INPSGGST	SEQ ID NO: 125 ARAGYCTINSCFNWFDP	SEQ ID NO: 126 QSVLYASRNKNY	SEQ ID NO: 127 WAS	SEQ ID NO: 128 QYYSTPFT
CD98hc 8	SEQ ID NO: 132	SEQ ID NO: 133 GYTFTSYY	SEQ ID NO: 134 FNPSGGST	SEQ ID NO: 135 ARGGVGATGYFDY	SEQ ID NO: 136 QSVLYRSNNKNY	SEQ ID NO: 137 WAS	SEQ ID NO: 138 QQYYGTPFT
CD98hc 9	SEQ ID NO: 142	SEQ ID NO: 143 GRTFSRYG	SEQ ID NO: 144 ISCSGTST	SEQ ID NO: 145 AADTRHCMGYTKDGGYAY			
CD98hc 10	SEQ ID NO: 149	SEQ ID NO: 150 GYTFTGYY	SEQ ID NO: 151 INPNSGGS	SEQ ID NO: 152 LRGKTFDP	SEQ ID NO: 153 QGISSH	SEQ ID NO: 154 AAS	SEQ ID NO: 155 QQLNNYPLT

CD98hc 11	SEQ ID NO: 159	SEQ ID NO: 160 GYTFTSYY	SEQ ID NO: 161 NPSGGST	SEQ ID NO: 162 ARAGYCRSTTSCFNWFDP	SEQ ID NO: 163 QSVLYNSNNKNY	SEQ ID NO: 164 WAS	SEQ ID NO: 165 QQYYSTPFT
CD98hc 12	SEQ ID NO: 169	SEQ ID NO: 170 GFTLSSSW	SEQ ID NO: 171 INSDGSST	SEQ ID NO: 172 ARWNWGWYFDL	SEQ ID NO: 173 QSLLHSHGDNY	SEQ ID NO: 174 LGS	SEQ ID NO: 175 MQTLETPYT
CD98hc 13	SEQ ID NO: 179	SEQ ID NO: 180 GFTFSSYW	SEQ ID NO: 181 INSDGSII	SEQ ID NO: 182 VREGRYTGSSLDY	SEQ ID NO: 183 NSNIGAGYD	SEQ ID NO: 184 GNS	SEQ ID NO: 185 QSYDSSLTGWV
CD98hc 14	SEQ ID NO: 193	SEQ ID NO: 194 GFTFSSYG	SEQ ID NO: 195 ISYDGSNK	SEQ ID NO: 196 ARAPSAFYFDY	SEQ ID NO: 197 QSVLFSSNNKNY	SEQ ID NO: 198 WAS	SEQ ID NO: 199 QQYYSTPPT
CD98hc 15	SEQ ID NO: 203	SEQ ID NO: 204 GFTFSSYG	SEQ ID NO: 205 ISYDGSNK	SEQ ID NO: 206 ARAPSHFYFDY	SEQ ID NO: 207 QSVLFSSNNKNY	SEQ ID NO: 208 WAS	SEQ ID NO: 209 QQYYSTPPT

三腳架建構體設計

【0135】 對於對抗CD98所產生的抗體針對與CD98之結合競爭進行篩選，且將非競爭性mAb格式化為三腳架mAb（亦稱為TTP mAb）架構中之scFv或奈米抗體並表徵。使用三腳架以將所關注物質（例如，單株抗體）遞送至腦部。更具體而言，開發含有針對CD98之抗體的抗原結合片段與所關注單株抗體(mAb)之融合的三腳架建構體（圖1），以協助mAb穿透BBB並導致明顯比單獨mAb更高的mAb腦部濃度。

【0136】 例如，由治療性mAb與CD98hc結合scFv或奈米抗體所組成之三腳架mAb使用短、可撓性連接子附接至一個抗體重鏈之C端。對三腳架mAb針對先前已描述增強胞吞轉送之特性（綜述於Goulatis and Shusta 2017）進行分析：價、結合親和力、pH依賴性結合、及腦部內皮細胞中之快速內化。

【0137】 將針對CD98之抗體的重鏈及輕鏈可變序列融合於單一基因建構體中作為單鏈可變片段(scFv)，其使用下列格式：

Hc_GTEGKSSGSGSESKST(SEQ ID NO: 189)_Lc

【0138】 接著將針對CD98之scFv或VHH融合至所關注抗體之一個重鏈(Hc)的C端，其使用GGSGGS (SEQ ID NO: 190)或GGAGGA (SEQ ID NO: 191)連接子。在抗體Hc中採用CH3中之Zymeworks異二聚化突變(Hc A: T350V_L351Y_F405A_Y407V; Hc B: T350V_T366L_K392L_T394W)，以產生三腳架建構體（圖1），其亦稱為三腳架mAb。三腳架mAb含有兩個具有相同胺基酸序列之輕鏈及兩個具有不同胺基酸序列之重鏈。這兩個重鏈中僅一者係融合至本發明之CD98抗體的scFv或VHH，且這兩個重鏈亦在其恆定區中有所不同，以促進這兩個重鏈之間的異二聚化。因此，根據本申請案之實施例的各三腳架mAb係與三個胺基酸序列相關聯：融合至CD98抗體之抗原結合片段的第一重鏈之胺基酸序列、輕鏈之胺基酸序列、及未融合至CD98抗體之抗原結合片段的第二重鏈之胺基酸序列。

三腳架表現及純化

【0139】 將三腳架mAb表現於CHO-Expi細胞中，並使用Protein A親和力層析法接著粒徑篩析層析法或離子交換層析法來純化。

【0140】 所製造之三腳架mAb的實例係提供於表1a中：

表 1a

三腳架名稱	mAb 組分名稱（目標）	scFv 組分名稱	VL SEQ ID NO	VH SEQ ID NOs
BBBB404	B21M IgG1 AAS	C98hc1	14	13/15
BBBB1058	抗 Tau IgG1 AAS YTE	C98hc1	17	16/18
BBB1056	抗 Tau IgG1	C98hc1	20	19/21
BBBB1097	抗 BAM IgG1 AAS YTE	C98hc1	23	22/24
BBBB1226	B21M IgG4	C98hc1	26	25/27
BBBB448	B21M IgG1 AAS	C98hc2	33	32/34
BBBB1061	抗 Tau IgG1 AAS YTE	C98hc2	36	35/37
BBBB1059	抗 Tau IgG1	C98hc2	39	38/40
BBBB1100	抗 BAM IgG1 AAS YTE	C98hc2	42	41/43
BBBB1228	B21M IgG4	C98hc2	45	44/46
BBBB449	B21M IgG1 AAS	C98hc3	52	51/53
BBBB1064	抗 Tau IgG1 AAS YTE	C98hc3	55	54/56
BBBB1062	抗 Tau IgG1	C98hc3	58	57/59
BBBB1103	抗 BAM IgG1 AAS YTE	C98hc3	61	60/62
BBBB1229	B21M IgG4	C98hc3	64	63/65
BBBB578	B21M IgG1 AAS	C98hc4	74	73/75
BBBB1067	抗 Tau IgG1 AAS YTE	C98hc4	77	76/78
BBBB1065	抗 Tau IgG1	C98hc4	80	79/81
BBBB1106	抗 BAM IgG1 AAS YTE	C98hc4	83	82/84
BBBB1230	B21M IgG4	C98hc4	86	85/87
BBBB584	B21M IgG1 AAS	C98hc5	96	95/97
BBBB1070	抗 Tau IgG1 AAS YTE	C98hc5	99	98/100
BBBB1068	抗 Tau IgG1	C98hc5	102	101/103
BBBB1109	抗 BAM IgG1 AAS YTE	C98hc5	105	104/106
BBBB1231	B21M IgG4	C98hc5	108	107/109
BBBB580	B21M IgG1 AAS	C98hc6	120	119/121
BBBB586	B21M IgG1 AAS	C98hc7	130	129/131
BBBB593	B21M IgG1 AAS	C98hc8	140	139/141
BBBB445	B21M IgG1 AAS	C98hc9	147	146/148
BBBB1227	B21M IgG4	C98hc9	220	219/221
BBBB589	B21M IgG1 AAS	C98hc10	157	156/158
BBBB594	B21M IgG1 AAS	C98hc11	167	166/168
BBBB602	B21M IgG1 AAS	C98hc12	177	176/178

三腳架名稱	mAb 組分名稱（目標）	scFv 組分名稱	VL SEQ ID NO	VH SEQ ID NOs
BBBB610	B21M IgG1 AAS	C98hc13	187	186/188

細胞結合及 *CD98hc* 特異性

【0141】 將人類腦部內皮細胞（hCMECD3，50,00個細胞）與10 ug/mL經純化三腳架mAb培養，然後使其在4℃下於10x莫耳濃度的huCD98hc (SEQ ID NO: 1)存在下培養整夜。在隔天早上將細胞固定並洗滌，與二級抗體(Jackson Immunosciences Cat# 109-546-170)培養，再次洗滌，接著藉由FACS分析。陽性結合劑係定義為結合信號比同型對照組大3倍以上（表2）。

表 2b：三腳架 mAb 之 hCMECD3 細胞結合。

mAb	SEQ ID NO:	Rep 1	Rep 2	平均信號
BBBB404	13, 14, 15	11944	10148	11046
BBBB448	32, 33, 34	12851	7458	10155
BBBB449	51, 52, 53	7359	5521	6440
BBBB578	73, 74, 75	23248	23583	23416
BBBB584	95, 96, 97	3771	3079	3425
BBBB580	119, 120, 121	13118	11030	12047
同型對照	110, 111	371	123	247

CD98hc 功能性評估

【0142】 將hCMECD3細胞接種至白色不透明的384孔板中，並在37℃下培養整夜。第二天，將細胞洗滌並用無鈉林格氏溶液(Ringer's Solution)在37℃脈衝30分鐘。用無鈉林格溶液再次洗滌細胞，並將抗CD98hc抗體(140 nM)、或LAT抑製劑BCH (50 mM)、及T3 (200 μM)添加至細胞。然後添加L-[3,4,5-3H(N)]-白胺酸(0.4 μCi)並培養5分鐘後，用冰冷的無鈉林格溶液將細胞洗滌兩次，然後用0.2% SDS的0.2 N NaOH溶液裂解細胞。將裂解物與Microscint-PS溶液在室溫下培養1小時，並在Perkin-Elmer TopCount NXT儀器上獲得閃爍計數。拮抗劑活性之標準是相對於Zymeworks三腳架同型對照組的^{3}H-白胺酸之抑制[平均值-(3 x SD)]（圖2）。基於該標準，測試抗體均未顯示出對^{3}H-白胺酸吸收的抑制，而

BCH及T3 LAT抑製劑均顯示出對^{3}H-白胺酸吸收的顯著抑制。包括CNTO3930（hIgG1同型對照組）作為額外陰性對照組且顯示無活性。

內化

【0143】 將人類腦部內皮細胞(hCMECD3)以10,000個細胞/孔接種於經膠原蛋白塗佈之384孔Cell Carrier Ultra盤(Perkin Elmer)中，然後使其在37℃下在加濕培養箱中附接16小時。接著將細胞（50,000個細胞）與200 ug/mL經純化三腳架mAb培養，並使其在37℃下培養一小時。將細胞固定、洗滌，然後與經螢光標示之二級抗體培養一小時。接著將細胞再次洗滌，然後與經螢光標示之肌動蛋白染料鬼筆環肽(Phalloidin)及核染料Hoeschst 33342培養。將細胞再次洗滌，然後使用ImageXpress Micro (Molecular Devices)以40x物鏡進行成像。基於與鬼筆環肽之共定位使用MetaXpress 6.0識別內化mAb（圖3中的實例）。所有mAb均對內化呈陽性。

親和力分析及 *pH* 依賴性結合、物種交叉反應性

【0144】 為了獲得額外的親和力測量精確度，三腳架mAb對huCD98hc之親和力係使用表面電漿共振(SPR)在BioRad ProteOn XPR36系統上判定。Fc捕捉表面係藉由使用胺偶合化學(BioRad)將抗IgG Fc mAb (Jackson ImmunoResearch)偶合至GLC晶片(BioRad)來產生。三腳架mAb係使用0.3 ug/mL之濃度，以60 uL/min流動30秒（針對200 RU之目標密度）來捕捉。然後使huCD98hc流過經固定之三腳架mAb（濃度從6.25至400 nM、800 nM、或100至1600 nM，以4倍連續稀釋）以進行4 min（以50 μL/min）締合，接著以50 uL/min進行解離30分鐘。將晶片表面用兩次18秒的100 mM H_3PO_4 (Sigma)脈衝以100 μL/min再生。將所收集之數據使用ProteOn Manager軟體V3.1.0.6 (BioRad)處理。首先，用間點將數據針對背景校正。接著，數據之雙參考減法係藉由使用緩衝液注射用於分析物注射來執行。使用Langmuir 1:1結合模型執行數據之動力學分析。各mAb之結

果係以Ka（結合速率）、Kd（解離速率）、及KD（平衡解離常數）之格式記述（表3及3a）。

表 3：三腳架 mAb 對 huCD98hc 的結合親和力

樣本 ID	SEQ ID NO:	ka (1/Ms)	kd (1/s)	KD (nM)
BBBB404	13, 14, 15	(4.23±1.32) E-04	(19.9±4.01) E-03	5.03±1.76
BBBB445	146, 147, 148	7.10E+05	4.48E-03	6.31
BBBB448	32, 33, 34	6.50E+05	1.49E-03	2.29
BBBB449	51, 52, 53	8.33E+05	2.79E-03	3.35
BBBB578	73, 74, 75	3.90E+05	1.54E-03	3.95
BBBB584	95, 96, 97	5.00E+04	5.65E-03	1.13
BBBB580	119, 120, 121	1.88E+05	9.65E-03	51.4
BBBB586	129, 130, 131	(3.00±0.23)E+05	(2.16±0.05)E-03	7.23
BBBB589	156, 157, 158	6.36E+05	2.63E-02	41.3
BBBB593	139, 140, 141	(1.05±0.04)E+05	(3.44±0.14)E-03	32.80
BBBB594	166, 167, 168	3.48E+05	1.39E-03	4.00
BBBB602	176, 177, 178	3.99E+04	8.71E-03	218
BBBB610	186, 187, 188	6.10E+05	8.89E-04	1.46
BBBB1201	200, 201, 202	3.57E+05	6.00E-03	16.85
BBBB1202	210, 211, 212	1.67E+05	8.82E-03	52.90

Table 3a. SPR binding for IgG4 mAbs

名稱	說明	ka (1/Ms)	kd (1/s)	KD (M)
BBBB1227	B21M IgG4 ZW BBBB445	(4.40±0.17)E+05	(2.42±0.64)E-03	(5.49±1.23)E-09
BBBB1228	B21M IgG4 ZW BBBB448	(4.26±1.13)E+05	(1.77±0.71)E-03	(4.21±2.34)E-09
BBBB1229	B21M IgG4 ZW BBBB449	(4.82±1.34)E+05	(3.36±2.38)E-03	(6.88±3.14)E-09

結果為平均值± 95%CI

【0145】 pH依賴性結合係使用上述SPR (proteon)方法評估，除了將生物素化CD98hc固定在鏈黴親和素晶片上，並在解離期間，緩衝劑pH係從7.4逐步下降至6.5再至6.0。評估個別感測圖，如果解離速率隨著pH降低而變快則針對pH依賴性結合給分（圖4中之實例）。

【0146】 物種交叉反應性係使用與判定結合親和力相同之方法評估，除了所使用之CD98hc係食蟹獼猴(SEQ ID NO: 2)、狨(SEQ ID NO: 3)、小鼠(SEQ ID

NO: 4)、及大鼠(SEQ ID NO: 5)。未識別出大鼠或小鼠交叉反應性mAb。識別出食蟹獼猴及狨交叉反應性三腳架mAb（表4）。

表 4：所選三腳架 mAb 之物種交叉反應性

mAb	SEQ ID NO:	食蟹獼猴 KD(M)	狨 KD (M)	人類 KD(M)
BBBB404	13, 14, 15	4.54E-08	無結合	5.03E-09
BBBB445	146, 147, 148	6.31E-09	1.38E-08	2.28E-09
BBBB448	32, 33, 34	5.32E-09	9.45E-09	2.29E-09
BBBB449	51, 52, 53	7.56E-09	1.97E-08	3.35E-09
BBBB578	73, 74, 75	6.22E-08	無結合	3.95E-09
BBBB584	95, 96, 97	1.85E-07	4.70E-07	1.13E-07
BBBB586	119, 120, 121	(2.02±0.15)E-08	未測量	(7.23±0.56)E-09
BBBB589	129, 130, 131	4.13E-08	無結合	9.17E-09
BBBB593	156, 157, 158	(3.35±0.08)E-07	未測量	(3.28±0.18)E-08
BBBB594	139, 140, 141	4.00E-09	無結合	2.17E-09
BBBB602	166, 167, 168	2.18E-07	弱結合	1.28E-07
BBBB610	176, 177, 178	1.46E-09	8.39E-08	2.18E-09

選擇用於食蟹獼猴研究的 *mAb* 及評估融合至抗 *Tau mAb* 之腦部穿梭劑

【0147】　對確認靶向CD98hc之三腳架mAb在人類中提升治療性抗體腦部暴露之能力而言，關鍵的是在非人類靈長類中展現出增強之腦部遞送。選擇BBBB578、BBBB448及BBBB584用於食蟹獼猴PK研究。抗CD98hc scFv融合至抗Tau mAb、PT1B844 (SEQ ID NOs: 110, 111)以產生BBBB1067/BBBB1065 (SEQ ID NOs: 76, 77, 78/SEQ ID NOs: 79, 80, 81)、BBBB1061 (SEQ ID NOs: 35, 36, 37)、及BBBB1070 (SEQ ID NOs: 98, 99, 100)。測量huCD98hc的親和力(表5)，且當融合至抗B21M mAb時類似於結合。

表 5.融合至抗 Tau mAb 的抗 CD98hc 腦部穿梭劑對 huCD98hc 的結合親和力

mAb 融合	SEQ ID NO:	ka (1/Ms)	kd (1/s)	KD (M)
BBBB1065	79, 80, 81	(4.70±0.21)E+05	(1.39±0.02)E-03	(2.96±0.17)E-09
BBBB1067	76, 77, 78	(4.39±0.15)E+05	(1.38±0.03)E-03	(3.15±0.13)E-09
BBBB1070	98, 99, 100	(5.57 ±0.94)E+04	(6.48±0.82)E-03	(1.18±0.21)E-07
BBBB1061	35, 36, 37	(9.35 ±1.16)E+05	(1.35±0.09)E-03	(1.46±0.18)E-09

【0148】 與先前研究類似，亦對內化進行評估，且腦部穿梭劑與抗Tau mAb之融合不會影響其在人類腦部內皮細胞中內化之能力（圖5）。

抗 *Tau* 腦部穿梭劑 *mAb* 之食蟹獼猴藥物動力學

【0149】 藉由IV注射（緩慢推注）對食蟹獼猴以所指示之劑量投予測試物品。在排定之時間點，在上身用鹽水灌注最少5分鐘後收集食蟹獼猴腦部並用冷鹽水溶液潤洗。將預定之腦部位置單離出來，在液態氮中急凍，然後儲存在-80℃下，直到組織均質化及微血管耗盡處理。

【0150】 將BBBB1067、BBBB1061、及BBB1070連同非腦部穿梭劑開啟之mAb PT1B844及PT1B916以10 mg/kg在食蟹獼猴中*i.v.*給藥。在4、24、及72小時採樣血漿。在上身用鹽水灌注最少5分鐘後收集食蟹獼猴腦部並用冷鹽水溶液潤洗。將預定之腦部位置單離出來，在液態氮中急凍，然後儲存在-80℃下，直到組織均質化及微血管耗盡處理。

【0151】 為了進行經微血管耗盡之腦部組織裂解物的樣本製備，獲得所收集腦部位置之個別重量。將腦部組織樣本添加至計算體積的經修飾dPBS緩衝劑（2.5 µL緩衝劑/1 mg組織）中，該緩衝劑含有蛋白酶抑制劑(Pierce; A32955)，然後將其轉移至裂解基質D (MP Biomedicals™; 6913-100)管中。使用Bead Ruptor 24 Elite (Omni International)將組織樣本以2.9 m/s均質化15秒。將總細胞懸浮液轉移至新的管中，然後與等體積的26%右旋糖酐緩衝劑混合（13%最終右旋糖酐濃度）。將經混合組織均質物在4℃下以2,000g離心10分鐘。小心地將上層（經微血管耗盡之部分）與剩餘樣本分離，然後轉移至含有10x RIPA裂解緩衝劑(Millipore™; 20-188)之新的管中。將經微血管耗盡之樣本加上裂解緩衝劑充份漩渦震盪，在4℃下以14,000 rpm離心30分鐘，然後將上清液轉移至新的管中。將腦部組織樣本裂解物冷凍儲存在-70℃下或使用BCA蛋白質檢定套組(Pierce™; 23227)測量蛋白質濃度。將最終腦部組織樣本裂解物標準化至7 mg/mL總蛋白質濃度，之後再進行BBB開啟(BBB-enabled) mAb之免疫檢定判定。

【0152】 BBB開啟mAb在食蟹獼猴腦部組織中之濃度（用於PK評估）係使用MesoScale Discovery (MSD®; Gaithersburg, MD) ECLIA技術判定，該技術係以典型三明治免疫檢定格式開發。檢定係在MSD Gold™ Small Spot Streptavidin 96孔盤(Cat: L45SA)上執行。將經鏈黴親和素塗佈之盤在室溫下用於1x磷酸鹽緩衝鹽水(PBS)中之1%牛血清白蛋白(BSA)阻斷30分鐘。標準曲線係在50%初始食蟹獼猴腦部組織裂解物中藉由連續稀釋來新鮮製備。將以2x的工作檢定濃度製備於初始食蟹獼猴腦部組織裂解物中的冷凍品管品(QC)稀釋並用各檢定進行測試。將含有捕捉（生物素化抗人類Fc mAb，1 μg/mL）及檢測（經釕標示之抗人類Fc mAb，0.5 μg/mL）試劑之預混物與經稀釋之標準品、QC、及樣本以1:1體積比率組合在檢定盤中。將混合物在室溫下振盪培養1小時。將檢定盤洗滌，並將MSD T讀取緩衝劑(1x)添加至所有孔中。在MSD SECTOR® S600成像器上讀取原始數據值。檢定之標準曲線範圍係在1至512 ng/mL下測試，且最小所需樣本稀釋(MRD)為1:2，從而在腦部組織裂解物中產生2 ng/mL之靈敏度限制。將具有原始ECL計數之MSD輸出檔案匯入Watson LIMS (Thermo Scientific)，然後以5參數邏輯擬合使用1/F2加權進行迴歸。

【0153】 跨各種區域判定四種mAb之腦部濃度（圖6）。所有含腦部穿梭劑之mAb的腦部暴露相對於不含腦部穿梭劑之mAb在每一個腦部區均有所增加。將數據轉換為注射劑量/kg腦%並在各個區域取平均值後，對腦部穿梭劑mAb，其腦部濃度可提高16倍。

【0154】 由於CD98hc的廣泛組織表現，能夠結合FcgR的三腳架mAb可以在多種組織上誘導ADCC/ADCP。為了避免這種可能性，藉由引入「AAS」突變至三腳架mAb中來利用效應靜默Fc。儘管避免ADCC/ADCP是治療性mAb之安全性的重要特徵，但一種潛在的治療性作用機制依賴於Tau聚集物的Fc依賴性小神經膠細胞吞噬作用。藉由抑制腦部穿梭劑mAb結合至FcγR，mAb便無法結合小神經膠細胞上之FcR以促進Tau聚集物之吞噬作用。然而，我們的腦部穿梭劑通過CD98hc介導的非Fc依賴性內化，利用了一種新穎的小神經膠細胞吸收機制。

【0155】 為了評估AAS IgG1三腳架mAb促進Tau聚集物在小神經膠細胞中吸收的潛力，將衍生自誘導性多能幹細胞(iPSC)之人類小神經膠細胞以每盤7000個細胞之稀釋液接種至384孔Perkin Elmer Cell Carrier Ultra盤上，並維持在具有Glutamax+、青黴素/鏈黴素、IL34 (100 ng/ml)、及GMCSF (10 ng/ml)之進階DMEM/F12培養基中。在檢定當天，使生物素化磷酸化tau寡聚物[序列：SCBiot-(dPEG4)GTPGSRSR(pT)PSLP(pT)PPTREPLL-醯胺(SEQ ID NO: 192)]與鏈黴親和素Alexa Flour 488 (AF488)以15倍莫耳過量複合。接著使經標示之磷酸化tau寡聚物以大約2X莫耳過量在室溫下結合測試mAb 30分鐘。接著將mAb:tau寡聚物複合體以20 µl/孔遞送至小神經膠細胞。在培養後2、4、及8小時，將細胞用磷酸鹽緩衝鹽水(PBS)洗滌兩次，然後在室溫下於4%多聚甲醛存在下固定15分鐘。在固定後，將細胞再次在PBS中洗滌兩次，然後與LAMP1一級抗體（一種溶體之標記）以4 ug/ml之濃度在4℃下於透化緩衝劑（0.1%皂素+1%魚皮明膠）中培養整夜。在培養後，將細胞用PBS洗滌兩次，然後用1 ug/ml接合至Alexa fluor 647之二級抗體在4℃下於透化緩衝劑中染色1小時。在培養後，將細胞用PBS洗滌兩次，用Hoechst DNA染料以1 ug/ml在室溫下於PBS中對比染色10分鐘。接著將細胞在PBS中洗滌最後一次，再懸浮於每孔20 µl的PBS中，然後在Opera Phenix共焦高通量顯微鏡上成像。使用Harmony及ImageJ分析軟體來分析所獲取之影像。針對在吞噬溶體結構內且經LAMP1抗體標示的Tau寡聚物之存在，對每條件大約500個細胞評分。

【0156】 相較於非腦部穿梭劑mAb (PT1B844)，腦部穿梭劑mAb BBBB1067促進等效吸收進入吞噬體（圖7），而BBBB1065出乎意料地糟。這些數據證明，消除與FcγR的結合不會影響抗Tau mAb之治療效力，事實上，CD98hc介導之內化及運輸至吞噬溶體似乎在小神經膠細胞中比傳統FcγR介導之吞噬作用更有效率。

討論

【0157】 為了達到基於受體介導之胞吞轉送的最佳化腦部遞送平台，產生以一範圍的親和力以pH依賴性方式特異性結合至人類CD98hc之mAb。結合親和力與胞吞轉送效率之間的關係在許多出版物中已被廣泛提及，其著重於平衡解離常數K_D。雖然K_D是一個重要的量度，但在本發明中已令人驚訝地證明結合動力學k_a及k_d對於胞吞轉送之關鍵性。發明人發現，結合速率及解離速率兩者均需要針對有效率胞吞轉送及所遞送治療性mAb之藥效動力學活性進行最佳化。基於這些結果，最佳胞吞轉送會發生在例如$k_a \geq 10^5\ M^{-1}\ s^{-1}$且中性$k_d = 8\times10^{-3}\ sec^{-1}$時。儘管不希望受理論束縛，假定結合速率與解離速率之間的相互作用對於確保有效率之跨細胞輸送通過各式各樣負責極化細胞中之蛋白質運輸的細胞內囊泡是關鍵的。

【0158】 已證明在食蟹獼猴中給藥三腳架mAb會導致腦部濃度相對於對照mAb有16x提升。酸性FcRn結合增加會導致末梢清除降低及腦部濃度提升。在正常生理條件下，FcRn介導之抗體自腦部外排可能藉由在腦部中避免非所要的發炎及免疫反應而對維持腦內恆定是關鍵的(Schlachetzki, Zhu et al. 2002, Roopenian and Akilesh 2007)。雖然優勢證據意味著FcRn介導之抗體外排扮演了重大角色，但關於此清除機制仍有一些爭議(Garg and Balthasar 2009, Abuqayyas and Balthasar 2013)。發明人發現，增加對FcRn之結合親和力對末梢及腦部濃度兩者皆具有正面影響，這意味著任何增強之外排在此系統中是不重要的。

【0159】 Fc誘變的明顯缺點是將效應功能自治療性mAb消除。對於腦部中之許多治療目標（像是β類澱粉蛋白及Tau）而言，據信ADP對於效力而言至關重要。發明人證明，多價貨物之此內源轉向可用作為ADP之替代、非典型、非FcγR機制。透過非典型及典型ADP內化之Tau係以類似方式在小神經膠細胞中運輸，其中Tau聚集物運輸通過內溶體(endolysosomal)系統至溶體以進行降解。可將所述之非典型ADP用於各種治療應用，其中ADP對於效力是必要的但典型ADP對安全性有害。

【0160】 數據指示，非典型ADP比典型ADP更有效率。已經在體外及患者中觀察到巨噬細胞耗竭(Baig, 2014)，指示這種耗竭表型可能影響具有效應功能的

mAb的治療功效。非典型ADP提供效力優點，藉由介導ADP而不活化小神經膠細胞（藉由結合FcγR）來避免此耗竭表型。

【0161】 非典型ADP之另一優點是藉由避免小神經膠細胞活化，ADP之發生不會刺激促發炎細胞介素的生產。對於使用效應功能健全之mAb在治療腦部中之疾病上的安全性仍有爭議，尤其是關於在已罹患慢性神經發炎之患者中增加神經發炎（綜述於Heneka, et al. Lancet Neurol.中）。2015 Apr; 14(4): 388-405)。此外，對於下列之關注正在不斷增加：發炎在涉及發炎增加之神經退化性疾病的致病機制中所扮演的角色、以及接合或進一活化可能已經耗竭之小神經膠細胞的爭論中能力。例如，已證明典型ADP對於神經元之毒性影響，並假定效應功能健全之mAb可能帶來安全性風險(Lee, etal. 2016)。總而言之，已對穩健之腦部遞送平台針對藥物動力學、藥效動力學、及安全性進行表徵，從而建立進展至臨床試驗所需之穩健臨床前表徵。

【0162】 將經最佳化之腦部穿梭劑融合至PT1B844（一種Tau結合mAb）。當在食蟹獼猴中*i.v.*給藥時，與腦部穿梭劑融合之PT1B844展示16倍之腦部濃度提升。腦部濃度之提升超過文獻中所報導之最佳腦部穿梭劑。除了優越的腦部PK以外，腦部穿梭劑經工程改造以降低Fc介導之效應功能，且在食蟹獼猴中不誘導快速網狀紅血球耗盡（如競爭者所曾報導）。重要的是，Fc功能之喪失不會影響治療性Tau mAb之有效性，因為腦部穿梭劑在介導Tau之小神經膠細胞吸收上比單獨PT1B844更有效率。

實例 2

【0163】 將所選抗CD98腦部穿梭劑融合至原型抗BACE（β-分泌酶）mAb，並使用與上述相同之方法重新評估結合親和力。當融合至B21M mAb（抗人類呼吸道融合病毒）及抗BACE拮抗劑mAb時，預期抗CD98腦部穿梭劑之親和力是類似的。針對所選分子評估內化，且預期發現其與當將抗CD98腦部穿梭劑融合至B21M mAb時所觀察到之內化並無變化。

【0164】 因為抗CD98腦部穿梭劑皆未結合至小鼠或大鼠CD98，將在huCD98hc敲入(KI)小鼠中使用抗BACE拮抗劑mAb進行體內嚙齒動物研究。選擇抗BACE拮抗劑mAb作為用於測量BACE1之抑制（透過其產物肽Aβ1-40之濃度）的模型PD系統，該抑制反映了運輸至腦部的mAb量。

【0165】 第一體內研究將評估huCD98hc小鼠視網膜中之PK/PD關係。將對敲入(KI)小鼠用抗BACE拮抗劑mAb及對照mAb以10 mg/kg *i.v.*給藥。將在給藥後4及24小時採集眼睛及血漿。在排定之時間點，將藉由吸入異氟烷將小鼠麻醉。將在用5 mL的0.9%鹽水溶液進行全身灌注後收集來自KI小鼠之小鼠眼睛。將所收集之眼睛樣本（除去視神經）在液態氮中急凍，然後儲存在-70℃下，直到組織均質化或準備用於免疫組織化學。

【0166】 BACE活性測量將藉由將小鼠眼睛在裂解基質D管中均質化來進行（每mg腦部重量8 µl的0.4% DEA/50 mM NaCl，Fast Prep-24在6/振盪/sec下進行20 sec）。接著將在設定為最高速度之Eppendorf離心機中將管在4℃下離心5 min。接著將均質物（上清液）轉移至經預冷之管中，接著將其在4℃下以13,000 rpm離心70分鐘。接著將上清液轉移至含有10%的0.5 M Tris/HCL之管中，然後冷凍在-80℃下直到進行檢定。接著將Aβ 1-40肽標準品及解凍之經處理眼睛均質物與經釕(Meso Scale Discovery (MSD), R91AN-1)標示之抗Aβ抗體以1:1預複合。將50 ul的複合體添加至含有針對Aβ 1-40之捕捉抗體的經阻斷盤中。在2至8℃下無振盪培養整夜之後，將盤洗滌並添加2x讀取緩衝劑(MSD, R92TC-1)。將使用Meso Sector S 600 (MSD, IC0AA)讀取盤。

【0167】 所屬技術領域中具有通常知識者將領會的是，能夠對以上所述的實施例進行變更而不違背其廣義的發明概念。因此，應了解本發明不限於所揭示之特定實施例，而是意欲涵蓋如隨附之申請專利範圍所定義的本發明之精神及範疇內的修改。

引用文獻

Abuqayyas, L. and J. P. Balthasar (2013). "Investigation of the role of FcgammaR and FcRn in mAb distribution to the brain." Mol Pharm **10**(5): 1505-1513.

Church, A. K., K. R. VanDerMeid, N. A. Baig, A. M. Baran, T. E. Witzig, G. S. Nowakowski and C. S. Zent (2016). "Anti-CD20 monoclonal antibody-dependent phagocytosis of chronic lymphocytic leukaemia cells by autologous macrophages." Clin Exp Immunol **183**(1): 90-101.

Cooper, P. R., G. J. Ciambrone, C. M. Kliwinski, E. Maze, L. Johnson, Q. Li, Y. Feng and P. J. Hornby (2013). "Efflux of monoclonal antibodies from rat brain by neonatal Fc receptor, FcRn." Brain Res **1534**: 13-21.

Dall'Acqua, W. F., P. A. Kiener and H. Wu (2006). "Properties of human IgG1s engineered for enhanced binding to the neonatal Fc receptor (FcRn)." J Biol Chem **281**(33): 23514-23524.

Garg, A. and J. P. Balthasar (2009). "Investigation of the influence of FcRn on the distribution of IgG to the brain." AAPS J **11**(3): 553-557.

Goulatis, L. I. and E. V. Shusta (2017). "Protein engineering approaches for regulating blood-brain barrier transcytosis." Curr Opin Struct Biol **45**: 109-115.

Johnsen, K. B., A. Burkhart, F. Melander, P. J. Kempen, J. B. Vejlebo, P. Siupka, M. S. Nielsen, T. L. Andresen and T. Moos (2017). "Targeting transferrin receptors at the blood-brain barrier improves the uptake of immunoliposomes and subsequent cargo transport into the brain parenchyma." Sci Rep **7**(1): 10396.

Robbie, G. J., R. Criste, W. F. Dall'acqua, K. Jensen, N. K. Patel, G. A. Losonsky and M. P. Griffin (2013). "A novel investigational Fc-modified humanized monoclonal antibody, motavizumab-YTE, has an extended half-life in healthy adults." Antimicrob Agents Chemother **57**(12): 6147-6153.

Roopenian, D. C. and S. Akilesh (2007). "FcRn: the neonatal Fc receptor comes of age." Nat Rev Immunol **7**(9): 715-725.

Schlachetzki, F., C. Zhu and W. M. Pardridge (2002). "Expression of the neonatal Fc receptor (FcRn) at the blood-brain barrier." J Neurochem **81**(1): 203-206.

Vandermeeren, M., M. Borgers, K. Van Kolen, C. Theunis, B. Vasconcelos, A. Bottelbergs, C. Wintmolders, G. Daneels, R. Willems, K. Dockx, L. Delbroek, A. Marreiro, L. Ver Donck, C. Sousa, R. Nanjunda, E. Lacy, T. Van De Casteele, D. Van Dam, P. P. De Deyn, J. A. Kemp, T. J. Malia and M. H. Mercken (2018). "Anti-Tau Monoclonal Antibodies Derived from Soluble and Filamentous Tau Show Diverse Functional Properties in vitro and in vivo." J Alzheimers Dis **65**(1): 265-281.

Yu, Y. J., J. K. Atwal, Y. Zhang, R. K. Tong, K. R. Wildsmith, C. Tan, N. Bien-Ly, M. Hersom, J. A. Maloney, W. J. Meilandt, D. Bumbaca, K. Gadkar, K. Hoyte, W. Luk, Y. Lu, J. A. Ernst, K. Scearce-Levie, J. A. Couch, M. S. Dennis and R. J. Watts (2014). "Therapeutic bispecific antibodies cross the blood-brain barrier in nonhuman primates." Sci Transl Med **6**(261): 261ra154.

Yu, Y. J., Y. Zhang, M. Kenrick, K. Hoyte, W. Luk, Y. Lu, J. Atwal, J. M. Elliott, S. Prabhu, R. J. Watts and M. S. Dennis (2011). "Boosting brain uptake of a therapeutic antibody by reducing its affinity for a transcytosis target." Sci Transl Med **3**(84): 84ra44.

Zent, C. S. and M. R. Elliott (2017). "Maxed out macs: physiologic cell clearance as a function of macrophage phagocytic capacity." FEBS J **284**(7): 1021-1039.

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Leu Glu Pro His Glu Gly Leu Leu Leu Arg Phe Pro Tyr Val Ala
420 425 430

<210> 3

<211> 431
<212> PRT
<213> 狨(Callithrix jacchus)

<400> 3

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His His His His His His Arg Ala Pro Arg Cys Arg Asp Leu Pro Val
1               5                  10                  15

Gln Lys Trp Trp His Thr Gly Ala Leu Tyr Arg Ile Gly Asp Leu Gln
            20                  25                  30

Gly Phe Gln Gly Asn Gly Ala Gly Asn Leu Ala Gly Leu Lys Gly His
        35                  40                  45

Leu Asp Tyr Leu Ser Ser Leu Lys Val Lys Gly Leu Val Leu Gly Pro
    50                  55                  60

Ile His Lys Asn Gln Lys Asp Asp Val Ala Gly Thr Asp Leu Leu Gln
65                  70                  75                  80

Ile Asp Pro Asn Phe Gly Ser Lys Glu Asp Phe Ala Ser Leu Leu Gln
                85                  90                  95

Ser Ala Lys Lys Lys Ser Ile Arg Ile Ile Leu Asp Leu Thr Pro Asn
            100                 105                 110

Tyr Gln Gly Glu Asn Ser Trp Phe Ser Thr Gln Val Asp Thr Val Ala
        115                 120                 125

Thr Lys Val Lys Asp Ala Leu Glu Phe Trp Leu Gln Ala Gly Val Asp
    130                 135                 140

Gly Phe Gln Val Arg Asp Ile Glu Asn Leu Lys Asp Ala Ser Ser Phe
145                 150                 155                 160

Leu Ala Glu Trp Gln Asn Ile Thr Lys Gly Phe Ser Glu Asp Arg Leu
                165                 170                 175
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Leu Ile Ala Gly Thr Asn Ser Ser Asp Leu Gln Gln Ile Leu Ser Leu
180 185 190

Leu Glu Ser Asn Lys Asp Leu Leu Leu Thr Ser Ser Tyr Leu Ser Asn
195 200 205

Ser Ser Phe Thr Gly Glu His Thr Lys Ser Leu Val Thr Gln Tyr Leu
210 215 220

Asn Ala Thr Gly Asn Arg Trp Cys Ser Trp Ser Leu Ser Gln Ala Gly
225 230 235 240

Leu Leu Thr Ser Phe Leu Pro Ala Gln Leu Leu Arg Leu Tyr Gln Leu
245 250 255

Met Leu Phe Thr Leu Pro Gly Thr Pro Val Phe Ser Tyr Gly Asp Glu
260 265 270

Ile Gly Leu Glu Ala Ala Ala Val Pro Gly Gln Pro Val Glu Ala Pro
275 280 285

Val Met Leu Trp Asp Glu Ser Ser Phe Pro Phe Ile Ser Ala Ala Gly
290 295 300

Ser Ala Asn Met Thr Val Lys Gly Gln Ser Glu Asp Pro Gly Ser Leu
305 310 315 320

Leu Ser Leu Phe Arg Arg Leu Ser Asp Gln Arg Ser Lys Glu Arg Ser
325 330 335

Leu Leu His Gly Asp Phe His Ala Leu Ser Ser Gly Pro Gly Phe Phe
340 345 350

Ser Tyr Ile Arg His Trp Asp Gln Asn Glu Arg Phe Leu Val Val Leu
355 360 365

Asn Phe Gly Asp Val Gly Leu Ser Ala Gly Leu Gln Ala Ser Asp Leu
370 375 380

Pro Ala Ser Ala Ser Leu Pro Ala Lys Ala Asp Leu Leu Leu Ser Thr
385 390 395 400

Gln Pro Gly Arg Asp Glu Gly Ser Pro Leu Glu Leu Glu Arg Leu Lys
405 410 415

Leu Glu Pro His Glu Gly Leu Leu Leu Arg Phe Pro Tyr Val Ala
420 425 430

<210> 4
<211> 434
<212> PRT
<213> 小鼠(Mus musculus)

<400> 4

His His His His His His Arg Ala Pro Arg Cys Arg Glu Leu Pro Val
1 5 10 15

Gln Arg Trp Trp His Lys Gly Ala Leu Tyr Arg Ile Gly Asp Leu Gln
20 25 30

Ala Phe Val Gly Arg Asp Ala Gly Gly Ile Ala Gly Leu Lys Ser His
35 40 45

Leu Glu Tyr Leu Ser Thr Leu Lys Val Lys Gly Leu Val Leu Gly Pro
50 55 60

Ile His Lys Asn Gln Lys Asp Glu Ile Asn Glu Thr Asp Leu Lys Gln
65 70 75 80

Ile Asn Pro Thr Leu Gly Ser Gln Glu Asp Phe Lys Asp Leu Leu Gln
85 90 95

Ser Ala Lys Lys Lys Ser Ile His Ile Ile Leu Asp Leu Thr Pro Asn
100 105 110

Tyr Gln Gly Gln Asn Ala Trp Phe Leu Pro Ala Gln Ala Asp Ile Val

115 120 125

Ala Thr Lys Met Lys Glu Ala Leu Ser Ser Trp Leu Gln Asp Gly Val
130 135 140

Asp Gly Phe Gln Phe Arg Asp Val Gly Lys Leu Met Asn Ala Pro Leu
145 150 155 160

Tyr Leu Ala Glu Trp Gln Asn Ile Thr Lys Asn Leu Ser Glu Asp Arg
165 170 175

Leu Leu Ile Ala Gly Thr Glu Ser Ser Asp Leu Gln Gln Ile Val Asn
180 185 190

Ile Leu Glu Ser Thr Ser Asp Leu Leu Leu Thr Ser Ser Tyr Leu Ser
195 200 205

Asn Ser Thr Phe Thr Gly Glu Arg Thr Glu Ser Leu Val Thr Arg Phe
210 215 220

Leu Asn Ala Thr Gly Ser Gln Trp Cys Ser Trp Ser Val Ser Gln Ala
225 230 235 240

Gly Leu Leu Ala Asp Phe Ile Pro Asp His Leu Leu Arg Leu Tyr Gln
245 250 255

Leu Leu Leu Phe Thr Leu Pro Gly Thr Pro Val Phe Ser Tyr Gly Asp
260 265 270

Glu Leu Gly Leu Gln Gly Ala Leu Pro Gly Gln Pro Ala Lys Ala Pro
275 280 285

Leu Met Pro Trp Asn Glu Ser Ser Ile Phe His Ile Pro Arg Pro Val
290 295 300

Ser Leu Asn Met Thr Val Lys Gly Gln Asn Glu Asp Pro Gly Ser Leu
305 310 315 320

Leu Thr Gln Phe Arg Arg Leu Ser Asp Leu Arg Gly Lys Glu Arg Ser
325 330 335

Leu Leu His Gly Asp Phe His Ala Leu Ser Ser Ser Pro Asp Leu Phe
340 345 350

Ser Tyr Ile Arg His Trp Asp Gln Asn Glu Arg Tyr Leu Val Val Leu
355 360 365

Asn Phe Arg Asp Ser Gly Arg Ser Ala Arg Leu Gly Ala Ser Asn Leu
370 375 380

Pro Ala Gly Ile Ser Leu Pro Ala Ser Ala Lys Leu Leu Leu Ser Thr
385 390 395 400

Asp Ser Ala Arg Gln Ser Arg Glu Glu Asp Thr Ser Leu Lys Leu Glu
405 410 415

Asn Leu Ser Leu Asn Pro Tyr Glu Gly Leu Leu Leu Gln Phe Pro Phe
420 425 430

Val Ala

<210> 5
<211> 435
<212> PRT
<213> 家鼠(Rattus rattus)

<400> 5

His His His His His His Arg Ala Pro Arg Cys Arg Glu Leu Pro Val
1 5 10 15

Gln Arg Trp Trp His Lys Gly Ala Leu Tyr Arg Ile Gly Asp Leu Gln
20 25 30

Ala Phe Val Gly Pro Glu Ala Arg Gly Ile Ala Gly Leu Lys Asn His
35 40 45

Leu Glu Tyr Leu Ser Thr Leu Lys Val Lys Gly Leu Val Leu Gly Pro
50 55 60

Ile His Lys Asn Gln Lys Asp Glu Val Asn Glu Thr Asp Leu Lys Gln
65 70 75 80

Ile Asp Pro Asp Leu Gly Ser Gln Glu Asp Phe Lys Asp Leu Leu Gln
85 90 95

Ser Ala Lys Lys Lys Ser Ile His Ile Ile Leu Asp Leu Thr Pro Asn
100 105 110

Tyr Lys Gly Gln Asn Ala Trp Phe Leu Pro Pro Gln Ala Asp Ile Val
115 120 125

Ala Thr Lys Met Lys Glu Ala Leu Ser Ser Trp Leu Gln Asp Gly Val
130 135 140

Asp Gly Phe Gln Val Arg Asp Val Gly Lys Leu Ala Asn Ala Ser Leu
145 150 155 160

Tyr Leu Ala Glu Trp Gln Asn Ile Thr Lys Asn Phe Ser Glu Asp Arg
165 170 175

Leu Leu Ile Ala Gly Thr Ala Ser Ser Asp Leu Gln Gln Ile Val Asn
180 185 190

Ile Leu Glu Ser Thr Ser Asp Leu Leu Leu Thr Ser Ser Tyr Leu Ser
195 200 205

Gln Pro Val Phe Thr Gly Glu His Ala Glu Leu Leu Val Ile Lys Tyr
210 215 220

Leu Asn Ala Thr Gly Ser Arg Trp Cys Ser Trp Ser Val Ser Gln Ala
225 230 235 240

Gly Leu Leu Thr Ser Phe Ile Pro Ala Gln Phe Leu Arg Leu Tyr Gln
245 250 255

Leu Leu Leu Phe Thr Leu Pro Gly Thr Pro Val Phe Ser Tyr Gly Asp
260 265 270

Glu Leu Gly Leu Gln Ala Val Ala Leu Pro Gly Gln Pro Met Glu Ala
275 280 285

Pro Phe Met Leu Trp Asn Glu Ser Ser Asn Ser Gln Thr Ser Ser Pro
290 295 300

Val Ser Leu Asn Met Thr Val Lys Gly Gln Asn Glu Asp Pro Gly Ser
305 310 315 320

Leu Leu Thr Gln Phe Arg Arg Leu Ser Asp Leu Arg Gly Lys Glu Arg
325 330 335

Ser Leu Leu His Gly Asp Phe Asp Ala Leu Ser Ser Ser Ser Gly Leu
340 345 350

Phe Ser Tyr Val Arg His Trp Asp Gln Asn Glu Arg Tyr Leu Val Val
355 360 365

Leu Asn Phe Gln Asp Val Gly Leu Ser Ala Arg Val Gly Ala Ser Asn
370 375 380

Leu Pro Ala Gly Ile Ser Leu Pro Ala Ser Ala Asn Leu Leu Leu Ser
385 390 395 400

Thr Asp Ser Thr Arg Leu Ser Arg Glu Glu Gly Thr Ser Leu Ser Leu
405 410 415

Glu Asn Leu Ser Leu Asn Pro Tyr Glu Gly Leu Leu Leu Gln Phe Pro
420 425 430

Phe Val Ala
435

<210> 6
<211> 247
<212> PRT
<213> 人工序列

<220>
<223> C98hc 1

<400> 6

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

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

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Ala Gly Pro Lys Trp Glu Leu Trp Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser
115 120 125

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gln Ser Ala Leu Thr Gln Pro
130 135 140

Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr
145 150 155 160

Gly Thr Ser Ser Asp Val Asp Asn Tyr Asn Tyr Val Ser Trp Tyr Leu
165 170 175

Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Asn
180 185 190

Arg Pro Ser Gly Ile Ser Thr Arg Phe Ser Gly Ser Lys Ser Gly Asn
195 200 205

Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp
210 215 220

Tyr Tyr Cys Ser Ser Phe Thr Ser Ser Ser Thr Trp Val Phe Gly Gly
225 230 235 240

Gly Thr Lys Leu Thr Val Leu
245

<210> 7
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> C98hc 1 HCDR1

<400> 7

Gly Gly Ser Ile Ser Ser Gly Ala Tyr Tyr Trp
1 5 10

<210> 8
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> C98hc 1 HCDR2

<400> 8

Ile Tyr Tyr Ser Gly Ser Thr
1 5

<210> 9
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> C98hc 1 HCDR3

<400> 9

Ala Arg Ala Gly Pro Lys Trp Glu Leu Trp Phe Asp Tyr
1 5 10

<210> 10
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> C98hc 1 LCDR1

<400> 10

Ser Ser Asp Val Asp Asn Tyr Asn Tyr
1 5

<210> 11
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> C98hc 1 LCDR2

<400> 11

Asp Val Ser Asn Arg Pro Ser
1 5

<210> 12
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> C98hc 1 LCDR3

<400> 12

Ser Ser Phe Thr Ser Ser Ser Thr Trp Val
1 5 10

<210> 13
<211> 702
<212> PRT
<213> 人工序列

<220>
<223> BBBB404 HC1

<400> 13

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro
450 455 460

Gly Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser
465 470 475 480

Gly Gly Ser Ile Ser Ser Gly Ala Tyr Tyr Trp Ser Trp Ile Arg Gln
485 490 495

His Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly
500 505 510

Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Leu
515 520 525

Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala
530 535 540

Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Gly Pro Lys Trp Glu
545 550 555 560

Leu Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
565 570 575

Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
580 585 590

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
595 600 605

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Asp Asn Tyr
610 615 620

Asn Tyr Val Ser Trp Tyr Leu Gln His Pro Gly Lys Ala Pro Lys Leu
625 630 635 640

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Ile Ser Thr Arg Phe
645 650 655

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
660 665 670

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Phe Thr Ser Ser
675 680 685

Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
690 695 700

<210> 14
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB404 LC

<400> 14

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 15
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB404 HC2

<400> 15

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 16
<211> 700
<212> PRT
<213> 人工序列

<220>
<223> BBBB1058 HC1

<400> 16

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
450 455 460

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly
465 470 475 480

Ser Ile Ser Ser Gly Ala Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro
485 490 495

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr
500 505 510

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

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
530 535 540

Thr Ala Val Tyr Tyr Cys Ala Arg Ala Gly Pro Lys Trp Glu Leu Trp
545 550 555 560

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr
565 570 575

Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gln Ser
580 585 590

Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
595 600 605

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Asp Asn Tyr Asn Tyr
610 615 620

Val Ser Trp Tyr Leu Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
625 630 635 640

Tyr Asp Val Ser Asn Arg Pro Ser Gly Ile Ser Thr Arg Phe Ser Gly
645 650 655

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
660 665 670

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Phe Thr Ser Ser Ser Thr
675 680 685

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
690 695 700

<210> 17
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> BBBB1058 LC

<400> 17

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 18
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1058 HC2

<400> 18

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
450 455 460

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly
465 470 475 480

Ser Ile Ser Ser Gly Ala Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro
485 490 495

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr
500 505 510

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

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
530 535 540

Thr Ala Val Tyr Tyr Cys Ala Arg Ala Gly Pro Lys Trp Glu Leu Trp
545 550 555 560

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr
565 570 575

Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gln Ser
580 585 590

Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
595 600 605

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Asp Asn Tyr Asn Tyr
610 615 620

Val Ser Trp Tyr Leu Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
625 630 635 640

Tyr Asp Val Ser Asn Arg Pro Ser Gly Ile Ser Thr Arg Phe Ser Gly
645 650 655

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
660 665 670

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Phe Thr Ser Ser Ser Thr
675 680 685

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
690 695 700

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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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

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<400> 21

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 22
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<212> PRT
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<400> 22

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

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

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

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Ala
435 440 445

Gly Gly Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
450 455 460

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
465 470 475 480

Ser Ser Gly Ala Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys
485 490 495

Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr
500 505 510

Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys
515 520 525

Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
530 535 540

Val Tyr Tyr Cys Ala Arg Ala Gly Pro Lys Trp Glu Leu Trp Phe Asp
545 550 555 560

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly
565 570 575

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gln Ser Ala Leu
580 585 590

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
595 600 605

Ser Cys Thr Gly Thr Ser Ser Asp Val Asp Asn Tyr Asn Tyr Val Ser
610 615 620

Trp Tyr Leu Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
625 630 635 640

Val Ser Asn Arg Pro Ser Gly Ile Ser Thr Arg Phe Ser Gly Ser Lys
645 650 655

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
660 665 670

Glu Ala Asp Tyr Tyr Cys Ser Ser Phe Thr Ser Ser Ser Thr Trp Val
675 680 685

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
690 695

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<223> BBBB1097 LC

<400> 23

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

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

Pro Arg Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

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

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

Thr His Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 24
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<212> PRT
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<220>
<223> BBBB1097 HC2

<400> 24

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

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

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

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 25
<211> 446
<212> PRT
<213> 人工序列

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<223> BBBB1226 HC1

<400> 25

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Ala Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 26
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<212> PRT
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<220>
<223> BBBB1226 LC

<400> 26

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 27
<211> 699

<212> PRT
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<220>
<223> BBBB1226 HC2

<400> 27

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
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Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Gly
435 440 445

Ser Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
450 455 460

Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser
465 470 475 480

Ile Ser Ser Gly Ala Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly
485 490 495

Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr
500 505 510

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

Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr
530 535 540

Ala Val Tyr Tyr Cys Ala Arg Ala Gly Pro Lys Trp Glu Leu Trp Phe
545 550 555 560

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu
565 570 575

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gln Ser Ala
580 585 590

Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr
595 600 605

Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Asp Asn Tyr Asn Tyr Val
610 615 620

Ser Trp Tyr Leu Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
625 630 635 640

Asp Val Ser Asn Arg Pro Ser Gly Ile Ser Thr Arg Phe Ser Gly Ser
645 650 655

Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
660 665 670

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Phe Thr Ser Ser Ser Thr Trp
675 680 685

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
690 695

<210> 28
<211> 125
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 2

<400> 28

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

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

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

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

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

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

Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys Asp Glu Gly Tyr
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> 29
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 2 HCDR1

<400> 29

Gly Arg Ala Phe Ser Ser Asn Gly
1 5

<210> 30
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 2 HCDR2

<400> 30

Ile Ser Cys Ser Gly Thr Ser Thr
1 5

<210> 31
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 2 HCDR3

<400> 31

Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys Asp Glu Gly Tyr
1 5 10 15

Ala Tyr

<210> 32
<211> 580
<212> PRT
<213> 人工序列

<220>
<223> BBBB448 HC1

<400> 32

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly
450 455 460

Gly Leu Val Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
465 470 475 480

Gly Arg Ala Phe Ser Ser Asn Gly Met Gly Trp Phe Arg Gln Ala Pro
485 490 495

Gly Lys Glu Arg Glu Phe Val Ala Thr Ile Ser Cys Ser Gly Thr Ser
500 505 510

Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
515 520 525

Asn Ala Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu
530 535 540

Asp Thr Ala Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly
545 550 555 560

Tyr Thr Lys Asp Glu Gly Tyr Ala Tyr Trp Gly Gln Gly Thr Gln Val
565 570 575

Thr Val Ser Ser
580

<210> 33
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB448 LC

<400> 33

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 34
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB448 HC2

<400> 34

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 35
<211> 578
<212> PRT
<213> 人工序列

<220>
<223> BBBB1061 HC1

<400> 35

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu
450 455 460

Val Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg
465 470 475 480

Ala Phe Ser Ser Asn Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys
485 490 495

Glu Arg Glu Phe Val Ala Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr
500 505 510

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
515 520 525

Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr
530 535 540

Ala Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr
545 550 555 560

Lys Asp Glu Gly Tyr Ala Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
565 570 575

Ser Ser

<210> 36
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> BBBB1061 LC

<400> 36

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 37
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1061 HC2

<400> 37

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 38
<211> 578
<212> PRT
<213> 人工序列

<220>
<223> BBBB1059 HC1

<400> 38

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu
450 455 460

Val Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg
465 470 475 480

Ala Phe Ser Ser Asn Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys
485 490 495

Glu Arg Glu Phe Val Ala Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr
500 505 510

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
515 520 525

Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr
530 535 540

Ala Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr
545 550 555 560

Lys Asp Glu Gly Tyr Ala Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
565 570 575

Ser Ser

<210> 39
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> BBBB1059 LC

<400> 39

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 40
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1059 HC2

<400> 40

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 41
<211> 576
<212> PRT
<213> 人工序列

<220>
<223> BBBB1100 HC1

<400> 41

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

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

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

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Ala
435 440 445

Gly Gly Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
450 455 460

Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ala Phe
465 470 475 480

Ser Ser Asn Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg
485 490 495

Glu Phe Val Ala Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr Tyr Ala
500 505 510

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
515 520 525

Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val
530 535 540

Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys Asp
545 550 555 560

Glu Gly Tyr Ala Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
565 570 575

<210> 42
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> BBBB1100 LC

<400> 42

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

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

Pro Arg Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

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

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

Thr His Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 43
<211> 445
<212> PRT
<213> 人工序列

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<223> BBBB1100 HC2

<400> 43

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

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

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

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 44
<211> 446
<212> PRT
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<400> 44

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Ala Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 45
<211> 218
<212> PRT
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<223> BBBB1228 LC

<400> 45

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 46
<211> 577
<212> PRT
<213> 人工序列

<220>

<223> BBBB1228 HC2

<400> 46

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
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Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Gly
435 440 445

Ser Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
450 455 460

Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ala
465 470 475 480

Phe Ser Ser Asn Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu
485 490 495

Arg Glu Phe Val Ala Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr Tyr
500 505 510

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
515 520 525

Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala
530 535 540

Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys
545 550 555 560

Asp Glu Gly Tyr Ala Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
565 570 575

Ser

<210> 47
<211> 125
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 3

<400> 47

Gln Val His Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

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

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

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

Leu Glu Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys His Gly Gly Tyr
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> 48
<211> 8
<212> PRT
<213> 人工序列

<220>

<223> CD98hc 3 HCDR1

<400> 48

Gly Arg Thr Ile Ser Thr Tyr Gly
1 5

<210> 49
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 3 HCDR2

<400> 49

Ser Cys Ser Gly Thr Ser Thr
1 5

<210> 50
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 3 HCDR3

<400> 50

Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys His Gly Gly Tyr
1 5 10 15

Asp Tyr

<210> 51
<211> 580
<212> PRT
<213> 人工序列

<220>
<223> BBBB449 HC1

<400> 51

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val His Leu Val Glu Ser Gly Gly
450 455 460

Gly Leu Val Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
465 470 475 480

Gly Arg Thr Ile Ser Thr Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro
485 490 495

Gly Lys Glu Arg Glu Phe Val Gly Thr Ile Ser Cys Ser Gly Thr Ser
500 505 510

Thr Tyr Tyr Thr Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
515 520 525

Asn Ala Lys Asn Thr Val Tyr Leu Glu Met Asn Ser Leu Lys Pro Glu
530 535 540

Asp Thr Ala Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly
545 550 555 560

Tyr Thr Lys His Gly Gly Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val
565 570 575

Thr Val Ser Ser
580

<210> 52
<211> 218

<212> PRT
<213> 人工序列

<220>
<223> BBBB449 LC

<400> 52

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 53
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB449 HC2

<400> 53

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 54
<211> 578
<212> PRT
<213> 人工序列

<220>
<223> BBBB1064 HC1

<400> 54

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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
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Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val His Leu Val Glu Ser Gly Gly Gly Leu
450 455 460

Val Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg
465 470 475 480

Thr Ile Ser Thr Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys
485 490 495

Glu Arg Glu Phe Val Gly Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr
500 505 510

Tyr Thr Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
515 520 525

Lys Asn Thr Val Tyr Leu Glu Met Asn Ser Leu Lys Pro Glu Asp Thr
530 535 540

Ala Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr
545 550 555 560

Lys His Gly Gly Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
565 570 575

Ser Ser

<210> 55
<211> 214

<212> PRT
<213> 人工序列

<220>
<223> BBBB1064 LC

<400> 55

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 56
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1064 HC2

<400> 56

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 57
<211> 578
<212> PRT
<213> 人工序列

<220>
<223> BBBB1062 HC1

<400> 57

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val His Leu Val Glu Ser Gly Gly Gly Leu
450 455 460

Val Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg
465 470 475 480

Thr Ile Ser Thr Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys
485 490 495

Glu Arg Glu Phe Val Gly Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr
500 505 510

Tyr Thr Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
515 520 525

Lys Asn Thr Val Tyr Leu Glu Met Asn Ser Leu Lys Pro Glu Asp Thr
530 535 540

Ala Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr
545 550 555 560

Lys His Gly Gly Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
565 570 575

Ser Ser

<210> 58
<211> 214
<212> PRT
<213> 人工序列

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<223> BBBB1062 LC

<400> 58

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 59
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1062 HC2

<400> 59

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 60
<211> 576
<212> PRT
<213> 人工序列

<220>
<223> BBBB1103 HC1

<400> 60

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

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

```
Asp Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225                 230                 235                 240
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Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Ala
435 440 445

Gly Gly Ala Gln Val His Leu Val Glu Ser Gly Gly Gly Leu Val Gln
450 455 460

Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Ile
465 470 475 480

Ser Thr Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg
485 490 495

Glu Phe Val Gly Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr Tyr Thr
500 505 510

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
515 520 525

Thr Val Tyr Leu Glu Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val
530 535 540

Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys His
545 550 555 560

Gly Gly Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
565 570 575

<210> 61
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> BBBB1103 LC

<400> 61

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

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

Pro Arg Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

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

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

Thr His Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 62
<211> 445
<212> PRT
<213> 人工序列

<220>
<223> BBBB1103 HC2

<400> 62

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

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

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

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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
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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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 63
<211> 446
<212> PRT
<213> 人工序列

<220>
<223> BBBB1229 HC1

<400> 63

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

```
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro
            340                 345                 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Ala Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445
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<210> 64
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB1229 LC

<400> 64

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 65
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> BBBB1229 HC2

<400> 65

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Gly
435 440 445

Ser Gly Gly Ser Gln Val His Leu Val Glu Ser Gly Gly Gly Leu Val
450 455 460

Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr
465 470 475 480

Ile Ser Thr Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu
485 490 495

Arg Glu Phe Val Gly Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr Tyr
500 505 510

Thr Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
515 520 525

Asn Thr Val Tyr Leu Glu Met Asn Ser Leu Lys Pro Glu Asp Thr Ala
530 535 540

Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys
545 550 555 560

His Gly Gly Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
565 570 575

Ser

<210> 66
<211> 247
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 4

<400> 66

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

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

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

Ala Ile Ile Ser Tyr Asp Gly Ser Asn Lys His 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 Ala Pro Ser Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly
115 120 125

Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Pro Asp Ser
130 135 140

Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser
145 150 155 160

Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr
165 170 175

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser
180 185 190

Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
195 200 205

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
210 215 220

Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln
225 230 235 240

Gly Thr Lys Val Val Ile Lys
245

<210> 67
<211> 8
<212> PRT
<213> 人工序列

<220>

<223> CD98hc 4 HCDR1

<400> 67

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 68
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 4 HCDR2

<400> 68

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 69
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 4 HCDR3

<400> 69

Ala Arg Ala Pro Ser Ser Phe Tyr Phe Asp Tyr
1 5 10

<210> 70
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 4 LCDR1

<400> 70

Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 71
<211> 3
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 4 LCDR2

<400> 71

Trp Ala Ser
1

<210> 72
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 4 LCDR3

<400> 72

Gln Gln Tyr Tyr Ser Thr Pro Pro Thr
1 5

<210> 73
<211> 702
<212> PRT
<213> 人工序列

<220>
<223> BBBB578 HC1

<400> 73

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

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

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

```
Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
    50                  55                  60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255
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Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly
450 455 460

Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser
465 470 475 480

Gly Phe Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro
485 490 495

Gly Lys Gly Leu Glu Trp Val Ala Ile Ile Ser Tyr Asp Gly Ser Asn
500 505 510

Lys His Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
515 520 525

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
530 535 540

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Pro Ser Ser Phe Tyr Phe
545 550 555 560

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu
565 570 575

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val
580 585 590

Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala
595 600 605

Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Phe Ser Ser Asn Asn
610 615 620

Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys
625 630 635 640

Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg
645 650 655

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
660 665 670

Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser
675 680 685

Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
690 695 700

<210> 74
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB578 LC

<400> 74

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 75
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB578 HC2

<400> 75

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

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

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

```
Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
    50                  55                  60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225                 230                 235                 240
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Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 76
<211> 700
<212> PRT
<213> 人工序列

<220>
<223> BBBB1067 HC1

<400> 76

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
450 455 460

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
465 470 475 480

Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys
485 490 495

Gly Leu Glu Trp Val Ala Ile Ile Ser Tyr Asp Gly Ser Asn Lys His
500 505 510

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
515 520 525

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
530 535 540

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Ala Val Tyr Tyr Cys Ala Arg Ala Pro Ser Ser Phe Tyr Phe Asp Tyr
545                 550                 555                 560

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys
                565                 570                 575

Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr
            580                 585                 590

Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile
        595                 600                 605

Asn Cys Lys Ser Ser Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn
    610                 615                 620

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
625                 630                 635                 640

Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser
                645                 650                 655

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
            660                 665                 670

Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro
        675                 680                 685

Pro Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
    690                 695                 700
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<210> 77
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> BBBB1067 LC

<400> 77

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 78
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1067 HC2

<400> 78

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 79
<211> 700
<212> PRT
<213> 人工序列

<220>
<223> BBBB1065 HC1

<400> 79

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
450 455 460

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
465 470 475 480

Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys
485 490 495

Gly Leu Glu Trp Val Ala Ile Ile Ser Tyr Asp Gly Ser Asn Lys His
500 505 510

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
515 520 525

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
530 535 540

Ala Val Tyr Tyr Cys Ala Arg Ala Pro Ser Ser Phe Tyr Phe Asp Tyr
545 550 555 560

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys
565 570 575

Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr
580 585 590

Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile
595 600 605

Asn Cys Lys Ser Ser Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn
610 615 620

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
625 630 635 640

Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser
645 650 655

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
660 665 670

Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro
675 680 685

Pro Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
690 695 700

<210> 80
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> BBBB1065 LC

<400> 80

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 81
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1065 HC2

<400> 81

Glu 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

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240
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Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 82
<211> 698
<212> PRT
<213> 人工序列

<220>
<223> BBBB1106 HC1

<400> 82

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

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

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

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Ala
435 440 445

Gly Gly Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
450 455 460

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
465 470 475 480

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
485 490 495

Glu Trp Val Ala Ile Ile Ser Tyr Asp Gly Ser Asn Lys His Tyr Ala
500 505 510

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
515 520 525

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
530 535 540

Tyr Tyr Cys Ala Arg Ala Pro Ser Ser Phe Tyr Phe Asp Tyr Trp Gly
545 550 555 560

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser
565 570 575

Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser
580 585 590

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
595 600 605

Lys Ser Ser Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn Tyr Leu
610 615 620

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
625 630 635 640

Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
645 650 655

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu
660 665 670

Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr
675 680 685

Phe Gly Gln Gly Thr Lys Val Val Ile Lys
690 695

<210> 83
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> BBBB1106 LC

<400> 83

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30

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

Pro Arg Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
    50                  55                  60

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

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

Thr His Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205
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Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 84
<211> 445
<212> PRT
<213> 人工序列

<220>
<223> BBBB1106 HC2

<400> 84

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

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

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

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 85
<211> 446
<212> PRT
<213> 人工序列

<220>
<223> BBBB1230 HC1

<400> 85

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

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

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

```
Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
    50                  55                  60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
    210                 215                 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255
```

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Ala Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 86
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB1230 LC

<400> 86

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


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


Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
    50                  55                  60


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


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


Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105                 110


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


Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140


Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160
```

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 87
<211> 699
<212> PRT
<213> 人工序列

<220>
<223> BBBB1230 HC2

<400> 87

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Gly
435 440 445

Ser Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val
450 455 460

Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
465 470 475 480

Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly
485 490 495

Leu Glu Trp Val Ala Ile Ile Ser Tyr Asp Gly Ser Asn Lys His Tyr
500 505 510

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
515 520 525

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
530 535 540

Val Tyr Tyr Cys Ala Arg Ala Pro Ser Ser Phe Tyr Phe Asp Tyr Trp
545 550 555 560

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser
565 570 575

Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln
580 585 590

Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn
595 600 605

Cys Lys Ser Ser Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn Tyr
610 615 620

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
625 630 635 640

Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
645 650 655

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
660 665 670

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro
675 680 685

Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
690 695

<210> 88
<211> 238
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 5

<400> 88

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

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

Gly Tyr Ile Tyr Asn Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

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

Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
        115                 120                 125

Lys Ser Thr Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr
    130                 135                 140

Ser Val Gly Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val
145                 150                 155                 160
```

Gly Ile Asn Val Ala Trp Tyr Gln Lys Lys Pro Gly Gln Pro Pro Lys
165 170 175

Ala Leu Ile Tyr Ser Ala Ala Tyr Arg Tyr Ser Gly Val Pro Asp Arg
180 185 190

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

Val Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser
210 215 220

Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
225 230 235

<210> 89
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 5 HCDR1

<400> 89

Gly Gly Ser Ile Ser Ser Ser Tyr
1 5

<210> 90
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 5 HCDR2

<400> 90

Ile Tyr Asn Ser Gly Ser Thr
1 5

<210> 91
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 5 HCDR3

<400> 91

Ala Arg Glu Thr Tyr Tyr Phe Asp Tyr
1 5

<210> 92
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 5 LCDR1

<400> 92

Gln Asn Val Gly Ile Asn
1 5

<210> 93
<211> 3
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 5 LCDR2

<400> 93

Ser Ala Ala
1

<210> 94
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 5 LCDR3

<400> 94

Gln Gln Tyr Asn Ser Tyr Pro Leu Thr
1 5

<210> 95
<211> 693
<212> PRT
<213> 人工序列

<220>
<223> BBBB584 HC1

<400> 95

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

```
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335
```

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro
450 455 460

Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser
465 470 475 480

Gly Gly Ser Ile Ser Ser Ser Tyr Trp Ser Trp Ile Arg Gln Pro Pro
485 490 495

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Asn Ser Gly Ser Thr
500 505 510

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

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
530 535 540

Thr Ala Val Tyr Tyr Cys Ala Arg Glu Thr Tyr Tyr Phe Asp Tyr Trp
545 550 555 560

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser
565 570 575

Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln
580 585 590

Ser Gln Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Val Thr
595 600 605

Cys Lys Ala Ser Gln Asn Val Gly Ile Asn Val Ala Trp Tyr Gln Lys
610 615 620

Lys Pro Gly Gln Pro Pro Lys Ala Leu Ile Tyr Ser Ala Ala Tyr Arg
625 630 635 640

Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
645 650 655

Phe Thr Leu Thr Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Glu Tyr
660 665 670

Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu Thr Phe Gly Ser Gly Thr
675 680 685

Lys Leu Glu Ile Lys
690

<210> 96
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB584 LC

<400> 96

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 97
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB584 HC2

<400> 97

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 98
<211> 691
<212> PRT
<213> 人工序列

<220>
<223> BBBB1070 HC1

<400> 98

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
450 455 460

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly
465 470 475 480

Ser Ile Ser Ser Ser Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys
485 490 495

Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Asn Ser Gly Ser Thr Asn Tyr
500 505 510

Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys
515 520 525

Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
530 535 540

Val Tyr Tyr Cys Ala Arg Glu Thr Tyr Tyr Phe Asp Tyr Trp Gly Gln
545 550 555 560

Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly
565 570 575

Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Gln
580 585 590

Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Val Thr Cys Lys
595 600 605

Ala Ser Gln Asn Val Gly Ile Asn Val Ala Trp Tyr Gln Lys Lys Pro
610 615 620

Gly Gln Pro Pro Lys Ala Leu Ile Tyr Ser Ala Ala Tyr Arg Tyr Ser
625 630 635 640

Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr
645 650 655

Leu Thr Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys
660 665 670

Gln Gln Tyr Asn Ser Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu
675 680 685

Glu Ile Lys
690

<210> 99
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> BBBB1070 LC

<400> 99

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 100
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1070 HC2

<400> 100

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 101
<211> 691
<212> PRT
<213> 人工序列

<220>
<223> BBBB1068 HC1

<400> 101

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
450 455 460

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly
465 470 475 480

Ser Ile Ser Ser Ser Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys
485 490 495

Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Asn Ser Gly Ser Thr Asn Tyr
500 505 510

Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys
515 520 525

Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
530 535 540

Val Tyr Tyr Cys Ala Arg Glu Thr Tyr Tyr Phe Asp Tyr Trp Gly Gln
545 550 555 560

Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly
565 570 575

Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Gln
580 585 590

Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Val Thr Cys Lys
595 600 605

Ala Ser Gln Asn Val Gly Ile Asn Val Ala Trp Tyr Gln Lys Lys Pro
610 615 620

Gly Gln Pro Pro Lys Ala Leu Ile Tyr Ser Ala Ala Tyr Arg Tyr Ser
625 630 635 640

Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr
645 650 655

Leu Thr Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys
660 665 670

Gln Gln Tyr Asn Ser Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu
675 680 685

Glu Ile Lys
690

<210> 102
<211> 214
<212> PRT
<213> 人工序列

<220>

<223> BBBB1068 LC

<400> 102

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 103
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1068 HC2

<400> 103

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 104
<211> 689
<212> PRT
<213> 人工序列

<220>
<223> BBBB1109 HC1

<400> 104

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

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

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

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225                 230                 235                 240
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Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Ala
435 440 445

Gly Gly Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
450 455 460

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
465 470 475 480

Ser Ser Ser Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu
485 490 495

Glu Trp Ile Gly Tyr Ile Tyr Asn Ser Gly Ser Thr Asn Tyr Asn Pro
500 505 510

Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln
515 520 525

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
530 535 540

Tyr Cys Ala Arg Glu Thr Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
545 550 555 560

Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly
565 570 575

Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Gln Lys Phe
580 585 590

Met Ser Thr Ser Val Gly Asp Arg Val Ser Val Thr Cys Lys Ala Ser
595 600 605

Gln Asn Val Gly Ile Asn Val Ala Trp Tyr Gln Lys Lys Pro Gly Gln
610 615 620

Pro Pro Lys Ala Leu Ile Tyr Ser Ala Ala Tyr Arg Tyr Ser Gly Val
625 630 635 640

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
645 650 655

Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln
660 665 670

Tyr Asn Ser Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile
675 680 685

Lys

<210> 105
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> BBBB1109 LC

<400> 105

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

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

Pro Arg Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

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

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

Thr His Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 106
<211> 445
<212> PRT
<213> 人工序列

<220>
<223> BBBB1109 HC2

<400> 106

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

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

```
Asp Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

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

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Val 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 Tyr Tyr Arg Tyr Ala Met 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220
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Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 107
<211> 446
<212> PRT
<213> 人工序列

<220>
<223> BBBB1231 HC1

<400> 107

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Ala Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 108
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB1231 LC

<400> 108

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 109
<211> 690
<212> PRT
<213> 人工序列

<220>

<223> BBBB1231 HC2

<400> 109

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
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Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Gly
435 440 445

Ser Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
450 455 460

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser
465 470 475 480

Ile Ser Ser Ser Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
485 490 495

Leu Glu Trp Ile Gly Tyr Ile Tyr Asn Ser Gly Ser Thr Asn Tyr Asn
500 505 510

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn
515 520 525

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
530 535 540

Tyr Tyr Cys Ala Arg Glu Thr Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
545 550 555 560

Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser
565 570 575

Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Gln Lys
580 585 590

Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Val Thr Cys Lys Ala
595 600 605

Ser Gln Asn Val Gly Ile Asn Val Ala Trp Tyr Gln Lys Lys Pro Gly
610 615 620

Gln Pro Pro Lys Ala Leu Ile Tyr Ser Ala Ala Tyr Arg Tyr Ser Gly
625 630 635 640

Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
645 650 655

Thr Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys Gln
660 665 670

Gln Tyr Asn Ser Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu
675 680 685

Ile Lys
690

<210> 110
<211> 448
<212> PRT
<213> 人工序列

<220>
<223> PT1B844 HC

<400> 110

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 111
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> PT1B844 LC

<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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 112
<211> 251
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 6

<400> 112

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Asp Pro Asn Asp Tyr Gly Gly Pro Lys Tyr Phe Pro His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser
115 120 125

Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln
130 135 140

Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn
145 150 155 160

Cys Arg Ser Ser Gln Ser Val Leu Tyr Arg Ser Asn Asn Lys Asn Tyr
165 170 175

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
180 185 190

Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
195 200 205

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
210 215 220

Glu Asp Val Ala Val Tyr Tyr Cys His Gln Tyr Tyr Ser Thr Pro Leu
225 230 235 240

Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys
245 250

<210> 113
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 6 HCDR1

<400> 113

Gly Tyr Thr Phe Thr Ser Tyr Tyr
1 5

<210> 114
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 6 HCDR2

<400> 114

Ile Asn Pro Ser Gly Gly Thr Thr
1 5

<210> 115
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 6 HCDR3

<400> 115

Ala Arg Asp Pro Asn Asp Tyr Gly Gly Pro Lys Tyr Phe Pro His
1 5 10 15

<210> 116
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 6 LCDR1

<400> 116

Gln Ser Val Leu Tyr Arg Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 117
<211> 3

<212> PRT
<213> 人工序列

<220>
<223> CD98hc 6 LCDR2

<400> 117

Trp Ala Ser
1

<210> 118
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc 6 LCDR3

<400> 118

His Gln Tyr Tyr Ser Thr Pro Leu Thr
1 5

<210> 119
<211> 706
<212> PRT
<213> 人工序列

<220>
<223> BBBB580 HC1

<400> 119

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255
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Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala
450 455 460

Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser
465 470 475 480

Gly Tyr Thr Phe Thr Ser Tyr Tyr Ile His Trp Val Arg Gln Ala Pro
485 490 495

Gly Gln Gly Leu Glu Trp Met Gly Leu Ile Asn Pro Ser Gly Gly Thr
500 505 510

Thr Asn Tyr Pro Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp
515 520 525

Thr Ser Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu
530 535 540

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Pro Asn Asp Tyr Gly Gly
545 550 555 560

Pro Lys Tyr Phe Pro His Trp Gly Gln Gly Thr Leu Val Thr Val Ser
565 570 575

Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser
580 585 590

Thr Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu
595 600 605

Gly Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Val Leu Tyr
610 615 620

Arg Ser Asn Asn Lys Asn Tyr Leu Gly Trp Tyr Gln Gln Lys Pro Gly
625 630 635 640

Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
645 650 655

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
660 665 670

Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His
675 680 685

Gln Tyr Tyr Ser Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Asp
690 695 700

Ile Lys
705

<210> 120
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB580 LC

<400> 120

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 121
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB580 HC2

<400> 121

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

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Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430
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Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 122
<211> 253
<212> PRT
<213> 人工序列

<220>
<223> CD98hc7

<400> 122

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

Ser Val Arg Val Ser Cys Lys Ala Ser Glu Tyr Thr Phe Thr Ser Tyr
20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Thr Thr Val Tyr
65 70 75 80

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

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

Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly
115 120 125

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met
130 135 140

Thr Gln Ser Pro Asp Ser Leu Ala Glu Ser Leu Gly Glu Arg Ala Thr
145 150 155 160

Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ala Ser Arg Asn Lys
165 170 175

Asn Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Pro Pro Lys Leu
180 185 190

Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe
195 200 205

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
210 215 220

Gln Ala Glu Asp Val Ala Ile Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr
225 230 235 240

Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
245 250

<210> 123
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc7 HCDR1

<400> 123

Glu Tyr Thr Phe Thr Ser Tyr Tyr
1 5

<210> 124
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc7 HCDR2

<400> 124

Ile Asn Pro Ser Gly Gly Ser Thr
1 5

<210> 125
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> CD98hc7 HCDR3

<400> 125

Ala Arg Ala Gly Tyr Cys Thr Ile Asn Ser Cys Phe Asn Trp Phe Asp
1 5 10 15

Pro

<210> 126
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> CD98hc7 LCDR1

<400> 126

Gln Ser Val Leu Tyr Ala Ser Arg Asn Lys Asn Tyr
1 5 10

<210> 127
<211> 3
<212> PRT
<213> 人工序列

<220>
<223> CD98hc7 LCDR2

<400> 127

Trp Ala Ser
1

<210> 128
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc7 LCDR3

<400> 128

Gln Gln Tyr Tyr Ser Thr Pro Phe Thr
1 5

<210> 129
<211> 708
<212> PRT
<213> 人工序列

<220>
<223> BBBB586 HC1

<400> 129

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala
    450                 455                 460

Glu Val Lys Lys Pro Gly Ala Ser Val Arg Val Ser Cys Lys Ala Ser
465                 470                 475                 480
```

Glu Tyr Thr Phe Thr Ser Tyr Tyr Met His Trp Ile Arg Gln Ala Pro
485 490 495

Gly Gln Gly Leu Glu Trp Met Gly Leu Ile Asn Pro Ser Gly Gly Ser
500 505 510

Thr Ser Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp
515 520 525

Thr Ser Thr Thr Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu
530 535 540

Asp Thr Ala Leu Tyr Tyr Cys Ala Arg Ala Gly Tyr Cys Thr Ile Asn
545 550 555 560

Ser Cys Phe Asn Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr
565 570 575

Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
580 585 590

Lys Ser Thr Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Glu
595 600 605

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val
610 615 620

Leu Tyr Ala Ser Arg Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Arg
625 630 635 640

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu
645 650 655

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
660 665 670

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Ile Tyr Tyr
675 680 685

Cys Gln Gln Tyr Tyr Ser Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys
690 695 700

Val Asp Ile Lys
705

<210> 130
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB586 LC

<400> 130

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 131
<211> 449
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<220>
<223> BBBB586 HC2

<400> 131

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 132
<211> 249
<212> PRT
<213> 人工序列

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<400> 132

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

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

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

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

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

Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly
        115                 120                 125

Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Pro
    130                 135                 140

Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys
145                 150                 155                 160
```

Ser Ser Gln Ser Val Leu Tyr Arg Ser Asn Asn Lys Asn Tyr Leu Ala
165 170 175

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp
180 185 190

Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
195 200 205

Ser Glu Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp
210 215 220

Val Ala Leu Tyr Tyr Cys Gln Gln Tyr Tyr Gly Thr Pro Phe Thr Phe
225 230 235 240

Gly Pro Gly Thr Lys Val Asp Ile Lys
245

<210> 133
<211> 8
<212> PRT
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<220>
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<400> 133

Gly Tyr Thr Phe Thr Ser Tyr Tyr
1 5

<210> 134
<211> 8
<212> PRT
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<220>
<223> CD98hc8 HCDR2

<400> 134

Phe Asn Pro Ser Gly Gly Ser Thr
1 5

<210> 135
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> CD98hc8 HCDR3

<400> 135

Ala Arg Gly Gly Val Gly Ala Thr Gly Tyr Phe Asp Tyr
1 5 10

<210> 136
<211> 12
<212> PRT
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<220>
<223> CD98hc8 LCDR1

<400> 136

Gln Ser Val Leu Tyr Arg Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 137
<211> 3
<212> PRT
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<220>
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<400> 137

Trp Ala Ser
1

<210> 138
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc8 LCDR3

<400> 138

Gln Gln Tyr Tyr Gly Thr Pro Phe Thr
1 5

<210> 139
<211> 704
<212> PRT
<213> 人工序列

<220>
<223> BBBB593 HC1

<400> 139

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val His Leu Val Gln Ser Gly Val
450 455 460

Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser
465 470 475 480

Gly Tyr Thr Phe Thr Ser Tyr Tyr Ile His Trp Val Arg Gln Ala Pro
485 490 495

Gly Gln Gly Leu Glu Trp Met Gly Leu Phe Asn Pro Ser Gly Gly Ser
500 505 510

Thr Ser Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Leu Thr Arg Asp
515 520 525

Thr Ser Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu
530 535 540

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Gly Val Gly Ala Thr Gly
545 550 555 560

Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
565 570 575

Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp
580 585 590

Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu
595 600 605

Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Arg Ser
610 615 620

Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro
625 630 635 640

Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro
645 650 655

Asp Arg Phe Ser Gly Ser Gly Ser Glu Thr Asp Phe Thr Leu Thr Ile
660 665 670

Ser Ser Leu Gln Ala Glu Asp Val Ala Leu Tyr Tyr Cys Gln Gln Tyr
675 680 685

Tyr Gly Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
690 695 700

<210> 140
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB593 LC

<400> 140

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 141
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB593 HC2

<400> 141

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 142
<211> 125
<212> PRT
<213> 人工序列

<220>
<223> CD98hc9

<400> 142

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

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

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

Ala Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr Tyr Ala Asp Ser Leu
50 55 60

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

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

Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys Asp Gly Gly Tyr
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> 143
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc9 HCDR1

<400> 143

Gly Arg Thr Phe Ser Arg Tyr Gly
1 5

<210> 144
<211> 8
<212> PRT
<213> 人工序列

<220>

<223> CD98hc9 HCDR2

<400> 144

Ile Ser Cys Ser Gly Thr Ser Thr
1 5

<210> 145
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> CD98hc9 HCDR3

<400> 145

Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys Asp Gly Gly Tyr
1 5 10 15

Ala Tyr

<210> 146
<211> 580
<212> PRT
<213> 人工序列

<220>
<223> BBBB445 HC1

<400> 146

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

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

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

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

```
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255
```

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly
450 455 460

Gly Leu Val Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
465 470 475 480

Gly Arg Thr Phe Ser Arg Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro
485 490 495

Gly Lys Glu Arg Glu Phe Val Ala Thr Ile Ser Cys Ser Gly Thr Ser
500 505 510

Thr Tyr Tyr Ala Asp Ser Leu Lys Gly Arg Phe Thr Ile Ser Arg Asp
515 520 525

Asn Ala Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu
530 535 540

Asp Thr Ala Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly
545 550 555 560

Tyr Thr Lys Asp Gly Gly Tyr Ala Tyr Trp Gly Gln Gly Thr Gln Val
565 570 575

Thr Val Ser Ser
580

<210> 147
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB445 LC

<400> 147

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 148
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB445 HC2

<400> 148

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


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


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


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


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


Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


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


Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125


Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140


Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
```

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 149
<211> 238
<212> PRT
<213> 人工序列

<220>
<223> CD98hc10

<400> 149

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

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

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

Gly Trp Ile Asn Pro Asn Ser Gly Gly Ser Asn Ser Ala Gln Lys Phe
50 55 60

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

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

Leu Arg Gly Lys Thr Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
115 120 125

Lys Ser Thr Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala
130 135 140

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile
145 150 155 160

Ser Ser His Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
165 170 175

Leu Leu Ile Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg
180 185 190

Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser
195 200 205

Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Asn
210 215 220

Tyr Pro Leu Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
225 230 235

<210> 150
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc10 HCDR1

<400> 150

Gly Tyr Thr Phe Thr Gly Tyr Tyr
1 5

<210> 151
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc10 HCDR2

<400> 151

Ile Asn Pro Asn Ser Gly Gly Ser
1 5

<210> 152
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc10 HCDR3

<400> 152

Leu Arg Gly Lys Thr Phe Asp Pro
1 5

<210> 153
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> CD98hc10 LCDR1

<400> 153

Gln Gly Ile Ser Ser His
1 5

<210> 154
<211> 3
<212> PRT
<213> 人工序列

<220>
<223> CD98hc10 LCDR2

<400> 154

Ala Ala Ser
1

<210> 155
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc10 LCDR3

<400> 155

Gln Gln Leu Asn Asn Tyr Pro Leu Thr
1 5

<210> 156
<211> 693
<212> PRT
<213> 人工序列

<220>
<223> BBBB589 HC1

<400> 156

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala
450 455 460

Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser
465 470 475 480

Gly Tyr Thr Phe Thr Gly Tyr Tyr Leu His Trp Val Arg Gln Ala Pro
485 490 495

Gly Gln Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly
500 505 510

Ser Asn Ser Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp
515 520 525

Thr Ser Ile Ser Thr Ala Tyr Met Glu Val Ser Arg Leu Thr Ser Asp
530 535 540

Asp Thr Ala Val Tyr Tyr Cys Leu Arg Gly Lys Thr Phe Asp Pro Trp
545 550 555 560

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser
565 570 575

Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Gln Leu Thr Gln
580 585 590

Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
595 600 605

Cys Arg Ala Ser Gln Gly Ile Ser Ser His Leu Ala Trp Tyr Gln Gln
610 615 620

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Thr Leu
625 630 635 640

Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu
645 650 655

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
660 665 670

Tyr Cys Gln Gln Leu Asn Asn Tyr Pro Leu Thr Phe Gly Gln Gly Thr
675 680 685

Arg Leu Glu Ile Lys
690

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<220>
<223> BBBB589 LC

<400> 157

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 158
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB589 HC2

<400> 158

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 159
<211> 253
<212> PRT
<213> 人工序列

<220>
<223> CD98hc11

<400> 159

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Ala Gly Tyr Cys Arg Ser Thr Thr Ser Cys Phe Asn Trp Phe
100 105 110

Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu
115 120 125

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val
130 135 140

Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala
145 150 155 160

Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Asn Ser Asn Asn
165 170 175

Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys
180 185 190

Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg
195 200 205

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Phe Ser Ser
210 215 220

Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser
225 230 235 240

Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
245 250

<210> 160
<211> 8
<212> PRT
<213> 人工序列

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<223> CD98hc11 HCDR1

<400> 160

Gly Tyr Thr Phe Thr Ser Tyr Tyr
1 5

<210> 161
<211> 7
<212> PRT
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<220>
<223> CD98hc11 HCDR2

<400> 161

Asn Pro Ser Gly Gly Ser Thr
1 5

<210> 162
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> CD98hc11 HCDR3

<400> 162

Ala Arg Ala Gly Tyr Cys Arg Ser Thr Thr Ser Cys Phe Asn Trp Phe
1 5 10 15

Asp Pro

<210> 163
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> CD98hc11 LCDR1

<400> 163

Gln Ser Val Leu Tyr Asn Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 164
<211> 3
<212> PRT
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<220>
<223> CD98hc11 LCDR2

<400> 164

Trp Ala Ser
1

<210> 165
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc11 LCDR3

<400> 165

Gln Gln Tyr Tyr Ser Thr Pro Phe Thr
1 5

<210> 166
<211> 708
<212> PRT
<213> 人工序列

<220>
<223> BBBB594 HC1

<400> 166

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala
450 455 460

Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser
465 470 475 480

Gly Tyr Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro
485 490 495

Gly Gln Gly Leu Glu Trp Met Gly Leu Ile Asn Pro Ser Gly Gly Ser
500 505 510

Thr Ser Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp
515 520 525

Thr Ser Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu
530 535 540

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Gly Tyr Cys Arg Ser Thr
545 550 555 560

Thr Ser Cys Phe Asn Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val
565 570 575

Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
580 585 590

Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
595 600 605

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
610 615 620

Val Leu Tyr Asn Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
625 630 635 640

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg
645 650 655

Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
660 665 670

Phe Thr Leu Thr Phe Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
675 680 685

Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Phe Thr Phe Gly Pro Gly Thr
690 695 700

Lys Val Asp Ile
705

<210> 167
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB594 LC

<400> 167

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 168
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB594 HC2

<400> 168

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 169
<211> 246
<212> PRT
<213> 人工序列

<220>
<223> CD98hc12

<400> 169

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Glu Val Gln Leu Val 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 Leu Ser Ser Ser
            20                  25                  30

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

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

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

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

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

Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Pro Leu Ser
    130                 135                 140

Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser
145                 150                 155                 160
```

Gln Ser Leu Leu His Ser His Gly Asp Asn Tyr Leu Asp Trp Phe Leu
165 170 175

Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn
180 185 190

Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
195 200 205

Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
210 215 220

Tyr Tyr Cys Met Gln Thr Leu Glu Thr Pro Tyr Thr Phe Gly Gln Gly
225 230 235 240

Thr Lys Leu Gln Ile Lys
245

<210> 170
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc12 HCDR1

<400> 170

Gly Phe Thr Leu Ser Ser Ser Trp
1 5

<210> 171
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc12 HCDR2

<400> 171

Ile Asn Ser Asp Gly Ser Ser Thr
1 5

<210> 172
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> CD98hc12 HCDR3

<400> 172

Ala Arg Trp Asn Trp Gly Trp Tyr Phe Asp Leu
1 5 10

<210> 173
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> CD98hc12 LCDR1

<400> 173

Gln Ser Leu Leu His Ser His Gly Asp Asn Tyr
1 5 10

<210> 174
<211> 3
<212> PRT
<213> 人工序列

<220>
<223> CD98hc12 LCDR2

<400> 174

Leu Gly Ser
1

<210> 175
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc12 LCDR3

<400> 175

Met Gln Thr Leu Glu Thr Pro Tyr Thr
1 5

<210> 176
<211> 701
<212> PRT
<213> 人工序列

<220>
<223> BBBB602 HC1

<400> 176

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly
450 455 460

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
465 470 475 480

Gly Phe Thr Leu Ser Ser Ser Trp Met His Trp Val Arg Gln Ala Pro
485 490 495

Gly Lys Gly Leu Val Trp Val Ser Arg Ile Asn Ser Asp Gly Ser Ser
500 505 510

Thr Ser Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
515 520 525

```
Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
    530                 535                 540

Asp Thr Ala Leu Tyr Tyr Cys Ala Arg Trp Asn Trp Gly Trp Tyr Phe
545                 550                 555                 560

Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu
                565                 570                 575

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val
            580                 585                 590

Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala
        595                 600                 605

Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser His Gly Asp
    610                 615                 620

Asn Tyr Leu Asp Trp Phe Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu
625                 630                 635                 640

Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe
                645                 650                 655

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val
            660                 665                 670

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr Leu Glu Thr
        675                 680                 685

Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Gln Ile Lys
    690                 695                 700
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<210> 177
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB602 LC

<400> 177

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
    50                  55                  60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105                 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175
```

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 178
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> BBBB602 HC2

<400> 178

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 179
<211> 247
<212> PRT
<213> 人工序列

<220>
<223> CD98hc13

<400> 179

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

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

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala 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

Val Arg Glu Gly Arg Tyr Thr Gly Ser Ser Leu Asp Tyr Trp Gly Gln
100 105 110

Gly Ala Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly
115 120 125

Ser Gly Ser Glu Ser Lys Ser Thr Gln Ser Val Leu Thr Gln Pro Pro
130 135 140

Ser Val Ser Gly Ala Pro Gly Gln Arg Val Ala Ile Ser Cys Thr Gly
145 150 155 160

Asn Asn Ser Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln
165 170 175

Leu Pro Gly Thr Ala Pro Gln Leu Leu Ile Tyr Gly Asn Ser Asp Arg
180 185 190

Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser
195 200 205

Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Ala Tyr
210 215 220

Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Thr Gly Trp Val Phe Gly Gly
225 230 235 240

Gly Thr Lys Leu Thr Val Leu
245

<210> 180
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc13 HCDR1

<400> 180

Gly Phe Thr Phe Ser Ser Tyr Trp
1 5

<210> 181
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc13 HCDR2

<400> 181

Ile Asn Ser Asp Gly Ser Ile Ile
1 5

<210> 182
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> CD98hc13 HCDR3

<400> 182

Val Arg Glu Gly Arg Tyr Thr Gly Ser Ser Leu Asp Tyr
1 5 10

<210> 183
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc13 LCDR1

<400> 183

Asn Ser Asn Ile Gly Ala Gly Tyr Asp
1 5

<210> 184
<211> 3
<212> PRT
<213> 人工序列

<220>
<223> CD98hc13 LCDR2

<400> 184

Gly Asn Ser
1

<210> 185
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> CD98hc13 LCDR3

<400> 185

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

<210> 186
<211> 702
<212> PRT
<213> 人工序列

<220>
<223> BBBB610 HC1

<400> 186

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
```

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly
450 455 460

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Val Ala Ser
465 470 475 480

Gly Phe Thr Phe Ser Ser Tyr Trp Met His Trp Val Arg Gln Ala Pro
485 490 495

Gly Lys Gly Leu Val Trp Val Ser Arg Ile Asn Ser Asp Gly Ser Ile
500 505 510

Ile Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
515 520 525

Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
530 535 540

Asp Thr Ala Val Tyr Tyr Cys Val Arg Glu Gly Arg Tyr Thr Gly Ser
545 550 555 560

Ser Leu Asp Tyr Trp Gly Gln Gly Ala Leu Val Thr Val Ser Ser Gly
565 570 575

Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gln
580 585 590

Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln Arg
595 600 605

Val Ala Ile Ser Cys Thr Gly Asn Asn Ser Asn Ile Gly Ala Gly Tyr
610 615 620

Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Gln Leu Leu
625 630 635 640

Ile Tyr Gly Asn Ser Asp Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
645 650 655

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
660 665 670

Ala Glu Asp Glu Ala Ala Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Leu
675 680 685

Thr Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
690 695 700

<210> 187
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB610 LC

<400> 187

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 188
<211> 449

<212> PRT
<213> 人工序列

<220>
<223> BBBB610 HC2

<400> 188

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
```

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 189
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 189

Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
1 5 10 15

<210> 190
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 190

Gly Gly Ser Gly Gly Ser
1 5

<210> 191
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 191

Gly Gly Ala Gly Gly Ala
1 5

<210> 192
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 生物素化磷酸化tau寡聚物

<400> 192

Gly Thr Pro Gly Ser Arg Ser Arg Pro Ser Leu Pro Pro Pro Thr Arg
1 5 10 15

Glu Pro Leu Leu
20

<210> 193
<211> 247
<212> PRT
<213> 人工序列

<220>
<223> CD98hc14

<400> 193

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

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

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

Ala Ile Ile Ser Tyr Asp Gly Ser Asn Lys His 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 Ala Pro Ser Ala Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly
115 120 125

Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Pro Asp Ser
130 135 140

Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser
145 150 155 160

Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr
165 170 175

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser
180 185 190

Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
195 200 205

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
210 215 220

Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln
225 230 235 240

Gly Thr Lys Val Val Ile Lys
245

<210> 194
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc14 HCDR1

<400> 194

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 195
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc14 HCDR2

<400> 195

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 196
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> CD98hc14 HCDR3

<400> 196

Ala Arg Ala Pro Ser Ala Phe Tyr Phe Asp Tyr
1 5 10

<210> 197
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> CD98hc14 LCDR1

<400> 197

Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 198
<211> 3
<212> PRT
<213> 人工序列

<220>
<223> CD98hc14 LCDR2

<400> 198

Trp Ala Ser
1

<210> 199
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc14 LCDR3

<400> 199

Gln Gln Tyr Tyr Ser Thr Pro Pro Thr
1 5

<210> 200
<211> 700
<212> PRT
<213> 人工序列

<220>
<223> BBBB1201 HC1

<400> 200

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
450 455 460

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
465 470 475 480

Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys
485 490 495

Gly Leu Glu Trp Val Ala Ile Ile Ser Tyr Asp Gly Ser Asn Lys His
500 505 510

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
515 520 525

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
530 535 540

Ala Val Tyr Tyr Cys Ala Arg Ala Pro Ser Ala Phe Tyr Phe Asp Tyr
545 550 555 560

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys
565 570 575

Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr
580 585 590

Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile
595 600 605

Asn Cys Lys Ser Ser Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn
610 615 620

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
625 630 635 640

Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser
645 650 655

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
660 665 670

Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro
675 680 685

Pro Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
690 695 700

<210> 201
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> BBBB1201 LC

<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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 202
<211> 447
<212> PRT
<213> 人工序列

<220>

<223> BBBB1201 HC2

<400> 202

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 203
<211> 247
<212> PRT
<213> 人工序列

<220>
<223> CD98hc15

<400> 203

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

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

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

Ala Ile Ile Ser Tyr Asp Gly Ser Asn Lys His 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 Ala Pro Ser His Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly
115 120 125

Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr Gln Ser Pro Asp Ser
130 135 140

Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser
145 150 155 160

Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr
165 170 175

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser
180 185 190

Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
195 200 205

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
210 215 220

Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln
225 230 235 240

Gly Thr Lys Val Val Ile Lys
245

<210> 204
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc15 HCDR1

<400> 204

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 205
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> CD98hc15 HCDR2

<400> 205

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 206
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> CD98hc15 HCDR3

<400> 206

Ala Arg Ala Pro Ser His Phe Tyr Phe Asp Tyr
1 5 10

<210> 207
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> CD98hc15 LCDR1

<400> 207

Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 208
<211> 3
<212> PRT
<213> 人工序列

<220>
<223> CD98hc15 LCDR2

<400> 208

Trp Ala Ser
1

<210> 209
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CD98hc15 LCDR3

<400> 209

Gln Gln Tyr Tyr Ser Thr Pro Pro Thr
1 5

<210> 210
<211> 700
<212> PRT
<213> 人工序列

<220>
<223> BBBB1202 HC1

<400> 210

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly
435 440 445

Gly Ala Gly Gly Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
450 455 460

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
465 470 475 480

Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys
485 490 495

Gly Leu Glu Trp Val Ala Ile Ile Ser Tyr Asp Gly Ser Asn Lys His
500 505 510

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
515 520 525

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
530 535 540

Ala Val Tyr Tyr Cys Ala Arg Ala Pro Ser His Phe Tyr Phe Asp Tyr
545 550 555 560

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Thr Glu Gly Lys
565 570 575

Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Asp Ile Val Met Thr
580 585 590

Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile
595 600 605

Asn Cys Lys Ser Ser Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn
610 615 620

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
625 630 635 640

Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser
645 650 655

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
660 665 670

Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro
675 680 685

Pro Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
690 695 700

<210> 211
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> BBBB1202 LC

<400> 211

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 Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

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

Tyr Arg Ala Asn Arg Leu Leu Asp 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 Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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

<210> 212
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> BBBB1202 HC2

<400> 212

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

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

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

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

Arg Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Val 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 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg
245 250 255

Glu Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 213
<211> 10

<212> PRT
<213> 人工序列

<220>
<223> PT1B844 HCDR1

<400> 213

Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5 10

<210> 214
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> PT1B844 HCDR2

<400> 214

Ser Ile Ser Lys Gly Gly Asn Thr Tyr
1 5

<210> 215
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> PT1B844 HCDR3

<400> 215

Gly Trp Gly Asp Tyr Gly Trp Phe Ala Tyr
1 5 10

<210> 216
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> PT1B844 LCDR1

<400> 216

Lys Ala Ser Gln Asp Ile Asn Arg Tyr Leu Asn
1 5 10

<210> 217
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> PT1B844 LCDR2

<400> 217

Arg Ala Asn Arg Leu Leu Asp
1 5

<210> 218
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> PT1B844 LCDR3

<400> 218

Gln Gln Tyr Asp Glu Phe Pro Leu Thr
1 5

<210> 219
<211> 446
<212> PRT
<213> 人工序列

<220>
<223> BBBB1227 HC1

<400> 219

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Ala Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 220
<211> 218
<212> PRT
<213> 人工序列

<220>
<223> BBBB1227 LC

<400> 220

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

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

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

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

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

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 221
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> BBBB1227 HC2

<400> 221

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

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

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Gly
435 440 445

Ser Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
450 455 460

Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr
465 470 475 480

Phe Ser Arg Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu
485 490 495

Arg Glu Phe Val Ala Thr Ile Ser Cys Ser Gly Thr Ser Thr Tyr Tyr
500 505 510

Ala Asp Ser Leu Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
515 520 525

Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala
530 535 540

Val Tyr Phe Cys Ala Ala Asp Thr Arg His Cys Met Gly Tyr Thr Lys
545 550 555 560

Asp Gly Gly Tyr Ala Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
565 570 575

Ser

429

【發明申請專利範圍】

【請求項1】 一種抗CD98抗體或其抗原結合片段，其用於將劑遞送至有需要之對象的腦部，其中該抗CD98抗體或其抗原結合片段在中性pH下以至少1 nM、較佳地1至500 nM之解離常數K_D且在酸性pH、較佳地pH 5下以至少10^{-4} sec^{-1}、較佳地10^{-4}至10^{-1} sec^{-1}之解離速率常數k_d結合至CD98、較佳地人類CD98hc。

【請求項2】 如請求項1所述之抗CD98抗體或其抗原結合片段，其在中性pH下具有2 x 10^{-2}至2 x 10^{-4} sec^{-1}、較佳地8 x 10^{-3} sec^{-1}之解離速率常數k_d。

【請求項3】 如請求項1或2所述之抗CD98抗體或其抗原結合片段，其包含：

(1) 包含重鏈互補決定區(HCDR) HCDR1、HCDR2、及 HCDR3 之重鏈可變區及包含輕鏈互補決定區(LCDR) LCDR1、LCDR2、及 LCDR3 之輕鏈可變區，其中該 HCDR1、HCDR2、HCDR3、LCDR1、LCDR2、及 LCDR3 具有下列之胺基酸序列：

i) 分別為 SEQ ID NO: 7、8、9、10、11、及 12；

(ii) 分別為 SEQ ID NO: 67、68、69、70、71、及 72；

(iii) 分別為 SEQ ID NO: 89、90、91、92、93、及 94；

(iv) 分別為 SEQ ID NO: 113、114、115、116、117、及 118；

(v) 分別為 SEQ ID NO: 123、124、125、126、127、及 128；

(vi) 分別為 SEQ ID NO: 133、134、135、136、137、及 138；

(vii) 分別為 SEQ ID NO: 150、151、152、153、154、及 155；

(viii) 分別為 SEQ ID NO: 160、161、162、163、164、及 165；

(ix) 分別為 SEQ ID NO: 170、171、172、173、174、及 175；

(x) 分別為 SEQ ID NO: 180、181、182、183、184、及 185；

(xi) 分別為 SEQ ID NO: 194、195、196、197、198、及 199；或

(xii) 分別為 SEQ ID NO: 204、205、206、207、208、及 209；或

(2) 重鏈上之單可變域(VHH)，其包含具有下列之胺基酸序列的重鏈互補決定區(HCDR) HCDR1、HCDR2、及 HCDR3：

(i) 分別為 SEQ ID NO: 29、30、及 31；

(ii) 分別為 SEQ ID NO: 48、49、及 50；

(iii) 分別為 SEQ ID NO: 143、144、及 145。

【請求項4】 如請求項1至3中任一項所述之抗CD98抗體或其抗原結合片段，其係VHH片段，該VHH片段包含與SEQ ID NO: 28、SEQ ID NO: 47、或SEQ ID NO: 142具有至少80%、諸如至少85%、90%、95%、或100%序列同一性之胺基酸序列。

【請求項5】 如請求項1至3中任一項所述之抗CD98抗體或其抗原結合片段，其係單鏈可變片段(scFv)，該單鏈可變片段包含經由連接子共價連接至該輕鏈可變區之該重鏈可變區，較佳地該連接子具有SEQ ID NO: 189之胺基酸序列，更佳地該scFv包含與下列之胺基酸序列具有至少80%、諸如至少85%、90%、95%、或100%序列同一性之胺基酸序列：SEQ ID NO: 6、SEQ ID NO: 66、SEQ ID NO: 88、SEQ ID NO: 112、SEQ ID NO: 122、SEQ ID NO: 132、SEQ ID NO: 149、SEQ ID NO: 159、SEQ ID NO: 169、SEQ ID NO: 179、SEQ ID NO: 193、或SEQ ID NO: 203。

【請求項6】 一種接合物，其包含偶合至治療劑或診斷劑的如請求項1至5中任一項所述之抗CD98抗體或其抗原結合片段，較佳地該接合物係包含第一抗原結合區及第二抗原結合區之多特異性抗體，該第一抗原結合區結合該CD98且包含如請求項1至5中任一項所述之抗原結合片段，該第二抗原結合區結合腦部目標，諸如選自由下列所組成之群組的腦部目標：β-分泌酶1 (BACE1)、β類澱粉蛋白(Aβ)、表皮生長因子受體(EGFR)、人類表皮生長因子受體2 (HER2)、Tau、載脂蛋白E4 (ApoE4)、α-突觸核蛋白、CD20、亨丁頓蛋白(huntingtin)、普里昂蛋白(PrP)、富白胺酸重複激酶2 (LRRK2)、parkin、早老素1、早老素2、

γ分泌酶、死亡受體6 (DR6)、類澱粉蛋白前驅蛋白(APP)、p75神經營養因子受體(p75NTR)、及凋亡蛋白酶6。

【請求項7】 一種融合建構體，其包含共價連接至第二抗體或其抗原結合片段的如請求項1至5中任一項所述之抗CD98抗體或其抗原結合片段，該第二抗體或其抗原結合片段結合至腦部目標，諸如選自由下列所組成之群組的腦部目標：β-分泌酶1 (BACE1)、β類澱粉蛋白(Aβ)、表皮生長因子受體(EGFR)、人類表皮生長因子受體2 (HER2)、Tau、載脂蛋白E4 (ApoE4)、α-突觸核蛋白、CD20、亨丁頓蛋白、普里昂蛋白(PrP)、富白胺酸重複激酶2 (LRRK2)、parkin、早老素1、早老素2、γ分泌酶、死亡受體6 (DR6)、類澱粉蛋白前驅蛋白(APP)、p75神經營養因子受體(p75NTR)、及凋亡蛋白酶6。

【請求項8】 如請求項7所述之融合建構體，其中該抗CD98抗體或其抗原結合片段經由連接子共價連接至該第二抗體或其抗原結合片段之該兩個重鏈中僅一者之羧基端，較佳地其中該連接子具有SEQ ID NO: 190或SEQ ID NO: 191之胺基酸序列。

【請求項9】 如請求項8所述之融合建構體，其中該第二抗體或其抗原結合片段之該兩個重鏈的各者包含一或多個異二聚體突變或一或多個鈕扣(knob and hole)突變，該異二聚體突變諸如經修飾異二聚體CH3域，如相較於野生型CH3域多肽。

【請求項10】如請求項9所述之融合建構體，其中該等異二聚體突變包含該第一重鏈之該經修飾異二聚體CH3域在位置T350、L351、F405、及Y407包含胺基酸修飾，且該第二重鏈之該經修飾異二聚體CH3域在位置T350、T366、K392、及T394包含胺基酸修飾，其中在位置T350之胺基酸修飾係T350V、T350I、T350L、或T350M；在位置L351之胺基酸修飾係L351Y；在位置F405之胺基酸修飾係F405A、F405V、F405T、或F405S；在位置Y407之胺基酸修飾係Y407V、Y407A、或Y407I；在位置T366之胺基酸修飾係T366L、T366I、T366V、或T366M，在位置K392之胺基酸修飾係K392F、K392L、或K392M，

且在位置T394之胺基酸修飾係T394W，且其中胺基酸殘基之編號係根據如Kabat中所陳述之EU索引。

【請求項11】如請求項10所述之融合建構體，其中該第一重鏈之該經修飾異二聚體CH3域包含突變T350V、L351Y、F405A、及Y407V，且該第二重鏈之該經修飾異二聚體CH3域包含突變T350V、T366L、K392L、及T394W。

【請求項12】如請求項7至11中任一項所述之融合，其中該第二抗體或其抗原結合片段在該Fc域中包含增強該融合與該新生兒Fc受體(RcRn)之結合的一或多個突變，較佳地該一或多個突變增強在酸性pH下之該結合，更佳地該Fc具有M252Y/S254T/T256E (YTE)突變，其中胺基酸殘基之編號係根據如Kabat中所陳述之EU索引。

【請求項13】如請求項7至12中任一項所述之融合，其中該第二抗體或其抗原結合片段在該Fc域中包含降低或消除效應功能的一或多個突變，較佳地該Fc在位置L234、L235、D270、N297、E318、K320、K322、P331、及P329具有一或多個胺基酸修飾，諸如L234A、L235A、及P331S中之一、二、或三個突變，其中胺基酸殘基之編號係根據如Kabat中所陳述之EU索引。

【請求項14】如請求項7至13中任一項所述之融合建構體，其中該第二抗體或其抗原結合片段結合至Tau且包含分別具有SEQ ID NO: 213至218之胺基酸序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2、及LCDR3，較佳地該第二抗體係單株抗體，該單株抗體包含具有SEQ ID NO: 110之胺基酸序列的重鏈及具有SEQ ID NO: 111之胺基酸序列的輕鏈。

【請求項15】如請求項7至14中任一項所述之融合建構體，其包含：

(1) 第一重鏈，其具有與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 13、16、19、22、25、32、35、38、41、44、51、54、57、60、63、73、76、79、82、85、95、98、101、104、107、119、129、139、146、156、166、176、186、200、210、及 219；

(2) 兩個輕鏈，其等各獨立地具有分別與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 14、17、20、23、26、33、36、42、45、52、55、58、61、64、74、77、80、83、86、96、99、102、105、108、120、130、140、147、157、167、177、187、201、211、及 220；及

(3) 第二重鏈，其具有分別與選自由下列所組成之群組的胺基酸序列至少 80%、諸如至少 85%、90%、95%、或 100%同一之胺基酸序列：SEQ ID NOs: 15、18、21、24、27、34、37、43、46、53、56、59、62、65、75、78、81、84、87、97、100、103、106、109、121、131、141、148、158、168、178、188、202、212、及 221。

【請求項16】一種經單離之核酸，其編碼如請求項1至5中任一項所述之抗體或抗原結合片段、如請求項6所述之接合物、或如請求項7至15中任一項所述之融合建構體。

【請求項17】一種載體，其包含如請求項16所述之經單離之核酸。

【請求項18】一種宿主細胞，其包含如請求項16所述之核酸或如請求項17所述之載體。

【請求項19】一種生產如請求項1至5中任一項所述之抗體或抗原結合片段、如請求項6所述之接合物、或如請求項7至15中任一項所述之融合建構體的方法，其包含在生產該抗體或抗原結合片段、該接合物、或該融合建構體之條件下，培養包含編碼該抗體或抗原結合片段、該接合物、或該融合建構體之核酸的細胞；及自該細胞或細胞培養物回收該抗體或抗原結合片段、該接合物、或該融合建構體。

【請求項20】一種醫藥組成物，其包含如請求項1至5中任一項所述之抗體或抗原結合片段、如請求項6所述之接合物、或如請求項7至15中任一項所述之融合建構體、及醫藥上可接受之載劑。

【請求項21】一種治療或檢測有需要之對象的病症、較佳地神經病症之方法，其包含向該對象投予如請求項1至5中任一項所述之抗體或抗原結合片段、如請求項6所述之接合物、或如請求項7至15中任一項所述之融合建構體、或如請求項20所述之醫藥組成物，較佳地該神經病症係選自由下列所組成之群組：神經退化性疾病（諸如路易氏體病(Lewy body disease)、脊髓灰質炎後症候群、Shy-Draeger症候群、橄欖體橋腦小腦萎縮、巴金森氏症、多系統萎縮、紋狀體與黑質體退化症、脊髓小腦性失調症、脊髓性肌萎縮）、tau蛋白病(tauopathy)（諸如阿茲海默症及核上神經麻痺症）、普里昂疾病（諸如牛海綿狀腦病、羊搔癢症、庫賈氏症候群(Creutz-feldt-Jakob syndrome)、庫魯病、吉斯曼-史特斯勤-先克病(Gerstmann-Straussler-Scheinker disease)、慢性消耗病、及致死性家族性失眠症）、延髓性麻痺、運動神經元疾病、及神經系統異退化性病症(nervous system heterodegenerative disorder)（諸如Canavan病、亨丁頓舞蹈症(Huntington's disease)、神經元蠟樣脂褐質儲積症、亞歷山大氏病(Alexander's disease)、妥瑞氏症候群(Tourette's syndrome)、Menkes氏捲髮症候群、柯凱因氏症候群(Cockayne syndrome)、Halervorden-Spatz氏症候群、拉弗拉病(lafora disease)、雷特氏症候群(Rett syndrome)、肝豆狀核變性、Lesch-Nyhan氏症候群、及Unverricht-Lundborg氏症候群）、失智症（諸如匹克症(Pick's disease)及脊髓小腦性失調症）、及CNS及/或腦部之癌症（諸如身體其他地方之癌症所致的腦部轉移）。

【請求項22】如請求項21所述之方法，其中該抗體或其抗原結合片段、該接合物、或該醫藥組成物經靜脈內投予。

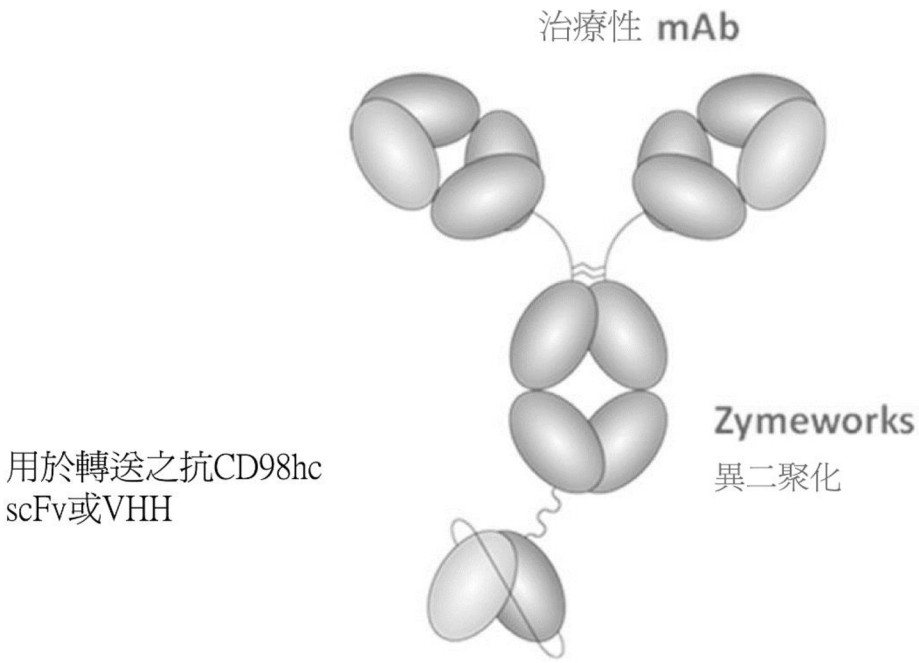
【請求項23】一種將治療劑或診斷劑遞送跨過有需要之對象的血腦障壁(BBB)之方法，其包含向該對象投予複合體，該複合體包含偶合至、較佳地共價接合至如請求項1至5中任一項所述之抗體或其抗原結合片段的該治療劑或診斷劑。

【請求項24】如請求項21至24中任一項所述之方法，其中該投予降低Fc介導之效應功能及/或不誘導快速網狀紅血球耗盡。

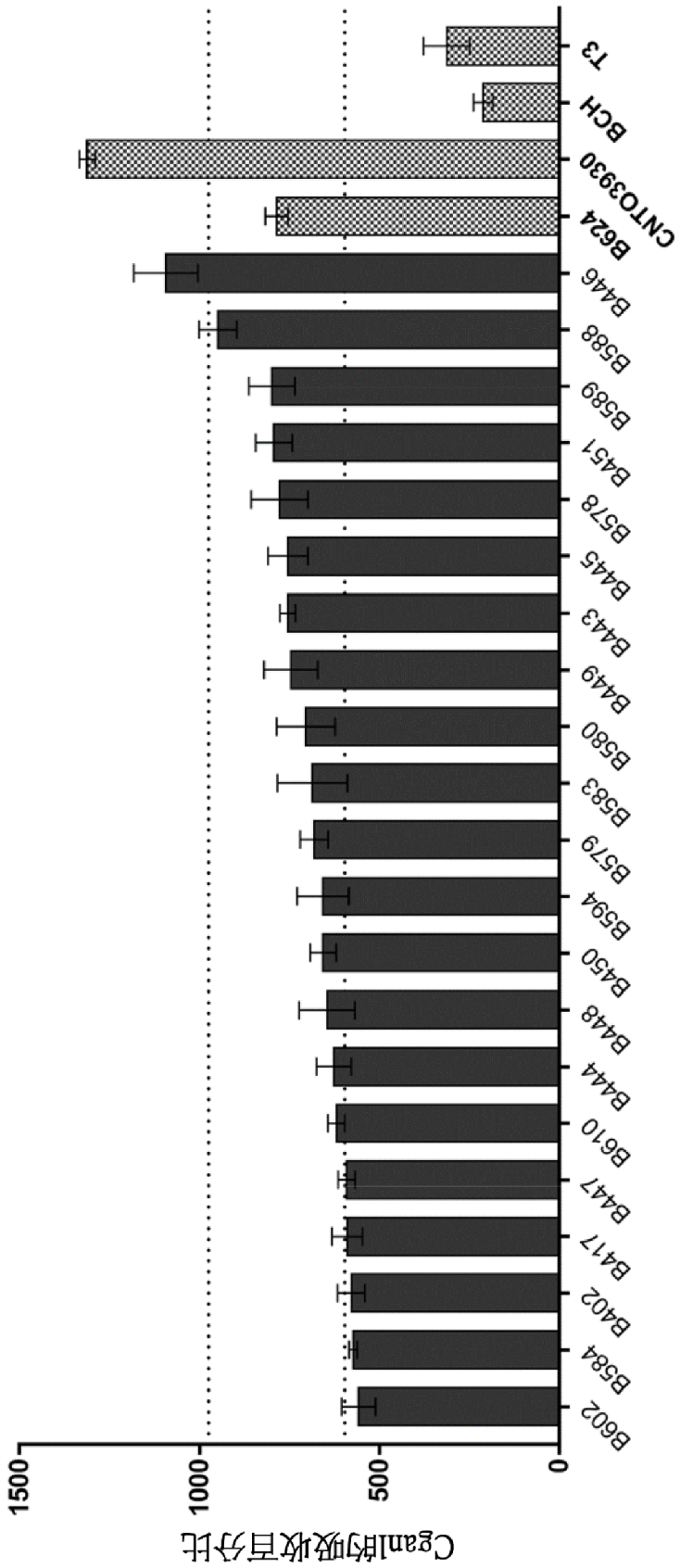
【請求項25】一種在有需要之對象中誘導抗體依賴性吞噬作用(ADP)而不刺激促發炎細胞介素的分泌之方法，其包含向該對象投予複合體，該複合體包含偶合至、較佳地共價接合至如請求項1至5中任一項所述之其抗原結合片段的治療性抗體或其抗原結合片段，其中該治療性抗體或其抗原結合片段在位置L234、L235、D270、N297、E318、K320、K322、P331、及P329包含一或多個胺基酸修飾，諸如L234A、L235A、及P331S中之一、二、或三個突變，其中胺基酸殘基之編號係根據如Kabat中所陳述之EU索引。

【請求項26】如請求項25所述之方法，其中該治療性抗體或其抗原結合片段特異性結合至tau聚集物。

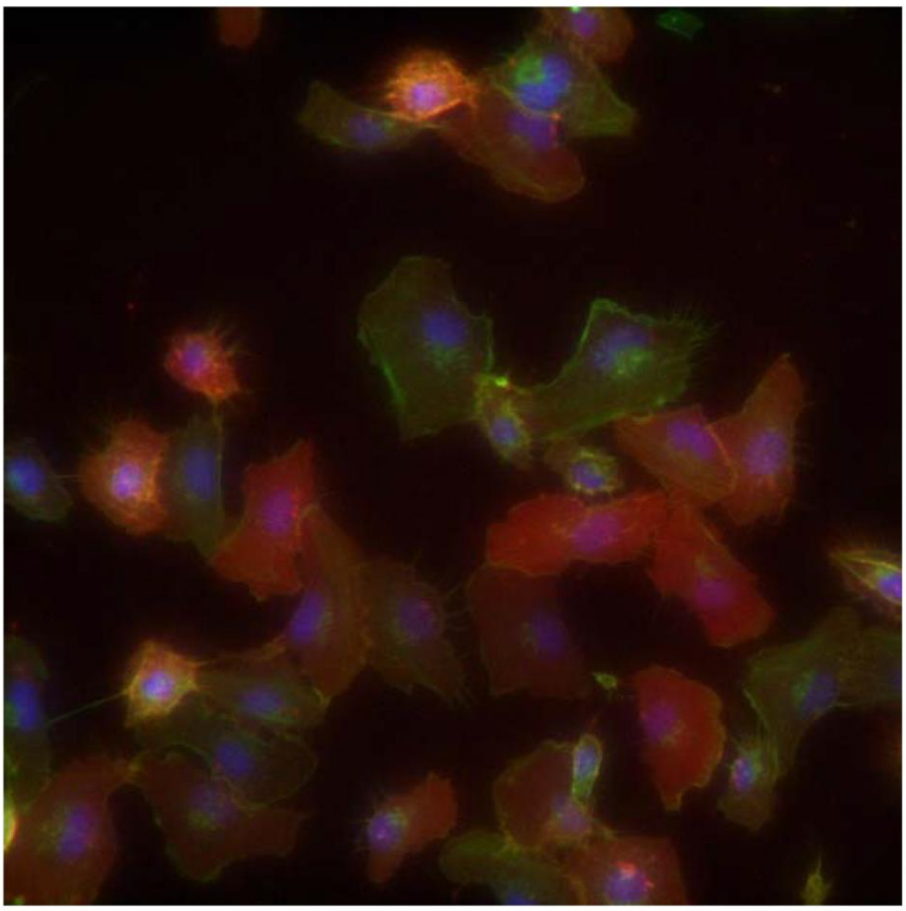
【發明圖式】



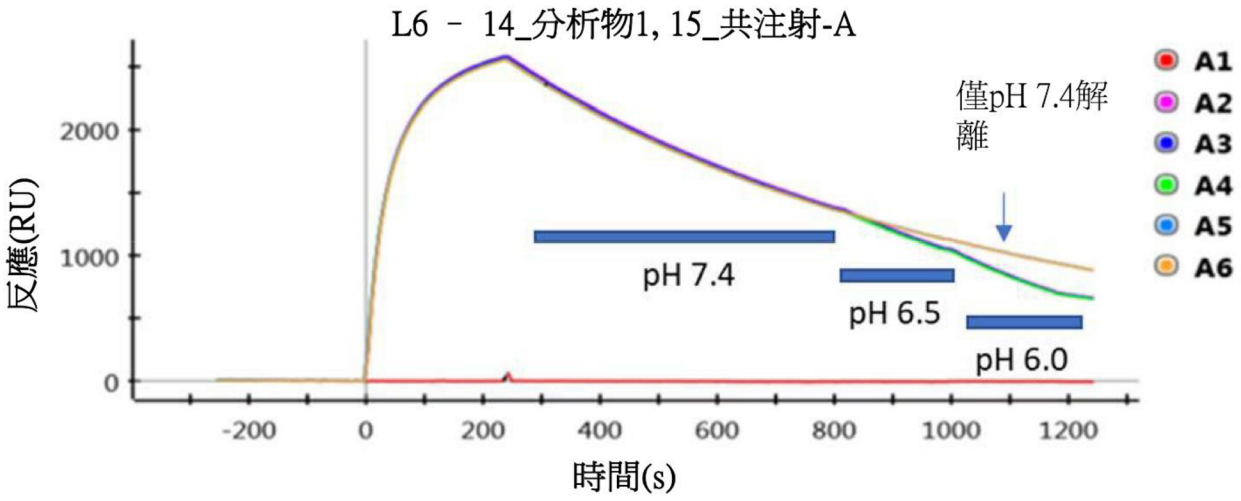
【圖1】


Cgan1的吸收百分比
1500
1000
500
0
T3
BCH
CNTO3930
B624
B446
B588
B589
B451
B578
B445
B443
B449
B580
B583
B579
B594
B450
B448
B444
B610
B447
B417
B402
B584
B602

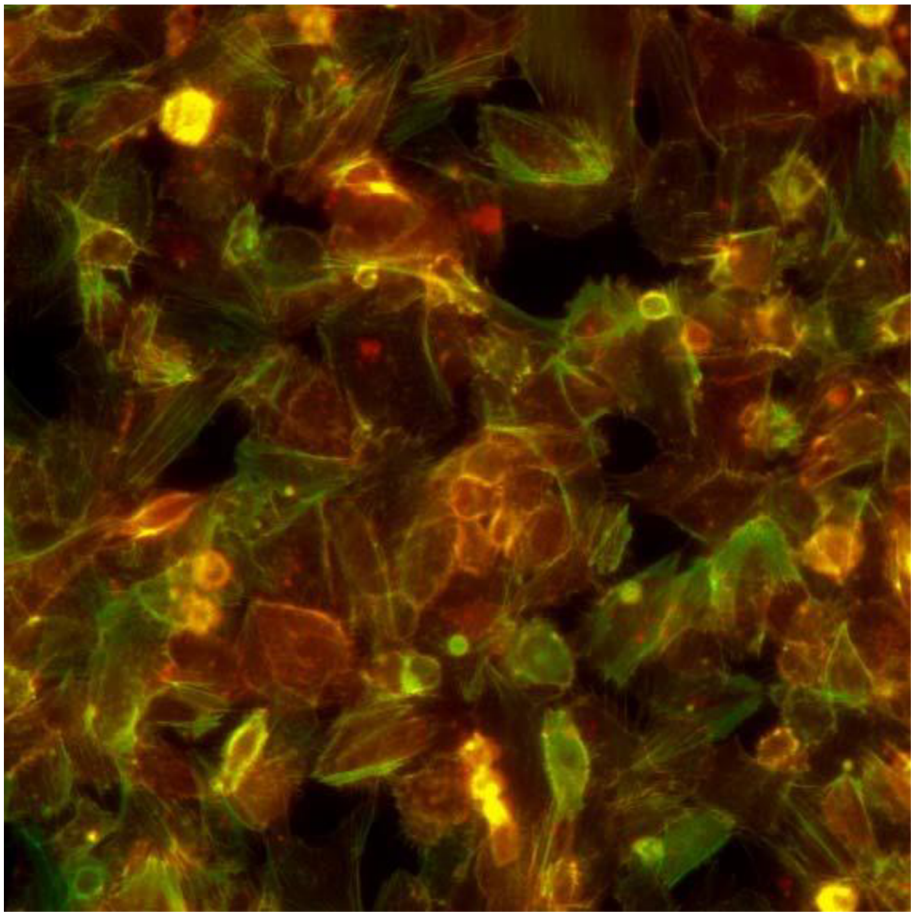
【圖2】



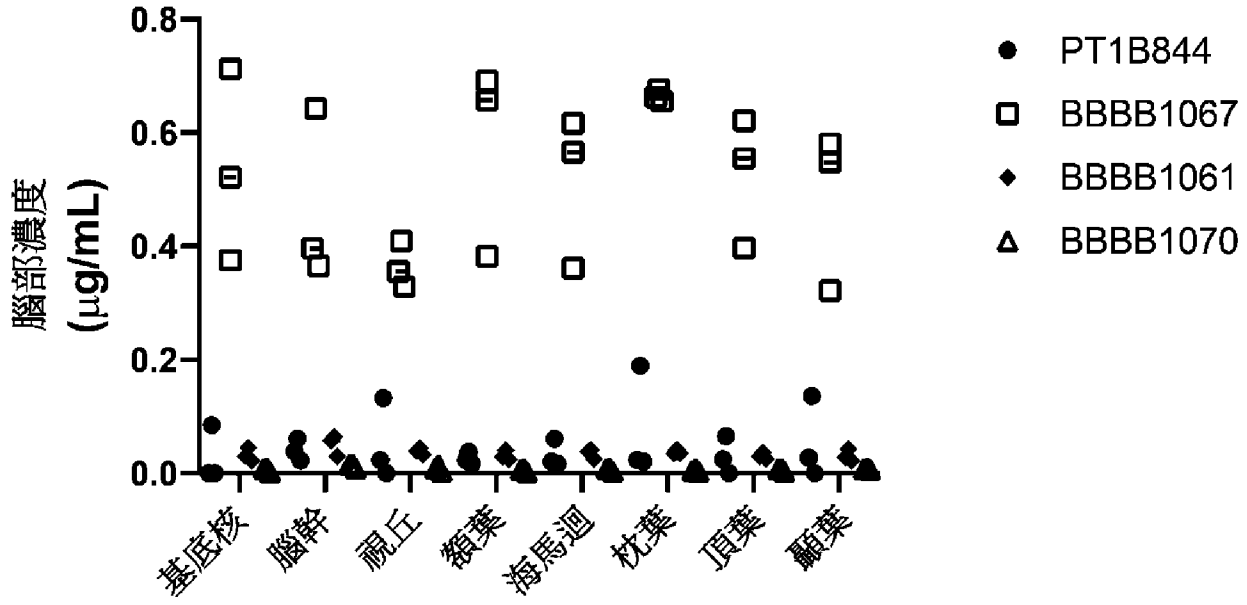
【圖3】


L6 - 14_分析物1, 15_共注射-A
僅pH 7.4解離
A1
A2
A3
A4
A5
A6
pH 7.4
pH 6.5
pH 6.0
反應(RU)
2000
1000
0
-200
0
200
400
600
800
1000
1200
時間(s)

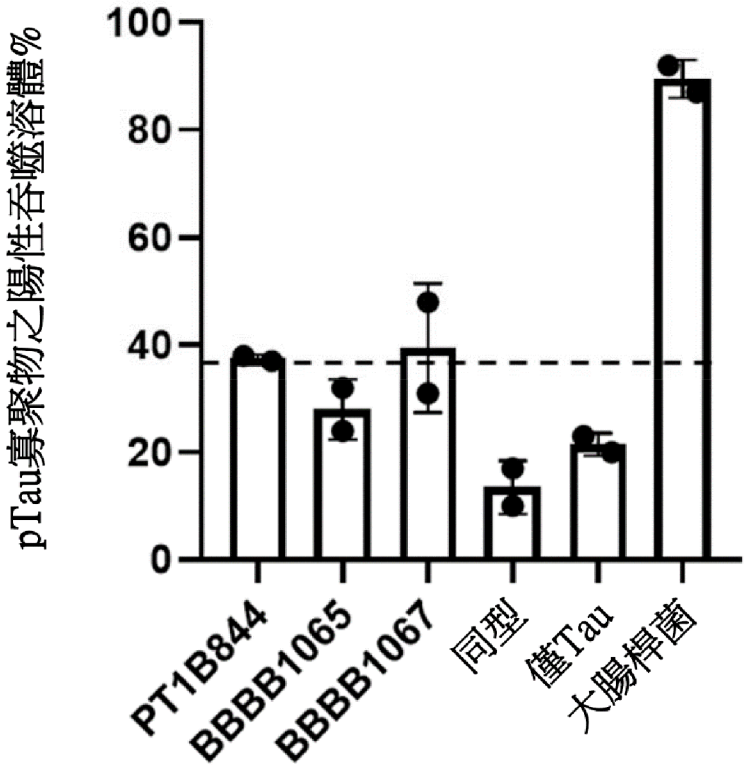
【圖4】



【圖5】


0.8
0.6
0.4
0.2
0.0
腦部濃度
(μg/mL)
基底核
腦幹
視丘
額葉
海馬迴
枕葉
頂葉
顳葉
PT1B844
BBBB1067
BBBB1061
BBBB1070

【圖6】


pTau寡聚物之陽性吞噬溶體%
100
80
60
40
20
0
PT1B844
BBBB1065
BBBB1067
同型
僅Tau
大腸桿菌

【圖7】