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(54)名稱

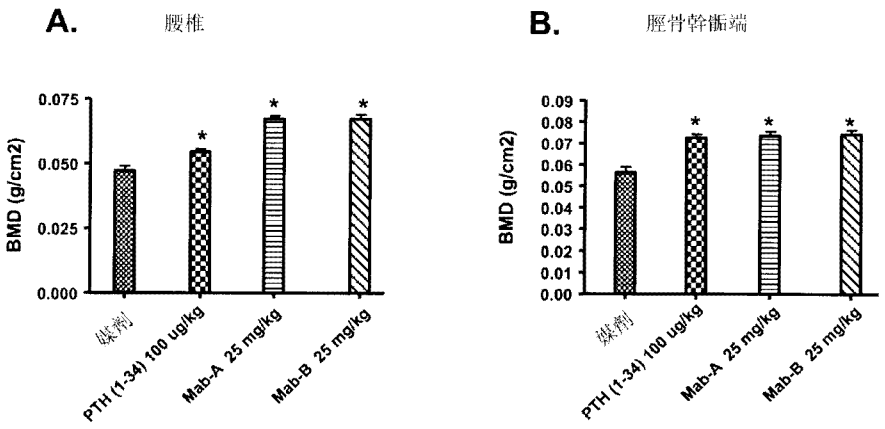
多肽、抗體或其抗原結合片段及其用途

(57)摘要

本發明提供關於殼硬蛋白(sclerostin protein)之抗原決定基及殼硬蛋白結合劑(諸如可結合至殼硬蛋白之抗體)的組合物及方法。

Compositions and methods relating to epitopes of sclerostin protein, and sclerostin binding agents, such as antibodies capable of binding to sclerostin, are provided.

指定代表圖：



＊ =在統計學上顯著不同於媒劑

誤差條形圖=平均值+/-標準差

【圖 5】

專利案號：111132950
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【發明摘要】

【中文發明名稱】

多肽、抗體或其抗原結合片段及其用途

【英文發明名稱】

POLYPEPTIDE, ANTIBODY OR ANTIGEN-BINDING FRAGMENT THEREOF, AND USES THEREOF

【中文】

本發明提供關於殼硬蛋白(sclerostin protein)之抗原決定基及殼硬蛋白結合劑(諸如可結合至殼硬蛋白之抗體)的組合物及方法。

【英文】

Compositions and methods relating to epitopes of sclerostin protein, and sclerostin binding agents, such as antibodies capable of binding to sclerostin, are provided.

【指定代表圖】

圖5

【發明說明書】

【中文發明名稱】

多肽、抗體或其抗原結合片段及其用途

【英文發明名稱】

POLYPEPTIDE, ANTIBODY OR ANTIGEN-BINDING FRAGMENT THEREOF, AND USES THEREOF

【技術領域】

本發明大體而言係關於殼硬蛋白(包括人類殼硬蛋白)之抗原決定基，及可結合至殼硬蛋白或其片段之結合劑(諸如抗體)。

【先前技術】

在個體生命中會發生兩個或三個不同之骨質改變期(參見*Riggs, West J. Med. 154:63-77 (1991)*)。第一階段發生於男性及女性兩者中且進行至達到尖峰骨質。此第一階段係經由軟骨內生長板之線性生長及歸因於骨膜並置速率之輻射狀生長來實現。對於小梁骨(諸如椎骨及骨盆之扁骨)而言，第二階段開始於30歲左右，且對於皮質骨(例如，四肢中可見之長骨)而言則開始於40歲左右，且持續至老年。此階段之特徵在於緩慢之骨流失且發生於男性及女性兩者中。在女性中，亦發生第三階段之骨流失，最大可能係歸因於絕經後雌激素缺乏。僅在此階段期間，女性可能流失來自皮質骨及來自小梁骨隔腔之額外骨質(參見上文之Riggs)。

骨礦質含量之流失可由多種病症而引起並會導致嚴重醫學問題。例如，骨質疏鬆症為人類中之一種衰弱性疾病，且其特徵在於骨骼骨質及礦質密度之顯著降低，骨結構惡化，包括骨微體系結構退化

及骨脆性之相應增加(意即，骨強度降低)，且在患病個體中易於骨折。人類骨質疏鬆症之前通常發生臨床骨質減少(在低於年輕成人骨之平均值下，骨礦物質密度大於一個標準偏差但小於2.5倍標準偏差)，此為在美國接近2千5百萬人中所發現之病症。美國另外7-8百萬患者已診斷患有臨床骨質疏鬆症(界定為骨礦質含量在低於成年年輕成人骨之骨礦物質含量下，高於2.5倍標準偏差)。人群中骨質疏鬆症之發生率隨年齡而增加。在高加索人中，骨質疏鬆症主要見於女性中，在美國占骨質疏鬆症患患者群之80%。老年人意外跌倒之較大風險加劇了此人群中骨骼骨之脆性增加且易於骨折。髖部、腕部及椎骨骨折為其中與骨質疏鬆症相關聯之最常見損傷。對於患者而言，尤其髖部骨折極為不適且昂貴，且對於女性而言，與高死亡率及發病率有關。

儘管已認為骨質疏鬆症係由於骨質減少而會增加骨折風險，少數目前可提供之骨骼病症之治療可增加成人之骨密度，且大多數目前可提供之治療主要係藉由抑制進一步之骨再吸收而非刺激新骨形成來起作用。現處方係提供雌激素來延遲骨流失。然而，對於患者是否得到任何長期受益，及雌激素對於超過75歲之患者是否具有任何影響仍存在一些爭議。此外，咸信使用雌激素會增加乳癌及子宮內膜癌之風險。對於絕經後女性亦已建議降鈣素，含有維生素K之骨鈣蛋白，或高劑量之含有或不含有維生素D之飲食鈣。然而，高劑量鈣常具有不良的胃腸副作用，且須持續監控血清及尿鈣含量(例如，Khosla及Riggs, *Mayo Clin. Proc.* 70:978982, 1995)。

目前骨質疏鬆症之其他治療方法包括雙膦酸鹽(例如，

Fosamax™、Actonel™、Bonviva™、Zometa™、奧帕膦酸鈉(olpadronate)、耐利膦酸鈉(neridronate)、替魯膦酸鈉(skelid)、骨復舒(bonefos))、副甲狀腺激素、鈣阻滯劑、鈣模擬劑(calcimimetics)(例如，擬鈣劑(cinacalcet))、斯他汀(statin)、合成代謝類固醇、鑭及鍶鹽及氟化鈉。然而，該等療法常與不良副作用相關聯(參見上文之Khosla及Riggs)。

殼硬蛋白(SOST基因之產物)不存在硬化性狹窄症中，硬化性狹窄症係一種特徵為骨頭過度生長及骨頭高度緻密之骨骼疾病(Brunkow等人，Am. J. Hum. Genet., 68:577-589, 2001；Balemans等人，Hum. Mol. Genet., 10:537-543, 2001)。人類殼硬蛋白之胺基酸序列係由Brunkow等人(如上)報導，及本文揭示為SEQ ID NO：1。

【發明內容】

本文所揭示之組合物及方法可用於增加骨形成、骨礦質密度、骨礦質含量、骨質、骨品質及骨強度之至少一者，且因此可用於治療多種其中需要增加骨形成、骨礦質密度、骨礦質含量、骨質、骨品質及骨強度之至少一者之病症。本發明亦提供本文所述之其他相關優勢。

本發明係關於由本文所揭示之結合劑識別之人類殼硬蛋白區域(抗原決定基)、使用該等抗原決定基之方法及製備該等抗原決定基之方法。

本發明亦係關於對於識別為環2之殼硬蛋白區域具有特異性之抗原決定基，及特異性結合至該區域之結合劑。

本發明亦係關於對於殼硬蛋白之胱胺酸結區域具有特異性之抗

原決定基，及特異性結合至該區域之結合劑，諸如抗體。

本發明係關於特異性結合至殼硬蛋白之結合劑，諸如抗體。該等結合劑之特徵可在於其交叉阻斷本文所揭示之至少一種抗體結合與殼硬蛋白之結合及/或由本文所揭示之至少一種抗體而交叉阻斷與殼硬蛋白之結合的能力。如本文所揭示，抗體及其他結合劑之特徵亦可在於其在"人類殼硬蛋白肽抗原決定基競爭結合分析"中與人類殼硬蛋白肽之結合圖案。

本發明係關於可增加哺乳動物中之骨形成、骨礦質密度、骨礦質含量、骨質、骨品質及骨強度之至少一者之結合劑，諸如抗體。

本發明係關於在細胞基礦質化分析中可阻斷殼硬蛋白之抑制效應的結合劑，諸如抗體。

本發明進一步係關於包含由至少一個二硫鍵連接之兩個、三個或四個多肽片段之多肽構造，其代表殼硬蛋白之胱胺酸結的核心區域，及可與其特異性結合之抗體。

本發明係關於獲得適合用作免疫原之抗原決定基的方法，其用於在哺乳動物中產生可特異性結合至殼硬蛋白之結合劑(諸如抗體)；在某些實施例中，所產生之結合劑可在活體內中和殼硬蛋白之活性。

本發明係關於一種組合物，其用於在將該組合物投予至動物時產生對殼硬蛋白具有特異性之抗體，該組合物包含具有胺基酸序列SEQ ID NO：6、SEQ ID NO：63、SEQ ID NO：64、SEQ ID NO：65、SEQ ID NO：66、SEQ ID NO：67、SEQ ID NO：68或SEQ ID NO：69之多肽。

本發明亦係關於一種組合物，其用於在將該組合物投予至動物

時產生對殼硬蛋白具有特異性之抗體，該組合物包含至少一種基本上由胺基酸序列SEQ ID NO：2、SEQ ID NO：3、SEQ ID NO：4或SEQ ID NO：5組成之多肽；該組合物可包含至少兩個或至少三個胺基酸序列SEQ ID NO：2、SEQ ID NO：3、SEQ ID NO：4及SEQ ID NO：5；且該組合物可包含所有四個胺基酸序列SEQ ID NO：2、SEQ ID NO：3、SEQ ID NO：4及SEQ ID NO：5。

本發明進一步係關於一種組合物，其用於在將該組合物投予至動物時產生對殼硬蛋白具有特異性之抗體，該組合物包含具有胺基酸序列SEQ ID NO：2、SEQ ID NO：3、SEQ ID NO：4及SEQ ID NO：5之多肽，其中SEQ ID NO：2及4由關於SEQ ID NO：1之胺基酸位置57及111處之二硫鍵而連接，且SEQ ID NO：3及5由(a)關於SEQ ID NO：1之胺基酸位置82及142處之二硫鍵及(b)關於SEQ ID NO：1之胺基酸位置86及144處之二硫鍵之至少一者而連接；該多肽可保持SEQ ID NO：1人類殼硬蛋白之相應多肽區域的三級結構。

本發明亦係關於基本上由SEQ ID NO：1之多重截斷人類殼硬蛋白組成之多肽T20.6，其中該多肽中缺失SEQ ID NO：1之胺基酸1-50、65-72、91-100、118-137及150-190；該多肽可由胰蛋白酶消化人類殼硬蛋白而獲得，且該蛋白可由HPLC分餾而分離。

本發明進一步係關於包含SEQ ID NO：1之胺基酸51-64、73-90、101-117及138-149之人類殼硬蛋白的免疫原性部分T20.6，其中該免疫原性部分包含以下之至少一者：

(a)胺基酸57與111之間之二硫鍵；

(b)胺基酸82與142之間之二硫鍵；及

(c)胺基酸86與144之間之二硫鍵；

該免疫原性部分可具有至少兩個該等二硫鍵；且該免疫原性部分可具有所有三個二硫鍵。

本發明進一步係關於一種包含SEQ ID NO：1之胺基酸57-64、73-86、111-117及138-144之人類殼硬蛋白的免疫原性部分T20.6衍生物，其中該免疫原性部分包含以下之至少一者：

(a)胺基酸57與111之間之二硫鍵；

(b)胺基酸82與142之間之二硫鍵；及

(c)胺基酸86與144之間之二硫鍵；

該免疫原性部分可具有至少兩個該等二硫鍵；且該免疫原性部分可具有所有三個二硫鍵。

本發明又進一步係關於一種基本上由在C-末端及N-末端截斷之SEQ ID NO：1之人類殼硬蛋白組成之多肽，其中該多肽中缺失SEQ ID NO：1之胺基酸1-85及112-190。

本發明亦係關於一種人類殼硬蛋白之免疫原性部分，其包含SEQ ID NO：1之胺基酸86-111；該免疫原性部分基本上可由鄰近胺基酸CGPARLLPNAIGRGKWWRPSGPDFRC (SEQ ID NO：6)組成。

本發明進一步係關於一種大鼠殼硬蛋白之免疫原性部分，其包含SEQ ID NO：98之胺基酸92-109；該免疫原性部分基本上可由鄰近胺基酸PNAIGRVKWWRPNGPDFR (SEQ ID NO：96)組成。

本發明更進一步係關於一種大鼠殼硬蛋白之免疫原性部分，其包含SEQ ID NO：98之胺基酸99-120；該免疫原性部分基本上可由鄰近胺基酸KWWRPNGPDFRCIPDRYRAQRV (SEQ ID NO：97)組成。

本發明係關於一種產生人類殼硬蛋白之免疫原性部分的方法，其包含以下步驟：

(a)處理人類殼硬蛋白以實現完全之胰蛋白酶消化；

(b)收集如在0.2 ml/min之流速下，以0.05%三氟乙酸至0.05% TFA中90%乙腈之線性梯度自逆相HPLC管柱溶離所測定之具有7,122.0道爾頓(理論質量為7121.5道爾頓)之平均分子量或約20.6分鐘之滯留時間之胰蛋白酶消化樣本；及

(c)純化該免疫原性部分。

本發明係關於一種產生可特異性結合至殼硬蛋白之抗體的方法，其包含：

(a)以包含SEQ ID NO：6、SEQ ID NO：63、SEQ ID NO：64、SEQ ID NO：65、SEQ ID NO：66、SEQ ID NO：67、SEQ ID NO：68、SEQ ID NO：69、SEQ ID NO：96或SEQ ID NO：97之多肽的組合物使動物免疫；

(b)自該動物收集血清；及

(c)自該血清分離可特異性結合至殼硬蛋白之抗體。

本發明亦係關於一種產生可特異性結合至殼硬蛋白之抗體的方法，其包含：

(a)以包含多肽T20.6或T20.6衍生物之組合物使動物免疫；

(b)自該動物收集血清；及

(c)自該血清分離可特異性結合至殼硬蛋白之抗體。

本發明進一步係關於一種偵測生物樣本中之抗-殼硬蛋白抗體的方法，其包含以下步驟：

(a)在允許抗體與多肽之間形成複合物之條件下，使生物樣本與基本上由SEQ ID NO：6、SEQ ID NO：63、SEQ ID NO：64、SEQ ID NO：65、SEQ ID NO：66、SEQ ID NO：67、SEQ ID NO：68、SEQ ID NO：69、SEQ ID NO：96或SEQ ID NO：97組成之多肽相接觸；及

(b)偵測該複合物之存在或缺失，

其中該複合物之存在表明該生物樣本含有抗-殼硬蛋白抗體。

本發明亦係關於一種偵測生物樣本中之抗-殼硬蛋白抗體的方法，其包含以下步驟：

(a)在允許抗體與多肽之間形成複合物之條件下，使生物樣本與多肽T20.6或T20.6衍生物相接觸；及

(b)偵測該複合物之存在或缺失，

其中該複合物之存在表明該生物樣本含有抗-殼硬蛋白抗體。

本發明進一步係關於一種交叉阻斷至少一種抗體Ab-A、Ab-B、Ab-C或Ab-D與殼硬蛋白之結合的殼硬蛋白結合劑，諸如抗體。殼硬蛋白結合劑亦可藉由至少一種抗體Ab-A、Ab-B、Ab-C或Ab-D而交叉阻斷與殼硬蛋白之結合。所分離之抗體或其抗原結合片段可為多株抗體、單株抗體、人化抗體、人類抗體、嵌合抗體或其類似物。

本發明進一步係關於一種由至少一種抗體Ab-A、Ab-B、Ab-C或Ab-D交叉阻斷與殼硬蛋白之結合的殼硬蛋白結合劑，諸如抗體。所分離之抗體或其抗原結合片段可為多株抗體、單株抗體、人化抗體、人類抗體、嵌合抗體或其類似物。

本發明進一步係關於一種交叉阻斷至少一種抗體1-24(Ab-1至Ab-

24)與殼硬蛋白之結合的殼硬蛋白結合劑，諸如經分離抗體。殼硬蛋白結合劑亦可由至少一種抗體1-24(Ab-1至Ab-24)阻斷與殼硬蛋白之結合。所分離之抗體或其抗原結合片段可為多株抗體、單株抗體、人化抗體、人類抗體或嵌合抗體。

本發明進一步係關於由至少一種抗體1-24(Ab-1至Ab-24)交叉阻斷與殼硬蛋白之結合的殼硬蛋白結合劑，諸如經分離抗體；所分離之抗體或其抗原結合片段可為多株抗體、單株抗體、人化抗體、人類抗體或嵌合抗體。

本發明進一步係關於一種結合劑，諸如經分離抗體，其在"人類殼硬蛋白肽抗原決定基競爭結合分析"中展現如至少一種抗體Ab-A、Ab-B、Ab-C或Ab-D所展現之類似於人類殼硬蛋白肽之結合圖案；所分離之抗體或其抗原結合片段可為多株抗體、單株抗體、人化抗體、人類抗體或嵌合抗體。

本發明更進一步係關於一種治療哺乳動物受檢者中與低骨形成、低骨礦質密度、低骨礦質含量、低骨質、低骨品質及低骨強度之至少一者相關聯之骨病症的方法，其包含對需要此治療之受檢者提供足以增加骨形成、骨礦質密度、骨礦質含量、骨質、骨品質及骨強度之至少一者之量的抗-殼硬蛋白結合劑，其中該抗-殼硬蛋白結合劑包含抗體或其殼硬蛋白結合片段。

本發明亦係關於一種經分離之殼硬蛋白多肽或其片段，其中該多肽含有6個保留的半胱胺酸殘基且其片段包含7至14個SEQ ID NO：2之胺基酸、8至17個SEQ ID NO：3之胺基酸、8至18個SEQ ID NO：4之殘基及6至12個SEQ ID NO：5之殘基，且該多肽或其片段由SEQ

ID NO：2與4之間及SEQ ID NO：3與5之間之二硫鍵來穩定；該多肽或片段可包含10-14個SEQ ID NO：2之胺基酸、14至17個SEQ ID NO：3之胺基酸、13至18個SEQ ID NO：4之胺基酸及8至12個SEQ ID NO：5之殘基；且該多肽或片段可包含SEQ ID NO：2、SEQ ID NO：3、SEQ ID NO：4及SEQ ID NO：5。

本文提供特異性結合至人類殼硬蛋白之抗體。該等抗體之特徵在於其交叉阻斷至少一種本文所揭示之抗體與人類殼硬蛋白之結合及/或由至少一種本文所揭示之抗體交叉阻斷與人類殼硬蛋白之結合的能力。

亦提供一種可增加哺乳動物中之骨形成、骨礦質密度、骨礦質含量、骨質、骨品質及骨強度之至少一者之經分離抗體或其抗原結合片段。

本發明亦提供一種在以細胞為基礎之礦質化分析中可阻斷殼硬蛋白之抑制效應的經分離抗體或其抗原結合片段。

本發明亦提供一種結合劑，諸如抗體，其特異性結合至人類殼硬蛋白且具有至少一種選自以下序列之CDR序列：SEQ ID NO: 39、40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、78、79、80、81、99、100、101、102、103、104、105、106、107、108、109、110、111、112、113、114、115、116、237、238、239、240、241、242、243、244、245、246、247、248、249、250、251、252、253、254、255、256、257、258、259、260、261、262、263、264、265、266、267、268、269、270、271、272、273、274、275、276、277、278、279、280、

281、282、283、284、285、286、287、288、289、290、291、292、293、294、295、296、297、298、351、352、353、358、359及360，及其變異體，其中該抗體或其抗原結合片段使殼硬蛋白中和。

亦提供一種結合劑，諸如抗體，其特異性結合至人類殼硬蛋白且具有至少一種選自以下序列之CDR序列：SEQ ID NO: 39、40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、78、79、80、81、99、100、101、102、103、104、105、106、107、108、109、110、111、112、113、114、115、116、237、238、239、240、241、242、243、244、245、246、247、248、249、250、251、252、253、254、255、256、257、258、259、260、261、262、263、264、265、266、267、268、269、270、271、272、273、274、275、276、277、278、279、280、281、282、283、284、285、286、287、288、289、290、291、292、293、294、295、296、297、298、351、352、353、358、359及360，及其變異體。

亦提供對於蛋白之活體內活性具有重要作用之人類殼硬蛋白區域。

參考以下詳細說明及附圖，本發明之該等及其他態樣將變得顯而易見。本文所揭示之所有參考文獻均如同各自個別併入而以全文引用的方式併入本文中。

【圖式簡單說明】

圖1描繪抗-人類殼硬蛋白及抗-小鼠殼硬蛋白抗體Ab-A之輕鏈(圖1A)(SEQ ID NO：23)及重鏈(圖1B)(SEQ ID NO：27)之成熟形式(訊號

肽切除)的胺基酸序列。

圖2描繪抗-人類殼硬蛋白及抗-小鼠殼硬蛋白抗體Ab-B之輕鏈(圖2A)(SEQ ID NO：31)及重鏈(圖2B)(SEQ ID NO：35)之成熟形式(訊號肽切除)的胺基酸序列。

圖3描繪抗-人類殼硬蛋白及抗-小鼠殼硬蛋白抗體Ab-C之輕鏈(圖3A)(SEQ ID NO：15)及重鏈(圖3B)(SEQ ID NO：19)之成熟形式(訊號肽切除)的胺基酸序列。

圖4描繪抗-人類殼硬蛋白及抗-小鼠殼硬蛋白抗體Ab-D之輕鏈(圖4A)(SEQ ID NO：7)及重鏈(圖4B)(SEQ ID NO：11)之成熟形式(訊號肽切除)的胺基酸序列。

圖5描繪在以媒劑、PTH(1-34)、Ab-A或Ab-B處理3週之後，在兩個骨骼位點(腰椎及脛骨幹骺端)量測之小鼠的骨礦質密度。

圖6展示在以媒劑、PTH(1-34)或Ab-C處理2週之後，在兩個骨骼位點(腰椎及脛骨幹骺端)量測之小鼠的骨礦質密度。

圖7描繪以媒劑或Ab-D處理3週之後，在兩個骨骼位點(腰椎及脛骨幹骺端)量測之小鼠的骨礦質密度。

圖8描繪人類殼硬蛋白之成熟形式(訊號肽切除)的胺基酸序列(SEQ ID NO：1)。亦描繪編碼人類殼硬蛋白之成熟形式的人類殼硬蛋白編碼區之核苷酸序列。八個半胱胺酸編號為C1至C8。由三個二硫鍵(C1-C5、C3-C7、C4-C8)形成胱胺酸結。C2與C6亦形成二硫鍵，然而此二硫鍵並非胱胺酸結之部分。

圖9描繪人類殼硬蛋白之基本結構示意圖。其具有N-末端臂(自第一個Q至C1)及C-末端臂(自C8至末端Y)。在該等臂之間為胱胺酸結結

構(由三個二硫鍵形成：C1-C5、C3-C7、C4-C8)及命名為環1、環2及環3之三個環。環1與環3之遠端區由C2-C6二硫鍵連接。標明潛在之胰蛋白酶裂解位點(精胺酸=R且離胺酸=K)。標明某些潛在之AspN裂解位點(僅展示天冬胺酸(D)殘基)。

圖10描繪以胰蛋白酶或AspN消化之後人類殼硬蛋白之HPLC肽圖。如同由AspN消化所產生之人類殼硬蛋白肽(AspN14.6、AspN18.6及AspN22.7-23.5)，標明由胰蛋白酶消化所產生之人類殼硬蛋白肽(T19.2、T20、T20.6及T21-22)。

圖11描繪由胰蛋白酶消化所產生之經分離人類殼硬蛋白二硫鍵連接之肽的序列及質量訊息。Seq. pos.=序列位置。Obs.=觀察。觀察質量由ESI-LC-MS分析來測定。

圖12描繪由AspN消化所產生之經分離人類殼硬蛋白肽的序列及質量訊息。AspN22.7-23.5肽含有4個二硫鍵。Seq. pos.=序列位置。Obs.=觀察。觀察質量由ESI-LC-MS分析來測定。

圖13展示由胰蛋白酶消化所產生之四種人類殼硬蛋白肽(T19.2、T20、T20.6及T21-22)的線性示意圖。

圖14展示由AspN消化所產生之五種人類殼硬蛋白肽(AspN14.6、AspN18.6及AspN22.7-23.5)的線性示意圖。AspN14.6 HPLC峰包含並非由任何二硫鍵所連接之三種肽。

圖15展示基於Biacore之"人類殼硬蛋白肽抗原決定基競爭結合分析"之共振單元(Ru)訊號。評估與結合至完整成熟形式人類殼硬蛋白(固定於Biacore晶片上)之Mab相比之結合至各種人類殼硬蛋白-肽(在溶液中)之相對Mab。所展示之數據為Ab-A。所用人類殼硬蛋白肽為

T19.2、T20、T20.6、T21-22、AspN14.6、AspN18.6及AspN22.7-23.5。

圖16展示基於Biacore之"人類殼硬蛋白肽抗原決定基競爭結合分析"之共振單元(Ru)訊號。評估與結合至完整成熟形式人類殼硬蛋白(固定於Biacore晶片上)之Mab相比之結合至各種人類殼硬蛋白-肽(在溶液中)之相對Mab。所展示之數據為Ab-B。所用人類殼硬蛋白肽為T19.2、T20、T20.6、T21-22、AspN14.6、AspN18.6及AspN22.7-23.5。

圖17展示基於Biacore之"人類殼硬蛋白肽抗原決定基競爭結合分析"之共振單元(Ru)訊號。評估與結合至完整成熟形式人類殼硬蛋白(固定於Biacore晶片上)之Mab相比之結合至各種人類殼硬蛋白-肽(在溶液中)之相對Mab。所展示之數據為Ab-C。所用人類殼硬蛋白肽為T19.2、T20、T20.6、T21-22、AspN14.6、AspN18.6及AspN22.7-23.5。

圖18展示基於Biacore之"人類殼硬蛋白肽抗原決定基競爭結合分析"之共振單元(Ru)訊號。評估與結合至完整成熟形式人類殼硬蛋白(固定於Biacore晶片上)之Mab相比之結合至各種人類殼硬蛋白-肽(在溶液中)之相對Mab。所展示之數據為Ab-A。所用人類殼硬蛋白肽為T19.2、T20、T20.6、T21-22、AspN14.6、AspN18.6及AspN22.7-23.5。

圖19展示人類殼硬蛋白之兩種Mab結合抗原決定基。圖19A展示用於使Ab-A及Ab-B結合至人類殼硬蛋白之環2抗原決定基序列(SEQ ID NO：6)。圖19B展示用於使Ab-C及Ab-D結合至人類殼硬蛋白之

T20.6抗原決定基的序列、二硫鍵結及示意圖(SEQ ID NO：2-5)。

圖20描繪在以胰蛋白酶消化之後人類殼硬蛋白之HPLC肽圖。圖20A展示人類殼硬蛋白Ab-D複合物之消化。圖20B展示單獨人類殼硬蛋白之消化。標明T19.2、T20、T20.6及T21-22肽峰。

圖21展示用於使Ab-D結合至人類殼硬蛋白之"T20.6衍生物1(胱胺酸結+ 4個臂)"抗原決定基的序列、二硫鍵結及示意圖(SEQ ID NO：70-73)。

圖22展示用於識別抗-殼硬蛋白中和Mab之MC3T3-E1-BF骨母細胞株礦質化分析的結果。使用1 μg/ml之小鼠殼硬蛋白(Scl)。使用10及5 μg/ml之單株抗體。藉由量測鈣來定量礦質化程度(各種類型之不溶性磷酸鈣)。

圖23描繪用於識別抗-殼硬蛋白中和Mab之MC3T3-E1-BF骨母細胞株礦質化分析的結果。使用1 μg/ml之人類殼硬蛋白(Scl)。使用8及4 μg/ml之單株抗體。藉由量測鈣來定量礦質化程度(各種類型之不溶性磷酸鈣)。

圖24展示用於識別抗-殼硬蛋白中和Mab之MC3T3-E1-BF骨母細胞株礦質化分析的結果。使用1 μg/ml之人類殼硬蛋白(Scl)。使用10 μg/ml之單株抗體。藉由量測鈣來定量礦質化程度(各種類型之不溶性磷酸鈣)。

圖25描繪發炎誘發之骨流失SCID小鼠模型的結果。當量測全骨礦質密度(圖25A)、椎骨密度(圖25B)及股骨密度(圖25C)時，Ab-A處理保護小鼠免於與結腸炎相關聯之發炎相關骨流失。

【實施方式】

本發明係關於含有由亦結合至全長殼硬蛋白之抗體識別之抗原決定基的人類殼硬蛋白區，及產生及使用該等抗原決定基之方法。本發明亦提供特異性結合至殼硬蛋白或部分殼硬蛋白之結合劑(諸如抗體)，及使用該等結合劑之方法。該等結合劑用於阻斷或削弱人類殼硬蛋白與一或多種配位體之結合。

重組人類殼硬蛋白/SOST可購自R&D系統(Minneapolis, MN, USA；2006目錄號1406-ST-025)。此外，重組小鼠殼硬蛋白/SOST可購自R&D系統(Minneapolis, MN, USA；2006目錄號1589-ST-025)。研究等級殼硬蛋白結合單株抗體可購自R&D系統(Minneapolis, MN, USA；小鼠單株：2006目錄號MAB1406；大鼠單株：2006目錄號MAB1589)。美國專利第6,395,511號及第6,803,453號及美國專利公開案第20040009535號及第20050106683號通常涉及抗-殼硬蛋白抗體。

如本文所用之術語人類殼硬蛋白意欲包括SEQ ID NO：1及其對偶基因變異體之蛋白。可藉由使用鹽梯度之肝素HP管柱溶離宿主細胞培養液之經過濾上清液而自已由編碼殼硬蛋白之基因轉染之293T宿主細胞來純化殼硬蛋白。實例1及2中描述製備及使用陽離子交換層析之進一步純化。

如本文所界定，本發明之結合劑較佳為抗體。術語"抗體"係指完整抗體，或其結合片段。抗體可包含全部抗體分子(包括具有全長重鏈及/或輕鏈之多株、單株、嵌合、人化或人類變體)或包含其抗原結合片段。抗體片段包括$F(ab')_2$、Fab、Fab'、Fv、Fc及Fd片段，且可併入單一結構域抗體、單鏈抗體、大型抗體、微型抗體、內抗體、二抗體、三抗體、四抗體、v-NAR及雙-scFv(參見，例如，Hollinger及

Hudson，2005，Nature Biotechnology, 23, 9, 1126-1136)。抗體多肽亦揭示於美國專利第6,703,199號中，包括纖維結合蛋白多肽單體。其他抗體多肽揭示於美國專利公開案第2005/0238646號中，其為單鏈多肽。

例如，可藉由蛋白水解抗體，例如，根據習知方法以胃蛋白酶或木瓜蛋白酶消化整個抗體而獲得源自該抗體之抗原結合片段。舉例而言，可藉由以胃蛋白酶酶促裂解抗體而產生抗體片段，以提供稱為$F(ab')_2$之5S片段。此片段可使用硫醇還原劑進一步裂解以提供3.5S Fab'單價片段。裂解反應視情況可使用對於由二硫鍵裂解而產生之氫硫基的阻斷基團來進行。或者，使用木瓜蛋白酶之酶促裂解直接產生兩個單價Fab片段及Fc片段。該等方法由以下文獻所描述，例如Goldenberg，美國專利第4,331,647號；Nisonoff等人，*Arch. Biochem. Biophys.* 89:230, 1960；Porter, *Biochem. J.* 73:119, 1959；Edelman等人，於*Methods in Enzymology*中1:422 (Academic Press 1967)；及Andrews, S.M.與Titus, J.A.於*Current Protocols in Immunology*(Coligan J.E等人編)，John Wiley & Sons, New York (2003).第2.8.1-2.8.10頁及第2.10A.1-2.10A.5頁中。只要片段結合至由完整抗體所識別之抗原，亦可使用其他裂解抗體之方法，諸如分離重鏈以形成單價輕-重鏈片段(Fd)，進一步裂解片段，或其他酶促、化學或基因技術。

抗體片段亦可為任何合成或基因工程蛋白。例如，抗體片段包括由輕鏈可變區組成之分離片段、由重鏈及輕鏈可變區組成之"Fv"片段、重組單鏈多肽分子，其中輕鏈及重鏈可變區由肽連接子(scFv蛋白)連接。

另一種形式之抗體片段為包含一或多個抗體互補判定區(CDR)之肽。CDR(亦稱為"最小識別單元"，或"高變區")可由建構編碼感興趣CDR之聚核苷酸而獲得。例如，藉由使用產生抗體之細胞的mRNA作為模板，使用聚合酶鏈反應以合成可變區來製備該等聚核苷酸(參見，例如，Larrick等人，*Methods: A Companion to Methods in Enzymology* 2:106, 1991；Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," 於 *Monoclonal Antibodies: Production, Engineering and Clinical Application*中，Ritter等人(編)，第166頁(Cambridge University Press 1995)；及Ward等人，"Genetic Manipulation and Expression of Antibodies,"於*Monoclonal Antibodies: Principles and Applications*中，Birch等人(編)，第137頁(Wiley-Liss, Inc. 1995))。

因此，在一實施例中，結合劑包含至少一個如本文所述之CDR。結合劑可包含至少兩個、三個、四個、五個或六個如本文所述之CDR。結合劑可進一步包含至少一個如本文所述之抗體的可變區結構域。可變區結構域可為任意大小或胺基酸組合物，且通常將包含至少一個負責用於結合至人類殼硬蛋白之CDR序列，例如CDR-H1、CDR-H2、CDR-H3及/或本文特定描述之輕鏈CDR，且該序列鄰近於一或多個框架序列或與一或多個框架序列一起位於框架內。概括而言，可變區(V)結構域可為免疫球蛋白重鏈(V_H)及/或輕鏈(V_L)可變結構域之任何合適配置。因此，舉例而言，V區結構域可為單體且為V_H或V_L結構域，其可如下文所述以至少等於$1x10^{-7}$ M或更小之親合力獨立結合人類殼硬蛋白。或者，V區結構域可為二聚體且含有V_H-V_H、V_H-V_L或

V_L-V_L二聚體。V區二聚體包含可為非共價締合之至少一個V_H及至少一個V_L鏈(下文稱為F_V)。若需要，該等鏈可直接(例如)經由兩個可變結構域之間之二硫鍵，或經由連接子(例如肽連接子)而共價偶合以形成單鏈Fv (scFV)。

可變區結構域可為任何天然產生之可變結構域或其工程變體。工程變體意謂已使用重組DNA工程技術而產生之可變區結構域。該等工程變體包括例如藉由特異性抗體胺基酸序列之插入、缺失或改變而自特異性抗體可變區產生之變體。特定實例包括含有第一抗體之至少一個CDR及視情況之一或多個框架胺基酸之工程可變區結構域，及第二抗體之可變區結構域的剩餘物。

可變區結構域可在C-末端胺基酸處共價連接至少一個其他抗體結構域或其片段。因此，例如，可變區結構域中存在之V_H結構域可連接至免疫球蛋白CH1結構域，或其片段。類似地，V_L結構域可連接至C_K結構域或其片段。以此方式，例如，抗體可為Fab片段，其中抗原結合結構域含有在其C-末端分別共價連接至CH1及C_K結構域之締合V_H及V_L結構域。CH1結構域可以另外之胺基酸而延伸，例如提供如在Fab'片段中所發現之鉸鏈區或部分鉸鏈區結構域，或提供另外之結構域，諸如抗體CH2及CH3結構域。

如本文所述，結合劑包含該等CDR之至少一者。例如，可將一或多個CDR併入已知抗體框架區(IgG1、IgG2等)，或結合至合適媒劑以提高其半衰期。合適媒劑包括(但不限於)Fc，聚乙二醇(PEG)、白蛋白、運鐵蛋白及其類似物。此項技術中已知該等及其他合適媒劑。該等經結合CDR肽可為單體、二聚體、四聚體或其他形式。在一實施例

中，在結合劑之一或多個特定位置處，例如在胺基末端，鍵結一或多個水溶性聚合物。

在某些較佳實施例中，結合劑包含一或多種水溶性聚合物連接物，包括(但不限於)聚乙二醇、聚氧乙烯乙二醇或聚丙二醇。參見，例如，美國專利第4,640,835號、第4,496,689號、第4,301,144號、第4,670,417號、第4,791,192及第4,179,337號。在某些實施例中，衍生結合劑包含以下各物之一或多者：單甲氧基-聚乙二醇、葡聚糖、纖維素或其他基於碳水化合物之聚合物、聚-(N-乙烯基咯啶酮)-聚乙二醇、丙二醇均聚物、聚氧化丙烯/氧化乙烯共聚物、聚氧乙基化多元醇(例如，甘油)及聚乙烯醇，以及該等聚合物之混合物。在某些實施例中，一或多種水溶性聚合物無規連接至一或多個側鏈上。在某些實施例中，PEG可用於改良結合劑(諸如抗體)之治療能力。例如，在美國專利第6,133,426號中討論某些該等方法，其為任何目的以引用的方式併入本文。

應瞭解，本發明之結合劑可具有至少一個胺基酸取代，其限制條件為該結合劑保持結合特異性。因此，在本發明之範疇中涵蓋對於結合劑結構之修飾。該等修飾可包括保守性或非保守性胺基酸取代，其並不破壞結合劑之殼硬蛋白結合能力。保守性胺基酸取代可涵蓋非天然產生之胺基酸殘基，其一般藉由化學肽合成而非於生物系統中合成而併入。該等取代包括肽模擬物及胺基酸部分之其他逆向或反向形式。保守性胺基酸取代亦可包括以標準殘基取代天然胺基酸殘基，以使得對於彼位置處胺基酸殘基之極性或電荷具有較小影響或無影響。

非保守性取代可包括以一類胺基酸或胺基酸模擬物之一員交換

另一類具有不同物理特性(例如，尺寸、極性、疏水性、電荷)之一員。該等經取代之殘基可引入至與非人類抗體同源之人類抗體區域中，或引入至分子非同源區域中。

此外，熟習此項技術者可產生在每一所要胺基酸殘基處均含有單一胺基酸取代之測試變異體。隨後可使用熟習此項技術者已知之活性分析來篩檢該等變異體。該等變異體可用於收集關於合適變異體之資訊。例如，若發現對於特定胺基酸殘基之改變導致受損、不良降低或不當之活性，則可避免具有此改變之變異體。換言之，基於自該等常規實驗所收集之資訊，熟習此項技術者可易於判定在應單獨或與其他突變組合避免進一步取代處之胺基酸。

熟習此項技術者將可使用熟知技術判定如本文所述多肽之合適變異體。在某些實施例中，熟習此項技術者可藉由定靶認為對於活性不具重要性之區域來識別可改變而不破壞活性之合適分子區域。在某些實施例中，可識別保留於類似多肽中之分子殘基及部分。在某些實施例中，甚至對於生物活性或對於結構可具有重要性之區域可經受保守性胺基酸取代而不破壞生物活性或對多肽結構無不利影響。

另外，熟習此項技術者可回顧關於識別在類似多肽中對於活性或結構具有重要性之殘基的結構-功能研究。鑒於此比較，可預測蛋白中對應於在類似蛋白中對於活性或結構具有重要性之胺基酸殘基的胺基酸殘基之重要性。熟習此項技術者可為該等經預測具有重要性之胺基酸殘基選擇化學上類似之胺基酸取代。

熟習此項技術者亦可分析類似多肽中之三維結構及關於該結構之胺基酸序列。鑒於此資訊，熟習此項技術者可預測抗體關於其三維

結構之胺基酸殘基比對。在某些實施例中，熟習此項技術者可選擇不對預測位於蛋白表面之胺基酸殘基進行根本改變，因為該等殘基可涉及與其他分子之重要交互作用。

諸多科學出版物已致力於預測二級結構。參見Moult J., Curr. Op. in Biotech., 7(4):422-427 (1996)，Chou等人，Biochemistry, 13(2):222-245 (1974)；Chou等人，Biochemistry, 113(2):211-222 (1974)；Chou等人，Adv. Enzymol. Relat. Areas Mol. Biol., 47:45-148 (1978)；Chou等人，Ann. Rev. Biochem.，47:251-276及Chou等人，Biophys. J., 26:367-384 (1979)。此外，電腦程式目前可用於輔助預測二級結構。一種預測二級結構之方法係基於同源模建。例如，具有大於30%之序列一致性，或大於40%之相似性之兩種多肽或蛋白常具有相似之結構拓撲。蛋白結構資料庫(PDB)近期之增長已提供對於二級結構增強之可預測性，包括多肽或蛋白結構中可能之折疊數目。參見Holm等人，Nucl. Acid. Res., 27(1):244-247 (1999)。已表明(Brenner等人，Curr. Op. Struct. Biol., 7(3):369-376 (1997))，在給定多肽或蛋白中具有有限數目之折疊，且一旦已解決結構之關鍵數目，則結構預測將顯著變得更為準確。

預測二級結構之額外方法包括"串線"(Jones, D., Curr. Opin. Struct. Biol., 7(3):377-87 (1997)；Sippl等人，Structure, 4(1):15-19 (1996))、"序表分析"(Bowie等人，Science, 253:164-170 (1991)；Gribskov等人，Meth. Enzym., 183:146-159 (1990)；Gribskov等人，Proc. Nat. Acad. Sci., 84(13):4355-4358 (1987))及"進化鍵接"(參見Holm，上文(1999)及Brenner，上文(1997))。

在某些實施例中，結合劑之變異體包括糖基化變異體，其中與親本多肽之胺基酸序列相比，糖基化位點之數目及/或類型已改變。在某些實施例中，變異體包含與原生蛋白相比較多或較少數目之N-連接糖基化位點。N-連接糖基化位點之特徵在於序列：Asn-X-Ser或Asn-X-Thr，其中指定為X之胺基酸殘基可為除脯胺酸之外之任何胺基酸殘基。產生此序列之胺基酸殘基取代為N-連接之碳水化合物鏈之加成提供潛在新穎位點。或者，消除此序列之取代將移除現存之N-連接之碳水化合物鏈。亦提供N-連接之碳水化合物鏈之重排，其中消除一或多個N-連接之糖基化位點(一般為彼等天然產生之位點)且產生一或多個新穎N-連接位點。額外之較佳抗體變異體包括半胱胺酸變異體，其中與親本胺基酸序列相比，除去一或多個半胱胺酸殘基或取代為另一胺基酸(例如，絲胺酸)。當抗體必須再折疊為生物活性構形時，諸如在分離不溶性包涵體之後，可使用半胱胺酸變異體。半胱胺酸變異體通常具有與原生蛋白相比較少之半胱胺酸殘基，且一般具有均等數目以最小化由不成對半胱胺酸而導致之交互作用。

在需要該等取代時，可由熟習此項技術者判定所要之胺基酸取代(無論為保守性或非保守性)。在某些實施例中，胺基酸取代可用於識別對於殼硬蛋白之重要抗體殘基，或用於增加或減少抗體與本文所述殼硬蛋白之親合力。

根據某些實施例，較佳胺基酸取代為以下之彼等取代：(1)減小對蛋白水解作用之敏感性，(2)減小對氧化作用之敏感性，(3)改變用於形成蛋白複合體之結合親合力，(4)改變結合親合力，及/或(5)賦予或修飾該等多肽之其他物理化學或功能特性。根據某些實施例，可在

天然產生之序列中(在某些實施例中，在形成份子間接觸之結構域以外的多肽部分中)進行單一或多次胺基酸取代(在某些實施例中為保守性胺基酸取代)。在某些實施例中，保守性胺基酸取代一般可大體上不改變親本序列之結構特徵(例如，置換胺基酸不應傾向於破壞親本序列中產生之螺旋，或不干擾表徵該親本序列之其他類型二級結構)。此項技術所公認之多肽二級及三級結構之實例描述於以下文獻中：Proteins, Structures and Molecular Principles(Creighton編，W. H. Freeman and Company, New York (1984))、Introduction to Protein Structure(C. Branden及J. Tooze編，Garland Publishing, New York, N.Y. (1991))及Thornton等人，Nature 354:105 (1991)，其各自以引用的方式併入本文中。

在某些實施例中，本發明之結合劑可與聚合物、脂質或其他部分化學鍵結。

該等結合劑可包含至少一種本文所述之CDR併入生物相容性框架結構中。在一實例中，該生物相容性框架結構包含足以形成構形穩定性結構支撐物，或框架，或支架之多肽或其部分，其可在局部表面區域中展示一或多個結合至抗原(例如，CDR、可變區等)之胺基酸序列。該等結構可為天然產生之多肽或多肽"折疊"(結構基元)，或相對於天然產生之多肽或折疊可具有一或多種修飾，諸如胺基酸之添加、去除或取代。該等支架可源於任何物種(或超過一個物種)之多肽，諸如人類、其他哺乳動物，其他脊椎動物、無脊椎動物、植物、細菌或病毒。

生物相容性框架結構一般係基於蛋白支架或骨架，而非免疫球

蛋白結構域。例如，可使用彼等基於纖維結合蛋白、錨蛋白、脂質運載蛋白、新製癌菌素、細胞色素b、CP1鋅指、PST1、捲曲螺旋、LACI-D1、Z結構域及tendramisat結構域之生物相容性框架結構(參見例如，Nygren及Uhlen, 1997, Current Opinion in Structural Biology, 7, 463-469)。

在較佳實施例中，應瞭解，本發明之結合劑包括本文所述之人化抗體。可使用熟習此項技術者已知之技術來生產諸如本文所述之彼等人化抗體(Zhang, W.等人，*Molecular Immunology. 42(12)*:1445-1451, 2005；Hwang W.等人，*Methods. 36(1)*:35-42, 2005；Dall'Acqua WF.等人，*Methods 36(1)*:43-60, 2005及Clark, M., *Immunology Today. 21(8)*:397-402, 2000)。

此外，熟習此項技術者將意識到合適結合劑包括該等抗體之部分，諸如一或多個如本文特定揭示之CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3。至少一個CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3區域可具有至少一個胺基酸取代，其限制條件為結合劑保持非取代CDR之結合特異性。結合劑之非CDR部分可為非蛋白分子，其中該結合劑交叉阻斷本文所揭示之抗體與殼硬蛋白之結合，及/或中和殼硬蛋白。結合劑之非CDR部分可為非蛋白分子，其中在該結合劑在"人類殼硬蛋白肽抗原決定基競爭結合分析"中展示與至少一個抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24所展示之類似之與人類殼硬蛋白

肽之結合圖案，及/或中和殼硬蛋白。結合劑之非CDR部分可包含胺基酸，其中該結合劑為重組結合蛋白或合成肽，且該重組結合蛋白交叉阻斷本文所揭示之抗體與殼硬蛋白之結合，及/或中和殼硬蛋白。結合劑之非CDR部分可包含胺基酸，其中該結合劑為重組結合蛋白，且該重組結合蛋白在人類殼硬蛋白肽抗原決定基競爭結合分析(描述於下文)中展示與至少一種抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24所展示之類似之與人類殼硬蛋白肽之結合圖案，及/或中和殼硬蛋白。

當抗體包含如上文所述之一或多個CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3時，其可藉由自含有編碼該等序列之DNA之宿主細胞中表現而獲得。編碼每一CDR序列之DNA可基於CDR之胺基酸序列來判定且可使用適當之寡核苷酸合成技術、定點突變及聚合酶鏈反應(PCR)技術而與任何所需之抗體可變區框架及恆定區DNA序列一起合成。熟習此項技術者可自基因序列資料庫(諸如GenBank®)廣泛獲得編碼可變區框架及恆定區之DNA。根據Kabat編號系統(Kabat等人，1987於*Sequences of Proteins of Immunological Interest*中，U.S. Department of Health and Human Services, NIH, USA)，上述每一CDR一般均位於重鏈之31-35(CDR-H1)、50-65(CDR-H2)及95-102(CDR-H3)位置處及輕鏈之24-34(CDR-L1)、50-56(CDR-L2)及89-97(CDR-L3)位置處之可變區框架中。

一旦合成，可根據任何多種熟知之供使用任何數目之已知表現

載體進行核酸切除、連接、轉型及轉染之程序來繁殖及表現編碼本發明之抗體或其片段之DNA。因此，在某些實施例中，較佳在原核宿主中表現抗體片段，諸如大腸桿菌(*Escherichia coli*)(參見例如Pluckthun等人，1989 *Methods Enzymol.* 178:497-515)中。在某些其他實施例中，較佳可在真核宿主細胞中表現抗體或其片段，包括酵母(例如，釀酒酵母(Saccharomyces cerevisiae)、裂殖酵母(Schizosaccharomyces pombe)及甲醇酵母(Pichia pastoris))、動物細胞(包括哺乳動物細胞)或植物細胞。合適動物細胞之實例包括(但不限於)骨髓瘤(諸如小鼠NSO株)、COS、CHO或融合瘤細胞。植物細胞之實例包括煙草、玉米、大豆及稻米細胞。

可製備一或多種含有編碼抗體可變區及/或恆定區之DNA的可複製表現載體且其用於轉型適當細胞株，例如，非生產骨髓瘤細胞株(諸如小鼠NSO株)或細菌(諸如大腸桿菌(E. coli))，其中將發生抗體之產生。為獲得有效轉錄及轉譯，各載體中之DNA序列應包括適當之調節序列，尤其為操作性連接至可變結構域序列之啟動子及前導序列。通常熟知且常規使用以此方式產生抗體之特定方法。例如，由Maniatis等人描述了基本之分子生物學程序(*Molecular Cloning, A Laboratory Manual*，第2版，Cold Spring Harbor Laboratory, New York, 1989；亦參見Maniatis等人，第3版，Cold Spring Harbor Laboratory, New York, (2001))。可如Sanger等人(PNAS 74:5463, (1977))及Amersham International plc測序手冊中所述來進行DNA測序，且可根據此項技術中已知之方法來進行定點突變(Kramer等人，*Nucleic Acids Res.* 12:9441, (1984)；Kunkel Proc. *Natl. Acad. Sci. USA*

82:488-92 (1985)；Kunkel等人，*Methods in Enzymol.* 154:367-82 (1987)；Anglian Biotechnology Ltd手冊)。此外，諸多出版物描述適用於藉由操控DNA、產生表現載體及轉型並培養適當細胞來製備抗體之技術(Mountain A及Adair, J R於*Biotechnology and Genetic Engineering Reviews*中(Tombs, M P編，10，第1章，1992, Intercept, Andover, UK)；"Current Protocols in Molecular Biology", 1999, F.M. Ausubel編，Wiley Interscience, New York)。

當需要改良根據本發明之含有一或多個上述CDR之抗體的親合力時，此可藉由多種親合力成熟實驗程序而獲得，包括保留CDR(Yang等人，*J. Mol. Biol.*, 254, 392-403, 1995)、鏈改組(Marks等人，*Bio/Technology*, 10, 779-783, 1992)、使用大腸桿菌之突變菌株(Low等人，*J. Mol. Biol.*, 250, 350-368, 1996)、DNA改組(Patten等人，*Curr. Opin. Biotechnol.*, 8, 724-733, 1997)、噬菌體呈現(Thompson等人，*J. Mol. Biol.*, 256, 7-88, 1996)及有性PCR(Crameri等人，*Nature*, 391, 288-291, 1998)。Vaughan等人(*Nature Biotechnology*, 16, 535-539, 1998)討論了所有該等親合力成熟之方法。

根據本發明之其他抗體可藉由如本文所述及此項技術中已知之習知免疫及細胞融合程序而獲得。可使用多種已知技術來產生本發明之單株抗體。一般而言，結合至特異性抗原之單株抗體可藉由熟習此項技術者已知之方法而獲得(參見，例如Kohler等人，*Nature* 256:495, 1975；Coligan等人編，*Current Protocols in Immunology*, 1:2.5.12.6.7 (John Wiley & Sons 1991)；美國專利第RE 32,011號、第4,902,614號、第4,543,439號及第4,411,993號；*Monoclonal Antibodies,*

Hybridomas: A New Dimension in Biological Analyses, Plenum Press, Kennett、McKearn及Bechtol編(1980)；及*Antibodies: A Laboratory Manual*, Harlow及Lane編，Cold Spring Harbor Laboratory Press (1988)；Picksley等人，於*DNA Cloning 2: Expression Systems*中之"Production of monoclonal antibodies against proteins expressed in E. coli"，第2版，Glover等人編，第93頁(Oxford University Press 1995))。可使用任何合適之標準技術，諸如蛋白水解消化，或視情況藉由在溫和還原二硫鍵及烷基化之後蛋白水解消化(例如，使用木瓜蛋白酶或胃蛋白酶)而自其衍生抗體片段。或者，如本文所述，該等片段亦可藉由重組基因工程技術而產生。

如此項技術中已知，可根據此項技術中已知及本文所述之方法，以包含SEQ ID NO：1之人類殼硬蛋白或其片段之免疫原對動物，例如，大鼠、倉鼠、兔，或較佳為小鼠(包括例如轉殖基因或基因剔除小鼠)注射而獲得單株抗體。在初始注射之後及/或追加注射之後，可藉由使用此項技術中已知及本文所述之若干種免疫偵測方法之任一種獲得血清樣本且偵測結合至人類殼硬蛋白或肽之抗體的存在來監控特異性抗體產生之存在。自產生所要抗體之動物移除淋巴樣細胞(來自脾或淋巴結之最常見細胞)以獲得B-淋巴細胞。隨後使B-淋巴細胞與藥物敏化骨髓瘤細胞融合搭配物融合，較佳為免疫動物同源且視情況具有其他所需特性之骨髓瘤細胞融合搭配物(例如，不可表現內源Ig基因產物，例如P3X63-Ag 8.653(ATCC No. CRL 1580)、NSO、SP20)，以產生融合瘤，其為永生真核細胞株。可將淋巴(例如，脾)細胞與骨髓瘤細胞與膜融合促進劑，諸如聚乙二醇或非離子型清潔

劑，組合數分鐘，且隨後以低密度塗於支撐融合瘤細胞生長而不支撐未融合之骨髓瘤細胞生長之選擇性培養基上。較佳選擇培養基為HAT(次黃嘌呤、胺基喋呤、胸苷)。足夠時間之後，通常約一至兩週，觀察到細胞集落。分離單一集落，且可使用此項技術已知及本文所述之多種免疫分析之任一種來測試細胞所產生之抗體與人類殼硬蛋白之結合活性。選殖融合瘤(例如，藉由有限之稀釋選殖或藉由軟瓊脂斑點分離)且選擇並培養產生對殼硬蛋白具特異性之抗體的陽性純系。可將來自融合瘤培養基之單株抗體自融合瘤培養基之上清層分離。用於產生鼠系單株抗體之另一方法為將融合瘤細胞注射入同源小鼠之腹膜腔，例如，經處理之小鼠(例如，經降植烷引發)，以促進形成含有單株抗體之腹水。可藉由多種發展成熟之技術來分離及純化單株抗體。該等分離技術包括以蛋白-A瓊脂糖之親合性層析、尺寸排阻層析及離子交換層析(參見，例如第2.7.1-2.7.12頁及第2.9.1-2.9.3頁之Coligan；Baines等人，於*Methods in Molecular Biology*，*第10卷*，第79-104頁之"Purification of Immunoglobulin G (IgG),"(The Humana Press, Inc. 1992))。可使用基於抗體之特定特性(例如，重鏈或輕鏈同型，結合特異性，等)選擇之適當配位體，藉由親合性層析法來純化單株抗體。固定於固體支撐物上之合適配位體之實例包括蛋白A、蛋白G、抗恆定區(輕鏈或重鏈)抗體、抗獨特型抗體及TGF-β結合蛋白，或其片段或變異體。

本發明之抗體亦可為人類單株抗體。可藉由熟習此項技術者所熟悉之任何多種技術來產生人類單株抗體。該等方法包括(但不限於)人類周邊血液細胞(例如，含有B淋巴細胞)之伊波病毒(Epstein Barr

Virus，EBV)轉型、人類B細胞之活體外免疫、來自載有插入之人類免疫球蛋白基因之經免疫轉殖基因小鼠之脾細胞的融合、自人類免疫球蛋白V區噬菌體庫分離，或此項技術中已知且基於本文揭示案之其他程序。例如，可自已經工程化以產生回應抗原攻擊之特異性人類抗體之轉殖基因小鼠來獲得人類單株抗體。用於自轉殖基因小鼠獲得人類抗體之方法描述於以下文獻中，例如Green等人，*Nature Genet.* 7:13, 1994；Lonberg等人，*Nature* 368:856, 1994；Taylor等人，*Int. Immun.* 6:579, 1994；美國專利第5,877,397號；Bruggemann等人，1997 *Curr. Opin. Biotechnol.* 8:455-58；Jakobovits等人，1995 *Ann. N. Y. Acad. Sci.* 764:525-35。在此技術中，將人類重鏈及輕鏈基因座元件引入至源於含有內源重鏈及輕鏈基因座之靶向破壞之胚胎幹細胞株的小鼠菌株中(亦參見Bruggemann等人，*Curr. Opin. Biotechnol.* 8:455-58 (1997))。例如，人類免疫球蛋白轉基因可為微小基因構造，或為酵母人工染色體上之轉基因座，其在小鼠淋巴組織中經受B細胞特異性DNA重排及超突變。人類單株抗體可藉由免疫轉殖基因小鼠而獲得，隨後可產生對殼硬蛋白具有特異性之人類抗體。根據本文所述之方法，經免疫轉殖基因小鼠之淋巴樣細胞可用於產生分泌人類抗體之融合瘤。亦可自經免疫動物之血液獲得含有人類抗體之多株血清。

另一種用於產生本發明之人類抗體之方法包括藉由EBV轉型來永生化人類周邊血液細胞。參見例如，美國專利第4,464,456號。此種產生特異性結合至殼硬蛋白之單株抗體的永生化B細胞株(或類淋巴母細胞株)可藉由如本文所提供之免疫偵測方法(例如ELISA)來識別，且隨後藉由標準選殖技術而分離。根據此項技術中已知之方法，可藉由將

經轉型細胞株與鼠骨髓瘤融合以產生小鼠-人類雜交細胞株，來改良產生抗-殼硬蛋白抗體之類淋巴母細胞株的穩定性(參見例如，Glasky等人，*Hybridoma* 8:377-89 (1989))。又一種產生人類單株抗體之方法為活體外免疫，其包括以人類殼硬蛋白引發人類脾B細胞，繼而將經引發之B細胞與異種雜交融合搭配物融合。參見例如，Boerner等人，1991 *J. Immunol.* 147:86-95。

在某些實施例中，選擇產生抗-人類殼硬蛋白抗體之B細胞且根據此項技術中(WO 92/02551；美國專利第5,627,052號；Babcook等人，*Proc. Natl. Acad. Sci. USA* 93:7843-48 (1996))已知及本文所述之分子生物學技術，自B細胞選殖輕鏈及重鏈可變區。藉由選擇產生特異性結合至殼硬蛋白之抗體的細胞，可將經免疫動物之B細胞自脾、淋巴結或周邊血液樣本中分離。B細胞亦可自人類分離，例如，自周邊血液樣本分離。此項技術中熟知用於偵測產生具有所要特異性之抗體之單一B細胞的方法，例如，藉由斑點形成、螢光激活細胞分類、活體外刺激繼而偵測特異性抗體，及其類似方法。例如，選擇產生特異性抗體之B細胞的方法包括在含有人類殼硬蛋白之軟瓊脂中製備B細胞之單一細胞懸浮液。B細胞所產生之特異性抗體與抗原之結合導致形成複合物，其可為可見之免疫沉澱物。在選擇產生所要抗體之B細胞之後，可根據此項技術中已知及本文所述之方法，藉由分離及擴增DNA或mRNA來選殖特異性抗體基因。

額外之用於獲得本發明之抗體之方法為藉由噬菌體呈現。參見，例如，Winter等人，1994 *Annu. Rev. Immunol.* 12:433-55；Burton等人，1994 *Adv. Immunol.* 57:191-280。可在噬菌體載體中產生人類或

鼠免疫球蛋白可變區基因組合庫，該等噬菌體載體可經篩檢以選擇特異性結合至TGF-β結合蛋白或其變異體或片段之Ig片段(Fab、Fv、sFv或其多聚體)。參見，例如美國專利第5,223,409號；Huse等人，1989 *Science* 246:1275-81；Sastry等人，*Proc. Natl. Acad. Sci. USA* 86:5728-32 (1989)；Alting-Mees等人，*Strategies in Molecular Biology* 3:1-9 (1990)；Kang等人，1991 *Proc. Natl. Acad. Sci. USA* 88:4363-66；Hoogenboom等人，1992 *J. Molec. Biol.* 227:381-388；Schlebusch等人，1997 *Hybridoma* 16:47-52及其中引用之文獻。例如，可將含有複數個編碼Ig可變區片段之聚核苷酸序列之庫插入具有編碼噬菌體外殼蛋白之序列之框架中之絲狀噬菌體基因組中，諸如M13或其變異體。融合蛋白可為外殼蛋白與輕鏈可變區結構域及/或與重鏈可變區結構域之融合。根據某些實施例，亦可在噬菌體顆粒上呈現免疫球蛋白Fab片段(參見，例如美國專利第5,698,426號)。

亦可在λ噬菌體中製備重鏈及輕鏈免疫球蛋白cDNA表現庫，例如使用λ免疫Zap™(H)及λ免疫Zap™(L)載體(Stratagene, La Jolla, California)。簡言之，自B細胞群分離mRNA，且用於在λ免疫Zap(H)及λ免疫Zap(L)載體中產生重鏈及輕鏈免疫球蛋白cDNA表現庫。該等載體可經個別篩檢或共表現以形成Fab片段或抗體(參見Huse等人，上文；亦參見Sastry等人，上文)。其後，可將陽性斑點轉化為允許高水平表現來自大腸桿菌之單株抗體片段的非溶解性質體。

在一實施例中，在融合瘤中使用核苷酸引子擴增表現感興趣單株抗體之基因可變區。該等引子可藉由熟習此項技術者來合成，或可購自市售來源。(參見，例如Stratagene(La Jolla, California)，其出售

用於小鼠及人類可變區之引子，其中包括用於V_{Ha}、V_{Hb}、V_{Hc}、V_{Hd}、C_{H1}、V_L及C_L區之引子。)該等引子可用於擴增重鏈或輕鏈可變區，其隨後可分別插入諸如免疫ZAP^{TM}H或免疫ZAP^{TM}L(Stratagene)之載體中。隨後可將該等載體引入大腸桿菌、酵母或基於哺乳動物之系統中以供表現。可使用該等方法來產生大量含有V_H及V_L結構域之融合的單鏈蛋白(參見Bird等人，*Science* 242:423-426, 1988)。

一旦已使用任何上述免疫及其他技術獲得產生根據本發明之抗體的細胞，則可根據本文所述之標準方法自其分離且擴增DNA或mRNA來選殖特異性抗體基因。可如先前所述對自其產生之抗體進行測序且操控所識別之CDR及編碼該等CDR之DNA，以產生根據本發明之其他抗體。

結合劑較佳特異性結合至殼硬蛋白。如同所有結合劑及結合分析，熟習此項技術者意識到，結合劑不應可偵測結合至其以供治療有效且合適之各種部分的列表將詳盡且不合實際。因此，對於本文所揭示之結合劑，術語"特異性結合"係指結合劑以與其結合至無關對照蛋白之親合力相比較大之親和力結合至殼硬蛋白(較佳為人類殼硬蛋白)的能力。對照蛋白較佳為雞蛋白溶菌酶。結合劑較佳以大於對照蛋白之親合力至少50、100、250、500、1000或10,000倍之親合力結合至殼硬蛋白。對於人類殼硬蛋白而言，結合劑可具有小於或等於$1x10^{-7}$ M、小於或等於$1x10^{-8}$ M、小於或等於$1x10^{-9}$ M、小於或等於$1x10^{-10}$ M、小於或等於$1x10^{-11}$ M或小於或等於$1x10^{-12}$ M之結合親合力。

可藉由親合力ELISA分析來測定親合力。在某些實施例中，可藉由BIAcore分析來測定親合力。在某些實施例中，可藉由動力學方法

來測定親合力。在某些實施例中，可藉由平衡/溶液方法來測定親合力。該等方法在本文中進一步詳述或為此項技術所已知。

本發明之殼硬蛋白結合劑較佳在本文所述之基於細胞之分析中及/或在本文所述之活體內分析中調節殼硬蛋白功能，及/或結合至本文所述之一或多種抗原決定基，及/或交叉阻斷本申請案中所述抗體之一的結合，及/或由本申請案所述抗體之一而交叉阻斷其與殼硬蛋白之結合。因此，可使用本文所述之分析來識別該等結合劑。

在某些實施例中，藉由首先識別抗體而產生結合劑，該等抗體結合至本文所提供之一或多種抗原決定基，及/或在本文所述之基於細胞及/或活體內分析中中和，及/或交叉阻斷本申請案中所述之抗體，及/或由本申請案中所述抗體之一而交叉阻斷其與殼硬蛋白之結合。隨後將來自該等抗體之CDR區用於插入適當生物相容性框架中，以產生殼硬蛋白結合劑。結合劑之非-CDR部分可包含胺基酸，或可為非蛋白分子。本文所述之分析允許表徵結合劑。本發明之結合劑較佳為本文所界定之抗體。

熟習此項技術者應瞭解，某些蛋白，諸如抗體，可經受多種轉譯後修飾。該等修飾之類型及程度常取決於用於表現蛋白之宿主細胞株以及培養條件。該等修飾可包括糖基化、甲硫胺酸氧化、二酮基哌嗪形成、天冬胺酸異構化及天冬醯胺酸脫醯胺中之改變。常見修飾為歸因於羧肽酶作用之羧基末端鹼性殘基(諸如離胺酸或精胺酸)之流失(如Harris, RJ. *Journal of Chromatography* 705:129-134, 1995中所述)。

下文描述稱為Ab-A、Ab-B、Ab-C、Ab-D及Ab-1之抗體。"HC"係指重鏈且"LC"係指輕鏈。對於下文之某些抗體，CDR經陰影框處理

且恆定區(C)以粗斜體顯示。

Ab-D

抗體D(本文亦稱為Ab-D及Mab-D)為小鼠抗體，其展示與殼硬蛋白之高親合力結合。圖18中展示Ab-D之BIAcore結合圖案。

成熟形式Ab-D輕鏈(移除訊號肽)之胺基酸序列：

1 DVQMIQSPSS LSASLGDIVT MTCQASQGTS INLNWFQQKP GKAPKLLIYG
51 SSNLEDGVPS RFSGSRYGTD FTLTISSLED EDLATYFCLQ HSYLPYTFGG
101 GTKLEIK***RAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI***
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:7)

編碼成熟形式Ab-D LC(移除訊號肽)之核酸序列如下：

1 GATGTCCAGA TGATTCAGTC TCCATCCTCC CTGTCTGCAT CTTTGGGAGA
51 CATAGTCACC ATGACTTGCC AGGCAAGTCA GGGCACTAGC ATTAATTTAA
101 ACTGGTTTCA GCAAAAACCA GGGAAGGCTC CTAAGCTCCT GATCTATGGT
151 TCAAGCAACT TGGAAGATGG GGTCCCATCA AGGTTCAGTG GCAGTAGATA
201 TGGGACAGAT TTCACTCTCA CCATCAGCAG CCTGGAGGAT GAAGATCTGG
251 CAACTTATTT CTGTCTACAA CATAGTTATC TCCCGTACAC GTTCGGAGGG
301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID NO:8)

包括訊號肽之Ab-D LC的胺基酸序列如下：

1 MNTRAPAEFL GFLLLWFLGA RCDVQMIQSP SSLSASLGDI VTMTCQASQG
51 TSINLNWFQQ KPGKAPKLLI YGSSNLEDGV PSRFSGSRYG TDFTLTISSL
101 EDEDLATYFC LQHSYLPYTF GGGTKLEIKR ADAAPTVSIF PPSSEQLTSG
151 GASVVCFLNN FYPKDINVKW KIDGSERQNG VLNSWTDQDS KDSTYSMSST
201 LTLTKDEYER HNSYTCEATH KTSTSPIVKS FNRNEC (SEQ ID NO:9)

包括訊號肽編碼序列之Ab-D LC的核酸序列：

1 ATGAACACGA GGGCCCCTGC TGAGTTCCTT GGGTTCCTGT TGCTCTGGTT
51 TTTAGGTGCC AGATGTGATG TCCAGATGAT TCAGTCTCCA TCCTCCCTGT

101 CTGCATCTTT GGGAGACATA GTCACCATGA CTTGCCAGGC AAGTCAGGGC
151 ACTAGCATTA ATTTAAACTG GTTTCAGCAA AAACCAGGGA AGGCTCCTAA
201 GCTCCTGATC TATGGTTCAA GCAACTTGGA AGATGGGGTC CCATCAAGGT
251 TCAGTGGCAG TAGATATGGG ACAGATTTCA CTCTCACCAT CAGCAGCCTG
301 GAGGATGAAG ATCTGGCAAC TTATTTCTGT CTACAACATA GTTATCTCCC
351 GTACACGTTC GGAGGGGGGA CCAAGCTGGA AATAAAACGG GCTGATGCTG
401 CACCAACTGT ATCCATCTTC CCACCATCCA GTGAGCAGTT AACATCTGGA
451 GGTGCCTCAG TCGTGTGCTT CTTGAACAAC TTCTACCCCA AAGACATCAA
501 TGTCAAGTGG AAGATTGATG GCAGTGAACG ACAAAATGGC GTCCTGAACA
551 GTTGGACTGA TCAGGACAGC AAAGACAGCA CCTACAGCAT GAGCAGCACC
601 CTCACGTTGA CCAAGGACGA GTATGAACGA CATAACAGCT ATACCTGTGA
651 GGCCACTCAC AAGACATCAA CTTCACCCAT TGTCAAGAGC TTCAACAGGA
701 ATGAGTGTTA G (SEQ ID NO:10)

成熟形式(移除訊號肽)Ab-D HC重鏈之胺基酸序列如下：

1 EVQLQQSGPE LVTPGASVKI SCKASGYTFT DHYMSWVKQS HGKSLEWIGD
51 INPYSGETTY NQKFKGTATL TVDKSSSIAY MEIRGLTSED SAVYYCARDD
101 YDASPFAYWG QGTLVTVSA***A KTTPPSVYPL APGSAAQTNS MVTLGCLVKG***
151 YFPEPVTVTW NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT
201 CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT
251 LTPKVTCVVV DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS
301 ELPIMHQDWL NGKEFKCRVN SPAFPAPIEK TISKTKGRPK APQVYTIPPP
351 KEQMAKDKVS LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMDTDGSY
401 FIYSKLNVQK SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK (SEQ ID NO:11)

編碼成熟形式(移除訊號肽)Ab-D HC之核酸序列為：

1 GAGGTCCAGC TGCAACAGTC TGGACCTGAA CTGGTGACGC CTGGGGCTTC
51 AGTGAAGATA TCTTGTAAGG CTTCTGGATA CACATTCACT GACCACTACA
101 TGAGCTGGGT GAAGCAGAGT CATGGAAAAA GCCTTGAGTG GATTGGAGAT
151 ATTAATCCCT ATTCTGGTGA AACTACCTAC AACCAGAAGT TCAAGGGCAC
201 GGCCACATTG ACTGTAGACA AGTCTTCCAG TATAGCCTAC ATGGAGATCC
251 GCGGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGAGATGAT
301 TACGACGCCT CTCCGTTTGC TTACTGGGGC CAAGGGACTC TGGTCACTGT
351 CTCTGCAGCC AAAACGACAC CCCCATCTGT CTATCCACTG GCCCCTGGAT
401 CTGCTGCCCA AACTAACTCC ATGGTGACCC TGGGATGCCT GGTCAAGGGC
451 TATTTCCCTG AGCCAGTGAC AGTGACCTGG AACTCTGGAT CCCTGTCCAG
501 CGGTGTGCAC ACCTTCCCAG CTGTCCTGCA GTCTGACCTC TACACTCTGA
551 GCAGCTCAGT GACTGTCCCC TCCAGCACCT GGCCCAGCGA GACCGTCACC
601 TGCAACGTTG CCCACCCGGC CAGCAGCACC AAGGTGGACA AGAAAATTGT
651 GCCCAGGGAT TGTGGTTGTA AGCCTTGCAT ATGTACAGTC CCAGAAGTAT
701 CATCTGTCTT CATCTTCCCC CCAAAGCCCA AGGATGTGCT CACCATTACT
751 CTGACTCCTA AGGTCACGTG TGTTGTGGTA GACATCAGCA AGGATGATCC

801 CGAGGTCCAG TTCAGCTGGT TTGTAGATGA TGTGGAGGTG CACACAGCTC
851 AGACGCAACC CCGGGAGGAG CAGTTCAACA GCACTTTCCG CTCAGTCAGT
901 GAACTTCCCA TCATGCACCA GGACTGGCTC AATGGCAAGG AGTTCAAATG
951 CAGGGTCAAC AGTCCAGCTT TCCCTGCCCC CATCGAGAAA ACCATCTCCA
1001 AAACCAAAGG CAGACCGAAG GCTCCACAGG TGTACACCAT TCCACCTCCC
1051 AAGGAGCAGA TGGCCAAGGA TAAAGTCAGT CTGACCTGCA TGATAACAGA
1101 CTTCTTCCCT GAAGACATTA CTGTGGAGTG GCAGTGGAAT GGGCAGCCAG
1151 CGGAGAACTA CAAGAACACT CAGCCCATCA TGGACACAGA TGGCTCTTAC
1201 TTCATCTACA GCAAGCTCAA TGTGCAGAAG AGCAACTGGG AGGCAGGAAA
1251 TACTTTCACC TGCTCTGTGT TACATGAGGG CCTGCACAAC CACCATACTG
1301 AGAAGAGCCT CTCCCACTCT CCTGGTAAAT GA (SEQ ID NO:12)

包括訊號肽之Ab-D HC之胺基酸序列為：

1 MRCRWIFLFL LSGTAGVLSE VQLQQSGPEL VTPGASVKIS CKASGYTFTD
51 HYMSWVKQSH GKSLEWIGDI NPYSGETTYN QKFKGTATLT VDKSSSIAYM
101 EIRGLTSEDS AVYYCARDDY DASPFAYWGQ GTLVTVSAAK TTPPSVYPLA
151 PGSAAQTNSM VTLGCLVKGY FPEPVTVTWN SGSLSSGVHT FPAVLQSDLY
201 TLSSSVTVPS STWPSETVTC NVAHPASSTK VDKKIVPRDC GCKPCICTVP
251 EVSSVFIFPP KPKDVLTITL TPKVTCVVVD ISKDDPEVQF SWFVDDVEVH
301 TAQTQPREEQ FNSTFRSVSE LPIMHQDWLN GKEFKCRVNS PAFPAPIEKT
351 ISKTKGRPKA PQVYTIPPPK EQMAKDKVSL TCMITDFFPE DITVEWQWNG
401 QPAENYKNTQ PIMDTDGSYF IYSKLNVQKS NWEAGNTFTC SVLHEGLHNH
451 HTEKSLSHSP GK (SEQ ID NO:13)

包括訊號肽編碼序列之Ab-D HC之核酸序列為：

1 ATGAGATGCA GGTGGATCTT TCTCTTTCTC CTGTCAGGAA CTGCAGGTGT
51 CCTCTCTGAG GTCCAGCTGC AACAGTCTGG ACCTGAACTG GTGACGCCTG
101 GGGCTTCAGT GAAGATATCT TGTAAGGCTT CTGGATACAC ATTCACTGAC
151 CACTACATGA GCTGGGTGAA GCAGAGTCAT GGAAAAAGCC TTGAGTGGAT
201 TGGAGATATT AATCCCTATT CTGGTGAAAC TACCTACAAC CAGAAGTTCA
251 AGGGCACGGC CACATTGACT GTAGACAAGT CTTCCAGTAT AGCCTACATG
301 GAGATCCGCG GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
351 AGATGATTAC GACGCCTCTC CGTTTGCTTA CTGGGGCCAA GGGACTCTGG
401 TCACTGTCTC TGCAGCCAAA ACGACACCCC CATCTGTCTA TCCACTGGCC
451 CCTGGATCTG CTGCCCAAAC TAACTCCATG GTGACCCTGG GATGCCTGGT
501 CAAGGGCTAT TTCCCTGAGC CAGTGACAGT GACCTGGAAC TCTGGATCCC
551 TGTCCAGCGG TGTGCACACC TTCCCAGCTG TCCTGCAGTC TGACCTCTAC
601 ACTCTGAGCA GCTCAGTGAC TGTCCCCTCC AGCACCTGGC CCAGCGAGAC
651 CGTCACCTGC AACGTTGCCC ACCCGGCCAG CAGCACCAAG GTGGACAAGA
701 AAATTGTGCC CAGGGATTGT GGTTGTAAGC CTTGCATATG TACAGTCCCA
751 GAAGTATCAT CTGTCTTCAT CTTCCCCCCA AAGCCCAAGG ATGTGCTCAC

801 CATTACTCTG ACTCCTAAGG TCACGTGTGT TGTGGTAGAC ATCAGCAAGG
851 ATGATCCCGA GGTCCAGTTC AGCTGGTTTG TAGATGATGT GGAGGTGCAC
901 ACAGCTCAGA CGCAACCCCG GGAGGAGCAG TTCAACAGCA CTTTCCGCTC
951 AGTCAGTGAA CTTCCCATCA TGCACCAGGA CTGGCTCAAT GGCAAGGAGT
1001 TCAAATGCAG GGTCAACAGT CCAGCTTTCC CTGCCCCCAT CGAGAAAACC
1051 ATCTCCAAAA CCAAAGGCAG ACCGAAGGCT CCACAGGTGT ACACCATTCC
1101 ACCTCCCAAG GAGCAGATGG CCAAGGATAA AGTCAGTCTG ACCTGCATGA
1151 TAACAGACTT CTTCCCTGAA GACATTACTG TGGAGTGGCA GTGGAATGGG
1201 CAGCCAGCGG AGAACTACAA GAACACTCAG CCCATCATGG ACACAGATGG
1251 CTCTTACTTC ATCTACAGCA AGCTCAATGT GCAGAAGAGC AACTGGGAGG
1301 CAGGAAATAC TTTCACCTGC TCTGTGTTAC ATGAGGGCCT GCACAACCAC
1351 CATACTGAGA AGAGCCTCTC CCACTCTCCT GGTAAATGA (SEQ ID NO:14)

Ab-D重鏈可變區中之CDR(互補判定區)序列如下：

CDR-H1: DHYMS (SEQ ID NO:39)

CDR-H2: DINPYSGETTYNQKFKG (SEQ ID NO:40)

CDR-H3: DDYDASPFAY (SEQ ID NO:41)

Ab-D輕鏈可變區CDR序列為：

CDR-L1: QASQGTSINLN (SEQ ID NO:42)

CDR-L2: GSSNLED (SEQ ID NO:43)

CDR-L3: LQHSYLPYT (SEQ ID NO:44)

Ab-C

抗體C(本文亦稱為Ab-C及Mab-C)為小鼠抗體，其展示與殼硬蛋白之高親合力結合。圖17中展示Ab-C之BIAcore結合圖案。成熟形式(移除訊號肽)Ab-C輕鏈之胺基酸序列如下：

1 DIVLTQSPAS LTVSLGLRAT ISCKASQSVD YDGDSYMNWY QQKPGQPPKL
51 LIYAASNLES GIPARFSGNG SGTDFTLNIH PVEEEDAVTY YCQQSNEDPW
101 TFGGGTKLEI K***RADAAPTVS IFPPSSEQLT SGGASVVCFL NNFYPKDINV***
151 KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS STLTLTKDEY ERHNSYTCEA
201 THKTSTSPIV KSFNRNEC (SEQ ID NO:15)

編碼成熟形式(移除訊號肽)Ab-C LC之核酸序列為：

1 GACATTGTGC TGACCCAATC TCCAGCTTCT TTGACTGTGT CTCTAGGCCT

51 GAGGGCCACC ATCTCCTGCA AGGCCAGCCA AAGTGTTGAT TATGATGGTG
101 ATAGTTATAT GAACTGGTAC CAGCAGAAAC CAGGACAGCC ACCCAAACTC
151 CTCATCTATG CTGCATCCAA TCTAGAATCT GGGATCCCAG CCAGGTTTAG
201 TGGCAATGGG TCTGGGACAG ACTTCACCCT CAACATCCAT CCTGTGGAGG
251 AGGAGGATGC TGTAACCTAT TACTGTCAAC AAAGTAATGA GGATCCGTGG
301 ACGTTCGGTG GAGGCACCAA GCTGGAAATC AAACGGGCTG ATGCTGCACC
351 AACTGTATCC ATCTTCCCAC CATCCAGTGA GCAGTTAACA TCTGGAGGTG
401 CCTCAGTCGT GTGCTTCTTG AACAACTTCT ACCCCAAAGA CATCAATGTC
451 AAGTGGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC TGAACAGTTG
501 GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC AGCACCCTCA
551 CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC CTGTGAGGCC
601 ACTCACAAGA CATCAACTTC ACCCATTGTC AAGAGCTTCA ACAGGAATGA
651 GTGTTAG (SEQ ID NO:16)

包括訊號肽之Ab-C LC之胺基酸序列為：

1 METDTILLWV LLLWVPGSTG DIVLTQSPAS LTVSLGLRAT ISCKASQSVD
51 YDGDSYMNWY QQKPGQPPKL LIYAASNLES GIPARFSGNG SGTDFTLNIH
101 PVEEEDAVTY YCQQSNEDPW TFGGGTKLEI KRADAAPTVS IFPPSSEQLT
151 SGGASVVCFL NNFYPKDINV KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS
201 STLTLTKDEY ERHNSYTCEA THKTSTSPIV KSFNRNEC (SEQ ID NO:17)

包括訊號肽編碼序列之Ab-C LC之核酸序列為：

1 ATGGAGACAG ACACAATCCT GCTATGGGTG CTGCTGCTCT GGGTTCCAGG
51 CTCCACTGGT GACATTGTGC TGACCCAATC TCCAGCTTCT TTGACTGTGT
101 CTCTAGGCCT GAGGGCCACC ATCTCCTGCA AGGCCAGCCA AAGTGTTGAT
151 TATGATGGTG ATAGTTATAT GAACTGGTAC CAGCAGAAAC CAGGACAGCC
201 ACCCAAACTC CTCATCTATG CTGCATCCAA TCTAGAATCT GGGATCCCAG
251 CCAGGTTTAG TGGCAATGGG TCTGGGACAG ACTTCACCCT CAACATCCAT
301 CCTGTGGAGG AGGAGGATGC TGTAACCTAT TACTGTCAAC AAAGTAATGA
351 GGATCCGTGG ACGTTCGGTG GAGGCACCAA GCTGGAAATC AAACGGGCTG
401 ATGCTGCACC AACTGTATCC ATCTTCCCAC CATCCAGTGA GCAGTTAACA
451 TCTGGAGGTG CCTCAGTCGT GTGCTTCTTG AACAACTTCT ACCCCAAAGA
501 CATCAATGTC AAGTGGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC
551 TGAACAGTTG GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC
601 AGCACCCTCA CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC
651 CTGTGAGGCC ACTCACAAGA CATCAACTTC ACCCATTGTC AAGAGCTTCA
701 ACAGGAATGA GTGTTAG (SEQ ID NO:18)

Ab-C重鏈

成熟形式(移除訊號肽)Ab-C HC之胺基酸序列為：

1 EVQLQQSGPE LVKPGTSVKM SCKASGYTFT DCYMNWVKQS HGKSLEWIGD
51 INPFNGGTTY NQKFKGKATL TVDKSSSTAY MQLNSLTSDD SAVYYCARSH
101 YYFDGRVPWD AMDYWGQGTS VTVSS***AKTTP PSVYPLAPGS AAQTNSMVTL***
151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW
201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
251 DVLTITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
301 TFRSVSELPI MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIM
401 DTDGSYFIYS KLNVQKSNWE AGNTFTCSVL HEGLHNHHTE KSLSHSPGK (SEQ ID NO:19)

編碼成熟形式(移除訊號肽)Ab-C HC之核酸序列如下：

1 GAGGTCCAGC TGCAACAATC TGGACCTGAG CTGGTGAAGC CTGGGACTTC
51 AGTGAAGATG TCCTGTAAGG CTTCTGGATA CACATTCACT GACTGCTACA
101 TGAACTGGGT GAAGCAGAGC CATGGGAAGA GCCTTGAATG GATTGGAGAT
151 ATTAATCCTT TCAACGGTGG TACTACCTAC AACCAGAAGT TCAAGGGCAA
201 GGCCACATTG ACTGTAGACA AATCCTCCAG CACAGCCTAC ATGCAGCTCA
251 ACAGCCTGAC ATCTGACGAC TCTGCAGTCT ATTACTGTGC AAGATCCCAT
301 TATTACTTCG ATGGTAGAGT CCCTTGGGAT GCTATGGACT ACTGGGGTCA
351 AGGAACCTCA GTCACCGTCT CCTCAGCCAA AACGACACCC CCATCTGTCT
401 ATCCACTGGC CCCTGGATCT GCTGCCCAAA CTAACTCCAT GGTGACCCTG
451 GGATGCCTGG TCAAGGGCTA TTTCCCTGAG CCAGTGACAG TGACCTGGAA
501 CTCTGGATCC CTGTCCAGCG GTGTGCACAC CTTCCCAGCT GTCCTGCAGT
551 CTGACCTCTA CACTCTGAGC AGCTCAGTGA CTGTCCCCTC CAGCACCTGG
601 CCCAGCGAGA CCGTCACCTG CAACGTTGCC CACCCGGCCA GCAGCACCAA
651 GGTGGACAAG AAAATTGTGC CCAGGGATTG TGGTTGTAAG CCTTGCATAT
701 GTACAGTCCC AGAAGTATCA TCTGTCTTCA TCTTCCCCCC AAAGCCCAAG
751 GATGTGCTCA CCATTACTCT GACTCCTAAG GTCACGTGTG TTGTGGTAGA
801 CATCAGCAAG GATGATCCCG AGGTCCAGTT CAGCTGGTTT GTAGATGATG
851 TGGAGGTGCA CACAGCTCAG ACGCAACCCC GGGAGGAGCA GTTCAACAGC
901 ACTTTCCGCT CAGTCAGTGA ACTTCCCATC ATGCACCAGG ACTGGCTCAA
951 TGGCAAGGAG TTCAAATGCA GGGTCAACAG TGCAGCTTTC CCTGCCCCCA
1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGCA GACCGAAGGC TCCACAGGTG
1051 TACACCATTC CACCTCCCAA GGAGCAGATG GCCAAGGATA AAGTCAGTCT
1101 GACCTGCATG ATAACAGACT TCTTCCCTGA AGACATTACT GTGGAGTGGC
1151 AGTGGAATGG GCAGCCAGCG GAGAACTACA AGAACACTCA GCCCATCATG
1201 GACACAGATG GCTCTTACTT CATCTACAGC AAGCTCAATG TGCAGAAGAG
1251 CAACTGGGAG GCAGGAAATA CTTTCACCTG CTCTGTGTTA CATGAGGGCC

1301 TGCACAACCA CCATACTGAG AAGAGCCTCT CCCACTCTCC TGGTAAATGA (SEQ ID NO:20)

包括訊號肽之Ab-C HC之胺基酸序列為：

1 MGWNWIFLFL LSGTAGVYSE VQLQQSGPEL VKPGTSVKMS CKASGYTFTD
51 CYMNWVKQSH GKSLEWIGDI NPFNGGTTYN QKFKGKATLT VDKSSSTAYM
101 QLNSLTSDDS AVYYCARSHY YFDGRVPWDA MDYWGQGTSV TVSSAKTTPP
151 SVYPLAPGSA AQTNSMVTLG CLVKGYFPEP VTVTWNSGSL SSGVHTFPAV
201 LQSDLYTLSS SVTVPSSTWP SETVTCNVAH PASSTKVDKK IVPRDCGCKP
251 CICTVPEVSS VFIFPPKPKD VLTITLTPKV TCVVVDISKD DPEVQFSWFV
301 DDVEVHTAQT QPREEQFNST FRSVSELPIM HQDWLNGKEF KCRVNSAAFP
351 APIEKTISKT KGRPKAPQVY TIPPPKEQMA KDKVSLTCMI TDFFPEDITV
401 EWQWNGQPAE NYKNTQPIMD TDGSYFIYSK LNVQKSNWEA GNTFTCSVLH
451 EGLHNHHTEK SLSHSPGK (SEQ ID NO:21)

包括訊號肽編碼序列之Ab-C HC之核酸序列為：

1 ATGGGATGGA ACTGGATCTT TCTCTTCCTC TTGTCAGGAA CTGCAGGTGT
51 CTACTCTGAG GTCCAGCTGC AACAATCTGG ACCTGAGCTG GTGAAGCCTG
101 GGACTTCAGT GAAGATGTCC TGTAAGGCTT CTGGATACAC ATTCACTGAC
151 TGCTACATGA ACTGGGTGAA GCAGAGCCAT GGGAAGAGCC TTGAATGGAT
201 TGGAGATATT AATCCTTTCA ACGGTGGTAC TACCTACAAC CAGAAGTTCA
251 AGGGCAAGGC CACATTGACT GTAGACAAAT CCTCCAGCAC AGCCTACATG
301 CAGCTCAACA GCCTGACATC TGACGACTCT GCAGTCTATT ACTGTGCAAG
351 ATCCCATTAT TACTTCGATG GTAGAGTCCC TTGGGATGCT ATGGACTACT
401 GGGGTCAAGG AACCTCAGTC ACCGTCTCCT CAGCCAAAAC GACACCCCCA
451 TCTGTCTATC CACTGGCCCC TGGATCTGCT GCCCAAACTA ACTCCATGGT
501 GACCCTGGGA TGCCTGGTCA AGGGCTATTT CCCTGAGCCA GTGACAGTGA
551 CCTGGAACTC TGGATCCCTG TCCAGCGGTG TGCACACCTT CCCAGCTGTC
601 CTGCAGTCTG ACCTCTACAC TCTGAGCAGC TCAGTGACTG TCCCCTCCAG
651 CACCTGGCCC AGCGAGACCG TCACCTGCAA CGTTGCCCAC CCGGCCAGCA
701 GCACCAAGGT GGACAAGAAA ATTGTGCCCA GGGATTGTGG TTGTAAGCCT
751 TGCATATGTA CAGTCCCAGA AGTATCATCT GTCTTCATCT TCCCCCCAAA
801 GCCCAAGGAT GTGCTCACCA TTACTCTGAC TCCTAAGGTC ACGTGTGTTG
851 TGGTAGACAT CAGCAAGGAT GATCCCGAGG TCCAGTTCAG CTGGTTTGTA
901 GATGATGTGG AGGTGCACAC AGCTCAGACG CAACCCCGGG AGGAGCAGTT
951 CAACAGCACT TTCCGCTCAG TCAGTGAACT TCCCATCATG CACCAGGACT
1001 GGCTCAATGG CAAGGAGTTC AAATGCAGGG TCAACAGTGC AGCTTTCCCT
1051 GCCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGCAGAC CGAAGGCTCC
1101 ACAGGTGTAC ACCATTCCAC CTCCCAAGGA GCAGATGGCC AAGGATAAAG
1151 TCAGTCTGAC CTGCATGATA ACAGACTTCT TCCCTGAAGA CATTACTGTG
1201 GAGTGGCAGT GGAATGGGCA GCCAGCGGAG AACTACAAGA ACACTCAGCC
1251 CATCATGGAC ACAGATGGCT CTTACTTCAT CTACAGCAAG CTCAATGTGC

1301 AGAAGAGCAA CTGGGAGGCA GGAAATACTT TCACCTGCTC TGTGTTACAT
1351 GAGGGCCTGC ACAACCACCA TACTGAGAAG AGCCTCTCCC ACTCTCCTGG
1401 TAAATGA (SEQ ID NO:22)

Ab-C重鏈可變區中之CDR(互補判定區)序列如下：

CDR-H1: DCYMN (SEQ ID NO:45)

CDR-H2: DINPFNGGTTYNQKFKG (SEQ ID NO:46)

CDR-H3: SHYYFDGRVPWDAMDY (SEQ ID NO:47)

Ab-C之輕鏈可變區CDR序列為：

CDR-L1: KASQSVDYDGDSYMN (SEQ ID NO:48)

CDR-L2: AASNLES (SEQ ID NO:49)

CDR-L3: QQSNEDPWT (SEQ ID NO:50)

Ab-A

抗體A(本文亦稱為Ab-A及Mab-A)為兔-小鼠嵌合抗體，其展示與殼硬蛋白之高親合力結合。圖15中展示Ab-A之BIAcore結合圖案。

Ab-A輕鏈

成熟形式(移除訊號肽)Ab-A LC之胺基酸序列：

1 AQVLTQTPAS VSAAVGGTVT INCQSSQSVY DNNWLAWFQQ KPGQPPKLLI
51 YDASDLASGV PSRFSGSGSG TQFTLTISGV QCADAATYYC QGAYNDVIYA
101 FGGGTEVVVK ***RTDAAPTVSI FPPSSEQLTS GGASVVCFLN NFYPKDINVK***
151 WKIDGSERQN GVLNSWTDQD SKDSTYSMSS TLTLTKDEYE RHNSYTCEAT
201 HKTSTSPIVK SFNRNEC (SEQ ID NO:23)

編碼成熟形式(移除訊號肽)Ab-A LC之核酸序列：

1 GCGCAAGTGC TGACCCAGAC TCCAGCCTCC GTGTCTGCAG CTGTGGGAGG
51 CACAGTCACC ATCAATTGCC AGTCCAGTCA GAGTGTTTAT GATAACAACT
101 GGTTAGCCTG GTTTCAGCAG AAACCAGGGC AGCCTCCCAA GCTCCTGATT
151 TATGATGCAT CCGATCTGGC ATCTGGGGTC CCATCGCGGT TCAGTGGCAG
201 TGGATCTGGG ACACAGTTCA CTCTCACCAT CAGCGGCGTG CAGTGTGCCG
251 ATGCTGCCAC TTACTACTGT CAAGGCGCTT ATAATGATGT TATTTATGCT
301 TTCGGCGGAG GGACCGAGGT GGTGGTCAAA CGTACGGATG CTGCACCAAC

351 TGTATCCATC TTCCCACCAT CCAGTGAGCA GTTAACATCT GGAGGTGCCT
401 CAGTCGTGTG CTTCTTGAAC AACTTCTACC CCAAAGACAT CAATGTCAAG
451 TGGAAGATTG ATGGCAGTGA ACGACAAAAT GGCGTCCTGA ACAGTTGGAC
501 TGATCAGGAC AGCAAAGACA GCACCTACAG CATGAGCAGC ACCCTCACGT
551 TGACCAAGGA CGAGTATGAA CGACATAACA GCTATACCTG TGAGGCCACT
601 CACAAGACAT CAACTTCACC CATTGTCAAG AGCTTCAACA GGAATGAGTG
651 TTAG (SEQ ID NO:24)

包括訊號肽之Ab-A LC之胺基酸序列為：

1 MDTRAPTQLL GLLLLWLPGA TFAQVLTQTP ASVSAAVGGT VTINCQSSQS
51 VYDNNWLAWF QQKPGQPPKL LIYDASDLAS GVPSRFSGSG SGTQFTLTIS
101 GVQCADAATY YCQGAYNDVI YAFGGGTEVV VKRTDAAPTV SIFPPSSEQL
151 TSGGASVVCF LNNFYPKDIN VKWKIDGSER QNGVLNSWTD QDSKDSTYSM
201 SSTLTLTKDE YERHNSYTCE ATHKTSTSPI VKSFNRNEC (SEQ ID NO:25)

包括訊號肽編碼序列之Ab-A LC之核酸序列為：

1 ATGGACACGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC TGCTCTGGCT
51 CCCAGGTGCC ACATTTGCGC AAGTGCTGAC CCAGACTCCA GCCTCCGTGT
101 CTGCAGCTGT GGGAGGCACA GTCACCATCA ATTGCCAGTC CAGTCAGAGT
151 GTTTATGATA ACAACTGGTT AGCCTGGTTT CAGCAGAAAC CAGGGCAGCC
201 TCCCAAGCTC CTGATTTATG ATGCATCCGA TCTGGCATCT GGGGTCCCAT
251 CGCGGTTCAG TGGCAGTGGA TCTGGGACAC AGTTCACTCT CACCATCAGC
301 GGCGTGCAGT GTGCCGATGC TGCCACTTAC TACTGTCAAG GCGCTTATAA
351 TGATGTTATT TATGCTTTCG GCGGAGGGAC CGAGGTGGTG GTCAAACGTA
401 CGGATGCTGC ACCAACTGTA TCCATCTTCC CACCATCCAG TGAGCAGTTA
451 ACATCTGGAG GTGCCTCAGT CGTGTGCTTC TTGAACAACT TCTACCCCAA
501 AGACATCAAT GTCAAGTGGA AGATTGATGG CAGTGAACGA CAAAATGGCG
551 TCCTGAACAG TTGGACTGAT CAGGACAGCA AAGACAGCAC CTACAGCATG
601 AGCAGCACCC TCACGTTGAC CAAGGACGAG TATGAACGAC ATAACAGCTA
651 TACCTGTGAG GCCACTCACA AGACATCAAC TTCACCCATT GTCAAGAGCT
701 TCAACAGGAA TGAGTGTTAG (SEQ ID NO:26)

成熟形式(移除訊號肽)Ab-A HC之胺基酸序列為：

1 QSLEESGGRL VTPGTPLTLT CTASGFSLSS YWMNWVRQAP GEGLEWIGTI
51 DSGGRTDYAS WAKGRFTISR TSTTMDLKMT SLTTGDTARY FCARNWNLWG
101 QGTLVTVSS***A STKGPSVYPL APGSAAQTNS MVTLGCLVKG YFPEPVTVTW***
151 NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT CNVAHPASST
201 KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT LTPKVTCVVV
251 DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS ELPIMHQDWL
301 NGKEFKCRVN SAAFPAPIEK TISKTKGRPK APQVYTIPPP KEQMAKDKVS
351 LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMNTNGSY FVYSKLNVQK

401 SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK (SEQ ID NO:27)

編碼成熟形式(移除訊號肽)Ab-A HC之核酸序列：

1 CAGTCGCTGG AGGAGTCCGG GGGTCGCCTG GTCACGCCTG GGACACCCCT
51 GACACTCACC TGCACAGCCT CTGGATTCTC CCTCAGTAGT TATTGGATGA
101 ACTGGGTCCG CCAGGCTCCA GGGGAGGGGC TGGAATGGAT CGGAACCATT
151 GATTCTGGTG GTAGGACGGA CTACGCGAGC TGGGCAAAAG GCCGATTCAC
201 CATCTCCAGA ACCTCGACTA CGATGGATCT GAAAATGACC AGTCTGACGA
251 CCGGGGACAC GGCCCGTTAT TTCTGTGCCA GAAATTGGAA CTTGTGGGGC
301 CAAGGCACCC TCGTCACCGT CTCGAGCGCT TCTACAAAGG GCCCATCTGT
351 CTATCCACTG GCCCCTGGAT CTGCTGCCCA AACTAACTCC ATGGTGACCC
401 TGGGATGCCT GGTCAAGGGC TATTTCCCTG AGCCAGTGAC AGTGACCTGG
451 AACTCTGGAT CCCTGTCCAG CGGTGTGCAC ACCTTCCCAG CTGTCCTGCA
501 GTCTGACCTC TACACTCTGA GCAGCTCAGT GACTGTCCCC TCCAGCACCT
551 GGCCCAGCGA GACCGTCACC TGCAACGTTG CCCACCCGGC CAGCAGCACC
601 AAGGTGGACA AGAAAATTGT GCCCAGGGAT TGTGGTTGTA AGCCTTGCAT
651 ATGTACAGTC CCAGAAGTAT CATCTGTCTT CATCTTCCCC CCAAAGCCCA
701 AGGATGTGCT CACCATTACT CTGACTCCTA AGGTCACGTG TGTTGTGGTA
751 GACATCAGCA AGGATGATCC CGAGGTCCAG TTCAGCTGGT TTGTAGATGA
801 TGTGGAGGTG CACACAGCTC AGACGCAACC CCGGGAGGAG CAGTTCAACA
851 GCACTTTCCG CTCAGTCAGT GAACTTCCCA TCATGCACCA GGACTGGCTC
901 AATGGCAAGG AGTTCAAATG CAGGGTCAAC AGTGCAGCTT TCCCTGCCCC
951 CATCGAGAAA ACCATCTCCA AAACCAAAGG CAGACCGAAG GCTCCACAGG
1001 TGTACACCAT TCCACCTCCC AAGGAGCAGA TGGCCAAGGA TAAAGTCAGT
1051 CTGACCTGCA TGATAACAGA CTTCTTCCCT GAAGACATTA CTGTGGAGTG
1101 GCAGTGGAAT GGGCAGCCAG CGGAGAACTA CAAGAACACT CAGCCCATCA
1151 TGGACACAGA TGGCTCTTAC TTCGTCTACA GCAAGCTCAA TGTGCAGAAG
1201 AGCAACTGGG AGGCAGGAAA TACTTTCACC TGCTCTGTGT TACATGAGGG
1251 CCTGCACAAC CACCATACTG AGAAGAGCCT CTCCCACTCT CCTGGTAAAT
1301 GA (SEQ ID NO:28)

包括訊號肽之Ab-A HC之胺基酸序列為：

1 METGLRWLLL VAVLKGVHCQ SLEESGGRLV TPGTPLTLTC TASGFSLSSY
51 WMNWVRQAPG EGLEWIGTID SGGRTDYASW AKGRFTISRT STTMDLKMTS
101 LTTGDTARYF CARNWNLWGQ GTLVTVSSAS TKGPSVYPLA PGSAAQTNSM
151 VTLGCLVKGY FPEPVTVTWN SGSLSSGVHT FPAVLQSDLY TLSSSVTVPS
201 STWPSETVTC NVAHPASSTK VDKKIVPRDC GCKPCICTVP EVSSVFIFPP
251 KPKDVLTITL TPKVTCVVVD ISKDDPEVQF SWFVDDVEVH TAQTQPREEQ
301 FNSTFRSVSE LPIMHQDWLN GKEFKCRVNS AAFPAPIEKT ISKTKGRPKA
351 PQVYTIPPPK EQMAKDKVSL TCMITDFFPE DITVEWQWNG QPAENYKNTQ
401 PIMNTNGSYF VYSKLNVQKS NWEAGNTFTC SVLHEGLHNH HTEKSLSHSP
451 GK (SEQ ID NO:29)

包括訊號肽編碼序列之Ab-A HC之核酸序列：

1 ATGGAGACTG GGCTGCGCTG GCTTCTCCTG GTCGCTGTGC TCAAAGGTGT
51 CCACTGTCAG TCGCTGGAGG AGTCCGGGGG TCGCCTGGTC ACGCCTGGGA
101 CACCCCTGAC ACTCACCTGC ACAGCCTCTG GATTCTCCCT CAGTAGTTAT
151 TGGATGAACT GGGTCCGCCA GGCTCCAGGG GAGGGGCTGG AATGGATCGG
201 AACCATTGAT TCTGGTGGTA GGACGGACTA CGCGAGCTGG GCAAAAGGCC
251 GATTCACCAT CTCCAGAACC TCGACTACGA TGGATCTGAA AATGACCAGT
301 CTGACGACCG GGGACACGGC CCGTTATTTC TGTGCCAGAA ATTGGAACTT
351 GTGGGGCCAA GGCACCCTCG TCACCGTCTC GAGCGCTTCT ACAAAGGGCC
401 CATCTGTCTA TCCACTGGCC CCTGGATCTG CTGCCCAAAC TAACTCCATG
451 GTGACCCTGG GATGCCTGGT CAAGGGCTAT TTCCCTGAGC CAGTGACAGT
501 GACCTGGAAC TCTGGATCCC TGTCCAGCGG TGTGCACACC TTCCCAGCTG
551 TCCTGCAGTC TGACCTCTAC ACTCTGAGCA GCTCAGTGAC TGTCCCCTCC
601 AGCACCTGGC CCAGCGAGAC CGTCACCTGC AACGTTGCCC ACCCGGCCAG
651 CAGCACCAAG GTGGACAAGA AAATTGTGCC CAGGGATTGT GGTTGTAAGC
701 CTTGCATATG TACAGTCCCA GAAGTATCAT CTGTCTTCAT CTTCCCCCCA
751 AAGCCCAAGG ATGTGCTCAC CATTACTCTG ACTCCTAAGG TCACGTGTGT
801 TGTGGTAGAC ATCAGCAAGG ATGATCCCGA GGTCCAGTTC AGCTGGTTTG
851 TAGATGATGT GGAGGTGCAC ACAGCTCAGA CGCAACCCCG GGAGGAGCAG
901 TTCAACAGCA CTTTCCGCTC AGTCAGTGAA CTTCCCATCA TGCACCAGGA
951 CTGGCTCAAT GGCAAGGAGT TCAAATGCAG GGTCAACAGT GCAGCTTTCC
1001 CTGCCCCCAT CGAGAAAACC ATCTCCAAAA CCAAAGGCAG ACCGAAGGCT
1051 CCACAGGTGT ACACCATTCC ACCTCCCAAG GAGCAGATGG CCAAGGATAA
1101 AGTCAGTCTG ACCTGCATGA TAACAGACTT CTTCCCTGAA GACATTACTG
1151 TGGAGTGGCA GTGGAATGGG CAGCCAGCGG AGAACTACAA GAACACTCAG
1201 CCCATCATGG ACACAGATGG CTCTTACTTC GTCTACAGCA AGCTCAATGT
1251 GCAGAAGAGC AACTGGGAGG CAGGAAATAC TTTCACCTGC TCTGTGTTAC
1301 ATGAGGGCCT GCACAACCAC CATACTGAGA AGAGCCTCTC CCACTCTCCT
1351 GGTAAATGA (SEQ ID NO:30)

Ab-A重鏈可變區中之CDR(互補判定區)序列如下：

CDR-H1: SYWMN (SEQ ID NO:51)

CDR-H2: TIDSGGRTDYASWAKG (SEQ ID NO:52)

CDR-H3: NWNL (SEQ ID NO:53)

Ab-A之輕鏈可變區CDR序列為：

CDR-L1: QSSQSVYDNNWLA (SEQ ID NO:54)

CDR-L2: DASDLAS (SEQ ID NO:55)

CDR-L3: QGAYNDVIYA (SEQ ID NO:56)

Ab-A經人化，且稱為抗體1(本文亦稱為Ab-1)，其具有以下序列：

包括訊號肽編碼序列之Ab-1 LC可變區之核酸序列為：

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGT
GCCACATTTGCTCAAGTTCTGACCCAGAGTCCAAGCAGTCTCTCCGCCAGCGTAGGC
GATCGTGTGACTATTACCTGTCAATCTAGTCAGAGCGTGTATGATAACAATTGGCTGG
CGTGGTACCAGCAAAAACCGGGCAAAGCCCCGAAGCTGCTCATCTATGACGCGTCC
GATCTGGCTAGCGGTGTGCCAAGCCGTTTCAGTGGCAGTGGCAGCGGTACTGACTTT
ACCCTCACAATTTCGTCTCTCCAGCCGGAAGATTTCGCCACTTACTATTGTCAAGGTG
CTTACAACGATGTGATTTATGCCTTCGGTCAGGGCACTAAAGTAGAAATCAAACGT
(SEQ ID NO:74)

包括訊號肽之Ab-1 LC可變區之胺基酸序列為：

MDTRAPTQLLGLLLLWLPGATFAQVLTQSPSSLSASVGDRVTITCQSSQSVYDNNWLAW
YQQKPGKAPKLLIYDASDLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQGAYNDVI
YAFGQGTKVEIKR (SEQ ID NO:75)

包括訊號肽編碼序列之Ab-1 HC可變區之核酸序列為：

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCACTGT
GAGGTGCAGCTGTTGGAGTCTGGAGGCGGGCTTGTCCAGCCTGGAGGGAGCCTGCG
TCTCTCTTGTGCAGCAAGCGGCTTCAGCTTATCCTCTTACTGGATGAATTGGGTGCGG
CAGGCACCTGGGAAGGGCCTGGAGTGGGTGGGCACCATTGATTCCGGAGGCCGTAC
AGACTACGCGTCTTGGGCAAAGGGCCGTTTCACCATTTCCCGCGACAACTCCAAAAA
TACCATGTACCTCCAGATGAACTCTCTCCGCGCAGAGGACACAGCACGTTATTACTGT
GCACGCAACTGGAATCTGTGGGGTCAAGGTACTCTTGTAACAGTCTCGAGC (SEQ ID
NO:76)

包括訊號肽之Ab-1 HC可變區之胺基酸序列：

METGLRWLLLVAVLKGVHCEVQLLESGGGLVQPGGSLRLSCAASGFSLSSYWMNWVRQ
APGKGLEWVGTIDSGGRTDYASWAKGRFTISRDNSKNTMYLQMNSLRAEDTARYYCAR
NWNLWGQGTLVTVSS (SEQ ID NO:77)

Ab-1重鏈可變區之CDR(互補判定區)序列如下：

CDR-H1: SYWMN (SEQ ID NO:51)

CDR-H2: TIDSGGRTDYASWAKG (SEQ ID NO:52)

CDR-H3: NWNL (SEQ ID NO:53)

Ab-1之輕鏈可變區CDR序列為：

CDR-L1: QSSQSVYDNNWLA (SEQ ID NO:54)

CDR-L2: DASDLAS (SEQ ID NO:55)

CDR-L3: QGAYNDVIYA (SEQ ID NO:56)

Ab-B

抗體B(本文亦稱為Ab-B及Mab-B)為小鼠抗體，其展示與殼硬蛋白之高親合力結合。圖16中展示Ab-B之BIAcore結合圖案。

Ab-B輕鏈

成熟形式(移除訊號肽)Ab-B LC之胺基酸序列為：

1 QIVLTQSPTI VSASPGEKVT LICSASSSVS FVDWFQQKPG TSPKRWIYRT
51 SNLGFGVPAR FSGGGSGTSH SLTISRMEAE DAATYYCQQR STYPPTFGAG
101 TKLELK***RADA APTVSIFPPS SEQLTSGGAS VVCFLNNFYP KDINVKWKID***
151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
201 TSPIVKSFNR NEC (SEQ ID NO:31)

編碼成熟形式(移除訊號肽)Ab-B LC之核酸序列為：

1 CAAATTGTTC TCACCCAGTC TCCAACAATC GTGTCTGCAT CTCCAGGGGA
51 GAAGGTCACC CTAATCTGCA GTGCCAGTTC AAGTGTAAGT TTCGTGGACT
101 GGTTCCAGCA GAAGCCAGGC ACTTCTCCCA AACGCTGGAT TTACAGAACA
151 TCCAACCTGG GTTTTGGAGT CCCTGCTCGC TTCAGTGGCG GTGGATCTGG
201 GACCTCTCAC TCTCTCACAA TCAGCCGAAT GGAGGCTGAA GATGCTGCCA
251 CTTATTACTG CCAGCAAAGG AGTACTTACC CACCCACGTT CGGTGCTGGG
301 ACCAAGCTGG AACTGAAACG GGCTGATGCT GCACCAACTG TATCCATCTT
351 CCCACCATCC AGTGAGCAGT TAACATCTGG AGGTGCCTCA GTCGTGTGCT
401 TCTTGAACAA CTTCTACCCC AAAGACATCA ATGTCAAGTG GAAGATTGAT
451 GGCAGTGAAC GACAAAATGG CGTCCTGAAC AGTTGGACTG ATCAGGACAG

501 CAAAGACAGC ACCTACAGCA TGAGCAGCAC CCTCACGTTG ACCAAGGACG
551 AGTATGAACG ACATAACAGC TATACCTGTG AGGCCACTCA CAAGACATCA
601 ACTTCACCCA TTGTCAAGAG CTTCAACAGG AATGAGTGTT AG (SEQ ID NO:32)

包括訊號肽之Ab-B LC之胺基酸序列為：

1 MHFQVQIFSF LLISASVIVS RGQIVLTQSP TIVSASPGEK VTLICSASSS
51 VSFVDWFQQK PGTSPKRWIY RTSNLGFGVP ARFSGGGSGT SHSLTISRME
101 AEDAATYYCQ QRSTYPPTFG AGTKLELKRA DAAPTVSIFP PSSEQLTSGG
151 ASVVCFLNNF YPKDINVKWK IDGSERQNGV LNSWTDQDSK DSTYSMSSTL
201 TLTKDEYERH NSYTCEATHK TSTSPIVKSF NRNEC (SEQ ID NO:33)

包括訊號肽編碼序列之Ab-B LC之核酸序列為：

1 ATGCATTTTC AAGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCCTCAGT
51 CATAGTGTCC AGAGGGCAAA TTGTTCTCAC CCAGTCTCCA ACAATCGTGT
101 CTGCATCTCC AGGGGAGAAG GTCACCCTAA TCTGCAGTGC CAGTTCAAGT
151 GTAAGTTTCG TGGACTGGTT CCAGCAGAAG CCAGGCACTT CTCCCAAACG
201 CTGGATTTAC AGAACATCCA ACCTGGGTTT TGGAGTCCCT GCTCGCTTCA
251 GTGGCGGTGG ATCTGGGACC TCTCACTCTC TCACAATCAG CCGAATGGAG
301 GCTGAAGATG CTGCCACTTA TTACTGCCAG CAAAGGAGTA CTTACCCACC
351 CACGTTCGGT GCTGGGACCA AGCTGGAACT GAAACGGGCT GATGCTGCAC
401 CAACTGTATC CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT
451 GCCTCAGTCG TGTGCTTCTT GAACAACTTC TACCCCAAAG ACATCAATGT
501 CAAGTGGAAG ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT
551 GGACTGATCA GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCTC
601 ACGTTGACCA AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC
651 CACTCACAAG ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG
701 AGTGTTAG (SEQ ID NO:34)

Ab-B重鏈

成熟形式(移除訊號肽)Ab-B HC之胺基酸序列：

1 QVTLKESGPG ILQPSQTLSL TCSFSGFSLS TSGMGVGWIR HPSGKNLEWL
51 AHIWWDDVKR YNPVLKSRLT ISKDTSNSQV FLKIANVDTA DTATYYCARI
101 EDFDYDEEYY AMDYWGQGTS VIVSS***AKTTP PSVYPLAPGS AAQTNSMVTL***
151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW

201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK

251 DVLTITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS

301 TFRSVSELPI MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV

351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIM

401 DTDGSYFVYS KLNVQKSNWE AGNTFTCSVL HEGLHNHHTE KSLSHSPGK (SEQ ID NO:35)

編碼成熟形式(移除訊號肽)Ab-B HC之核酸序列：

1 CAGGTTACTC TGAAAGAGTC TGGCCCTGGG ATATTGCAGC CCTCCCAGAC
51 CCTCAGTCTG ACTTGTTCTT TCTCTGGGTT TTCACTGAGC ACTTCTGGTA
101 TGGGTGTAGG CTGGATTCGT CACCCATCAG GGAAGAATCT GGAGTGGCTG
151 GCACACATTT GGTGGGATGA TGTCAAGCGC TATAACCCAG TCCTGAAGAG
201 CCGACTGACT ATCTCCAAGG ATACCTCCAA CAGCCAGGTA TTCCTCAAGA
251 TCGCCAATGT GGACACTGCA GATACTGCCA CATACTACTG TGCTCGAATA
301 GAGGACTTTG ATTACGACGA GGAGTATTAT GCTATGGACT ACTGGGGTCA
351 AGGAACCTCA GTCATCGTCT CCTCAGCCAA AACGACACCC CCATCTGTCT
401 ATCCACTGGC CCCTGGATCT GCTGCCCAAA CTAACTCCAT GGTGACCCTG
451 GGATGCCTGG TCAAGGGCTA TTTCCCTGAG CCAGTGACAG TGACCTGGAA
501 CTCTGGATCC CTGTCCAGCG GTGTGCACAC CTTCCCAGCT GTCCTGCAGT
551 CTGACCTCTA CACTCTGAGC AGCTCAGTGA CTGTCCCCTC CAGCACCTGG
601 CCCAGCGAGA CCGTCACCTG CAACGTTGCC CACCCGGCCA GCAGCACCAA
651 GGTGGACAAG AAAATTGTGC CCAGGGATTG TGGTTGTAAG CCTTGCATAT
701 GTACAGTCCC AGAAGTATCA TCTGTCTTCA TCTTCCCCCC AAAGCCCAAG
751 GATGTGCTCA CCATTACTCT GACTCCTAAG GTCACGTGTG TTGTGGTAGA
801 CATCAGCAAG GATGATCCCG AGGTCCAGTT CAGCTGGTTT GTAGATGATG
851 TGGAGGTGCA CACAGCTCAG ACGCAACCCC GGGAGGAGCA GTTCAACAGC
901 ACTTTCCGCT CAGTCAGTGA ACTTCCCATC ATGCACCAGG ACTGGCTCAA
951 TGGCAAGGAG TTCAAATGCA GGGTCAACAG TGCAGCTTTC CCTGCCCCCA
1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGCA GACCGAAGGC TCCACAGGTG
1051 TACACCATTC CACCTCCCAA GGAGCAGATG GCCAAGGATA AAGTCAGTCT
1101 GACCTGCATG ATAACAGACT TCTTCCCTGA AGACATTACT GTGGAGTGGC
1151 AGTGGAATGG GCAGCCAGCG GAGAACTACA AGAACACTCA GCCCATCATG

1201 GACACAGATG GCTCTTACTT CGTCTACAGC AAGCTCAATG TGCAGAAGAG
1251 CAACTGGGAG GCAGGAAATA CTTTCACCTG CTCTGTGTTA CATGAGGGCC
1301 TGCACAACCA CCATACTGAG AAGAGCCTCT CCCACTCTCC TGGTAAATGA
(SEQ ID NO:36)

包括訊號肽之Ab-B HC之胺基酸序列：

1 MGRLTSSFLL LIVPAYVLSQ VTLKESGPGI LQPSQTLSLT CSFSGFSLST
51 SGMGVGWIRH PSGKNLEWLA HIWWDDVKRY NPVLKSRLTI SKDTSNSQVF
101 LKIANVDTAD TATYYCARIE DFDYDEEYYA MDYWGQGTSV IVSSAKTTPP
151 SVYPLAPGSA AQTNSMVTLG CLVKGYFPEP VTVTWNSGSL SSGVHTFPAV
201 LQSDLYTLSS SVTVPSSTWP SETVTCNVAH PASSTKVDKK IVPRDCGCKP
251 CICTVPEVSS VFIFPPKPKD VLTITLTPKV TCVVVDISKD DPEVQFSWFV
301 DDVEVHTAQT QPREEQFNST FRSVSELPIM HQDWLNGKEF KCRVNSAAFP
351 APIEKTISKT KGRPKAPQVY TIPPPKEQMA KDKVSLTCMI TDFFPEDITV
401 EWQWNGQPAE NYKNTQPIMD TDGSYFVYSK LNVQKSNWEA GNTFTCSVLH
451 EGLHNHHTEK SLSHSPGK (SEQ ID NO:37)

包括訊號肽編碼序列之Ab-B HC之核酸序列：

1 ATGGGCAGGC TTACTTCTTC ATTCCTGCTA CTGATTGTCC CTGCATATGT
51 CCTGTCCCAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT
101 CCCAGACCCT CAGTCTGACT TGTTCTTTCT CTGGGTTTTC ACTGAGCACT
151 TCTGGTATGG GTGTAGGCTG GATTCGTCAC CCATCAGGGA AGAATCTGGA
201 GTGGCTGGCA CACATTTGGT GGGATGATGT CAAGCGCTAT AACCCAGTCC
251 TGAAGAGCCG ACTGACTATC TCCAAGGATA CCTCCAACAG CCAGGTATTC
301 CTCAAGATCG CCAATGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGC
351 TCGAATAGAG GACTTTGATT ACGACGAGGA GTATTATGCT ATGGACTACT
401 GGGGTCAAGG AACCTCAGTC ATCGTCTCCT CAGCCAAAAC GACACCCCCA
451 TCTGTCTATC CACTGGCCCC TGGATCTGCT GCCCAAACTA ACTCCATGGT
501 GACCCTGGGA TGCCTGGTCA AGGGCTATTT CCCTGAGCCA GTGACAGTGA
551 CCTGGAACTC TGGATCCCTG TCCAGCGGTG TGCACACCTT CCCAGCTGTC
601 CTGCAGTCTG ACCTCTACAC TCTGAGCAGC TCAGTGACTG TCCCCTCCAG
651 CACCTGGCCC AGCGAGACCG TCACCTGCAA CGTTGCCCAC CCGGCCAGCA

701 GCACCAAGGT GGACAAGAAA ATTGTGCCCA GGGATTGTGG TTGTAAGCCT
751 TGCATATGTA CAGTCCCAGA AGTATCATCT GTCTTCATCT TCCCCCCAAA
801 GCCCAAGGAT GTGCTCACCA TTACTCTGAC TCCTAAGGTC ACGTGTGTTG
851 TGGTAGACAT CAGCAAGGAT GATCCCGAGG TCCAGTTCAG CTGGTTTGTA
901 GATGATGTGG AGGTGCACAC AGCTCAGACG CAACCCCGGG AGGAGCAGTT
951 CAACAGCACT TTCCGCTCAG TCAGTGAACT TCCCATCATG CACCAGGACT
1001 GGCTCAATGG CAAGGAGTTC AAATGCAGGG TCAACAGTGC AGCTTTCCCT
1051 GCCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGCAGAC CGAAGGCTCC
1101 ACAGGTGTAC ACCATTCCAC CTCCCAAGGA GCAGATGGCC AAGGATAAAG
1151 TCAGTCTGAC CTGCATGATA ACAGACTTCT TCCCTGAAGA CATTACTGTG
1201 GAGTGGCAGT GGAATGGGCA GCCAGCGGAG AACTACAAGA ACACTCAGCC
1251 CATCATGGAC ACAGATGGCT CTTACTTCGT CTACAGCAAG CTCAATGTGC
1301 AGAAGAGCAA CTGGGAGGCA GGAAATACTT TCACCTGCTC TGTGTTACAT
1351 GAGGGCCTGC ACAACCACCA TACTGAGAAG AGCCTCTCCC ACTCTCCTGG
1401 TAAATGA (SEQ ID NO:38)

Ab-B重鏈可變區中之CDR(互補判定區)序列如下：

CDR-H1: TSGMGVG (SEQ ID NO:57)

CDR-H2: HIWWDDVKRYNPVLKS (SEQ ID NO:58)

CDR-H3: EDFDYDEEYYAMDY (SEQ ID NO:59)

Ab-B之輕鏈可變區CDR序列為：

CDR-L1: SASSSVSFVD (SEQ ID NO:60)

CDR-L2: RTSNLGF (SEQ ID NO:61)

CDR-L3: QQRSTYPPT (SEQ ID NO:62)

本文所揭示之抗體結合至對於蛋白之活體內活性具有重要性之人類殼硬蛋白區域。例如，抗體結合至殼硬蛋白可與藉由活體內使用諸如實例5及9(小鼠)及實例12(猴)中所述之抗體而達成之骨礦物質密度增加相關聯。骨形成、骨礦物質含量、骨質、骨品質及骨強度中至少一者之增加亦可藉由活體內使用諸如實例5及9(小鼠)及實例12(猴)

中所述之抗體而達成。由於抗體與殼硬蛋白之結合主要由其CDR序列來判定，可利用在適當框架中之所有或某些所揭示之CDR序列來產生用於實踐本發明之抗體，其中該抗體保持特異性結合至殼硬蛋白之能力，且可預期達成，例如，骨礦物質密度之增加。該等抗體用於治療由低骨形成、低骨礦物質密度、低骨礦物質含量、低骨質、低骨品質及低骨強度之至少一者所導致、與其相關聯或導致其之人類或動物病症。熟習此項技術者已知用於構建及表現包含本發明之CDR之抗體及其片段的方法。

因此，在一實施例中，本發明係關於一種經分離抗體(包括Ab-A)或其抗原結合片段，其特異性結合至殼硬蛋白且其中重鏈之可變結構域包含至少一個具有CDR-H1之SEQ ID NO：51、CDR-H2之SEQ ID NO：52及CDR-H3之SEQ ID NO：53中給定序列之CDR。抗體或其抗原結合片段可包含重鏈可變結構域，其中CDR由CDR-H1之SEQ ID NO：51、CDR-H2之SEQ ID NO：52及CDR-H3之SEQ ID NO：53之至少一種肽組成。

當本發明之抗體中存在輕鏈時，該輕鏈可為任何合適之互補鏈且尤其可選自其中可變結構域包含至少一個具有CDR-L1之SEQ ID NO：54、CDR-L2之SEQ ID NO：55及CDR-L3之SEQ ID NO：56中給定序列之CDR的輕鏈。抗體或其抗原結合片段可包含輕鏈可變結構域，其中CDR由CDR-L1之SEQ ID NO：54、CDR-L2之SEQ ID NO：55及CDR-L3之SEQ ID NO：56之至少一種肽組成。

本發明進一步係關於一種經分離抗體(包括Ab-B)或其抗原結合片段，其特異性結合至殼硬蛋白且其中重鏈可變結構域包含至少一個具

有CDR-H1之SEQ ID NO：57、CDR-H2之SEQ ID NO：58及CDR-H3之SEQ ID NO：59中給定序列之CDR。抗體或其抗原結合片段可包含重鏈可變結構域，其中CDR由CDR-H1之SEQ ID NO：57、CDR-H2之SEQ ID NO：58及CDR-H3之SEQ ID NO：59之至少一種肽組成。

當本發明之抗體中存在輕鏈時，該輕鏈可為任何合適之互補鏈且尤其可選自其中可變結構域包含至少一個具有CDR-L1之SEQ ID NO：60、CDR-L2之SEQ ID NO：61及CDR-L3之SEQ ID NO：62中給定序列之CDR的輕鏈。抗體或其抗原結合片段可包含輕鏈可變結構域，其中CDR由CDR-L1之SEQ ID NO：60、CDR-L2之SEQ ID NO：61及CDR-L3之SEQ ID NO：62之至少一種肽組成。

本發明更進一步係關於一種經分離抗體(包括Ab-C)或其抗原結合片段，其特異性結合至殼硬蛋白且其中重鏈可變結構域包含至少一個具有CDR-H1之SEQ ID NO：45、CDR-H2之SEQ ID NO：46及CDR-H3之SEQ ID NO：47中給定序列之CDR。抗體或其抗原結合片段可包含重鏈可變結構域，其中CDR由CDR-H1之SEQ ID NO：45、CDR-H2之SEQ ID NO：46及CDR-H3之SEQ ID NO：47之至少一種肽組成。

當本發明抗體中存在輕鏈時，該輕鏈可為任何合適之互補鏈且尤其可選自其中可變結構域包含至少一個具有CDR-L1之SEQ ID NO：48、CDR-L2之SEQ ID NO：49及CDR-L3之SEQ ID NO：50中給定序列之CDR的輕鏈。抗體或其抗原結合片段可包含輕鏈可變結構域，其中CDR由CDR-L1之SEQ ID NO：48、CDR-L2之SEQ ID NO：49及CDR-L3之SEQ ID NO：50之至少一種肽組成。

本發明亦係關於一種經分離抗體(包括Ab-D)或其抗原結合片段，

其可特異性結合至殼硬蛋白且其中重鏈可變結構域包含至少一個具有CDR-H1之SEQ ID NO：39、CDR-H2之SEQ ID NO：40及CDR-H3之SEQ ID NO：41中給定序列之CDR。抗體或其抗原結合片段可包含重鏈可變結構域，其中CDR由CDR-H1之SEQ ID NO：39、CDR-H2之SEQ ID NO：40及CDR-H3之SEQ ID NO：41之至少一種肽組成。

當本發明抗體中存在輕鏈時，該輕鏈可為任何合適之互補鏈，且尤其可選自其中可變結構域包含至少一個具有CDR-L1之SEQ ID NO：42、CDR-L2之SEQ ID NO：43及CDR-L3之SEQ ID NO：44中給定序列之CDR的輕鏈。抗體或其抗原結合片段可包含輕鏈可變結構域，其中CDR係由CDR-L1之SEQ ID NO：42、CDR-L2之SEQ ID NO：43及CDR-L3之SEQ ID NO：44之至少一種肽組成。

下文描述額外之抗-殼硬蛋白抗體。對於某些胺基酸序列，互補判定區(CDR)經陰影框處理，而恆定區為粗斜體。

Ab-2

抗體2(亦稱為Ab-2)LC及HC之序列如下：

Ab-2輕鏈：

成熟形式(移除訊號肽)Ab-2 LC之胺基酸序列：

1 QIVLSQSPAI LSTSPGEKVT MTCRASSSVY YMHWYQQKPG SSPKPWIYAT
51 SNLASGVPVR FSGSGSGTSY SLTITRVEAE DAATYYCQQW SSDPLTFGAG
101 TKLELK***RADA APTVSIFPPS SEQLTSGGAS VVCFLNNFYP KDINVKWKID***
151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
201 TSPIVKSFNR NEC (SEQ ID NO:117)

編碼成熟形式(移除訊號肽)Ab-2 LC之核酸序列：

1 CAAATTGTTC TCTCCCAGTC TCCAGCAATC CTGTCTACAT CTCCAGGGGA
51 GAAGGTCACA ATGACTTGCA GGGCCAGCTC AAGTGTATAT TACATGCACT
101 GGTACCAGCA GAAGCCAGGA TCCTCCCCCA AACCCTGGAT TTATGCCACA

151 TCCAACCTGG CTTCTGGAGT CCCTGTTCGC TTCAGTGGCA GTGGGTCTGG
201 GACCTCTTAC TCTCTCACAA TCACCAGAGT GGAGGCTGAA GATGCTGCCA
251 CTTATTACTG CCAGCAGTGG AGTAGTGACC CACTCACGTT CGGTGCTGGG
301 ACCAAGCTGG AGCTGAAACG GGCTGATGCT GCACCAACTG TATCCATCTT
351 CCCACCATCC AGTGAGCAGT TAACATCTGG AGGTGCCTCA GTCGTGTGCT
401 TCTTGAACAA CTTCTACCCC AAAGACATCA ATGTCAAGTG GAAGATTGAT
451 GGCAGTGAAC GACAAAATGG CGTCCTGAAC AGTTGGACTG ATCAGGACAG
501 CAAAGACAGC ACCTACAGCA TGAGCAGCAC CCTCACGTTG ACCAAGGACG
551 AGTATGAACG ACATAACAGC TATACCTGTG AGGCCACTCA CAAGACATCA
601 ACTTCACCCA TTGTCAAGAG CTTCAACAGG AATGAGTGTT AG (SEQ ID NO:118)

包括訊號肽之Ab-2 LC之胺基酸序列：

1 MDFQVQIFSF LLISASVIMS RGQIVLSQSP AILSTSPGEK VTMTCRASSS
51 VYYMHWYQQK PGSSPKPWIY ATSNLASGVP VRFSGSGSGT SYSLTITRVE
101 AEDAATYYCQ QWSSDPLTFG AGTKLELKRA DAAPTVSIFP PSSEQLTSGG
151 ASVVCFLNNF YPKDINVKWK IDGSERQNGV LNSWTDQDSK DSTYSMSSTL
201 TLTKDEYERH NSYTCEATHK TSTSPIVKSF NRNEC (SEQ ID NO:119)

包括訊號肽編碼序列之Ab-2 LC之核酸序列：

1 ATGGATTTTC AAGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCTTCAGT
51 CATTATGTCC AGGGGACAAA TTGTTCTCTC CCAGTCTCCA GCAATCCTGT
101 CTACATCTCC AGGGGAGAAG GTCACAATGA CTTGCAGGGC CAGCTCAAGT
151 GTATATTACA TGCACTGGTA CCAGCAGAAG CCAGGATCCT CCCCCAAACC
201 CTGGATTTAT GCCACATCCA ACCTGGCTTC TGGAGTCCCT GTTCGCTTCA
251 GTGGCAGTGG GTCTGGGACC TCTTACTCTC TCACAATCAC CAGAGTGGAG
301 GCTGAAGATG CTGCCACTTA TTACTGCCAG CAGTGGAGTA GTGACCCACT
351 CACGTTCGGT GCTGGGACCA AGCTGGAGCT GAAACGGGCT GATGCTGCAC
401 CAACTGTATC CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT
451 GCCTCAGTCG TGTGCTTCTT GAACAACTTC TACCCCAAAG ACATCAATGT
501 CAAGTGGAAG ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT
551 GGACTGATCA GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCTC
601 ACGTTGACCA AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC
651 CACTCACAAG ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG
701 AGTGTTAG (SEQ ID NO:120)

Ab-2重鏈

成熟形式(移除訊號肽)Ab-2 HC之胺基酸序列：

1 EVQVQQSGPE LVKPGASVKL SCTASGFNIK DYFIHWVKQR PEQGLEWIGR
51 LDPEDGESDY APKFQDKAIM TADTSSNTAY LQLRSLTSED TAIYYCERED
101 YDGTYTFFPY WGQGTLVTVS A***AKTTPPSVY PLAPGSAAQT NSMVTLGCLV***

151 KGYFPEPVTV TWNSGSLSSG VHTFPAVLQS DLYTLSSSVT VPSSTWPSET
201 VTCNVAHPAS STKVDKKIVP RDCGCKPCIC TVPEVSSVFI FPPKPKDVLT
251 ITLTPKVTCV VVDISKDDPE VQFSWFVDDV EVHTAQTQPR EEQFNSTFRS
301 VSELPIMHQD WLNGKEFKCR VNSAAFPAPI EKTISKTKGR PKAPQVYTIP
351 PPKEQMAKDK VSLTCMITDF FPEDITVEWQ WNGQPAENYK NTQPIMDTDG
401 SYFIYSKLNV QKSNWEAGNT FTCSVLHEGL HNHHTEKSLS HSPGK (SEQ ID NO:121)

編碼成熟形式(移除訊號肽)Ab-2 HC之核酸序列：

1 GAGGTTCAGG TGCAGCAGTC TGGGCCAGAA CTTGTGAAGC CAGGGGCCTC
51 AGTCAAGTTG TCCTGCACAG CTTCTGGCTT CAACATTAAA GACTACTTTA
101 TACACTGGGT GAAGCAGAGG CCTGAACAGG GCCTGGAGTG GATTGGAAGG
151 CTTGATCCTG AGGATGGTGA AAGTGATTAT GCCCCGAAGT TCCAGGACAA
201 GGCCATTATG ACAGCAGACA CATCATCCAA CACAGCCTAT CTTCAGCTCA
251 GAAGCCTGAC ATCTGAGGAC ACTGCCATCT ATTATTGTGA GAGAGAGGAC
301 TACGATGGTA CCTACACCTT TTTTCCTTAC TGGGGCCAAG GGACTCTGGT
351 CACTGTCTCT GCAGCCAAAA CGACACCCCC ATCTGTCTAT CCACTGGCCC
401 CTGGATCTGC TGCCCAAACT AACTCCATGG TGACCCTGGG ATGCCTGGTC
451 AAGGGCTATT TCCCTGAGCC AGTGACAGTG ACCTGGAACT CTGGATCCCT
501 GTCCAGCGGT GTGCACACCT TCCCAGCTGT CCTGCAGTCT GACCTCTACA
551 CTCTGAGCAG CTCAGTGACT GTCCCCTCCA GCACCTGGCC CAGCGAGACC
601 GTCACCTGCA ACGTTGCCCA CCCGGCCAGC AGCACCAAGG TGGACAAGAA
651 AATTGTGCCC AGGGATTGTG GTTGTAAGCC TTGCATATGT ACAGTCCCAG
701 AAGTATCATC TGTCTTCATC TTCCCCCCAA AGCCCAAGGA TGTGCTCACC
751 ATTACTCTGA CTCCTAAGGT CACGTGTGTT GTGGTAGACA TCAGCAAGGA
801 TGATCCCGAG GTCCAGTTCA GCTGGTTTGT AGATGATGTG GAGGTGCACA
851 CAGCTCAGAC GCAACCCCGG GAGGAGCAGT TCAACAGCAC TTTCCGCTCA
901 GTCAGTGAAC TTCCCATCAT GCACCAGGAC TGGCTCAATG GCAAGGAGTT
951 CAAATGCAGG GTCAACAGTG CAGCTTTCCC TGCCCCCATC GAGAAAACCA
1001 TCTCCAAAAC CAAAGGCAGA CCGAAGGCTC CACAGGTGTA CACCATTCCA
1051 CCTCCCAAGG AGCAGATGGC CAAGGATAAA GTCAGTCTGA CCTGCATGAT
1101 AACAGACTTC TTCCCTGAAG ACATTACTGT GGAGTGGCAG TGGAATGGGC
1151 AGCCAGCGGA GAACTACAAG AACACTCAGC CCATCATGGA CACAGATGGC
1201 TCTTACTTCA TCTACAGCAA GCTCAATGTG CAGAAGAGCA ACTGGGAGGC
1251 AGGAAATACT TTCACCTGCT CTGTGTTACA TGAGGGCCTG CACAACCACC
1301 ATACTGAGAA GAGCCTCTCC CACTCTCCTG GTAAATGA (SEQ ID NO:122)

包括訊號肽之Ab-2 HC之胺基酸序列：

1 MKCSWVIFFL MAVVTGVNSE VQVQQSGPEL VKPGASVKLS CTASGFNIKD
51 YFIHWVKQRP EQGLEWIGRL DPEDGESDYA PKFQDKAIMT ADTSSNTAYL
101 QLRSLTSEDT AIYYCEREDY DGTYTFFPYW GQGTLVTVSA AKTTPPSVYP
151 LAPGSAAQTN SMVTLGCLVK GYFPEPVTVT WNSGSLSSGV HTFPAVLQSD

201 LYTLSSSVTV PSSTWPSETV TCNVAHPASS TKVDKKIVPR DCGCKPCICT
251 VPEVSSVFIF PPKPKDVLTI TLTPKVTCVV VDISKDDPEV QFSWFVDDVE
301 VHTAQTQPRE EQFNSTFRSV SELPIMHQDW LNGKEFKCRV NSAAFPAPIE
351 KTISKTKGRP KAPQVYTIPP PKEQMAKDKV SLTCMITDFF PEDITVEWQW
401 NGQPAENYKN TQPIMDTDGS YFIYSKLNVQ KSNWEAGNTF TCSVLHEGLH
451 NHHTEKSLSH SPGK (SEQ ID NO:123)

包括訊號肽編碼序列之Ab-2 HC之核酸序列：

1 ATGAAATGCA GCTGGGTCAT CTTCTTCCTG ATGGCAGTGG TTACAGGGGT
51 CAATTCAGAG GTTCAGGTGC AGCAGTCTGG GCCAGAACTT GTGAAGCCAG
101 GGGCCTCAGT CAAGTTGTCC TGCACAGCTT CTGGCTTCAA CATTAAAGAC
151 TACTTTATAC ACTGGGTGAA GCAGAGGCCT GAACAGGGCC TGGAGTGGAT
201 TGGAAGGCTT GATCCTGAGG ATGGTGAAAG TGATTATGCC CCGAAGTTCC
251 AGGACAAGGC CATTATGACA GCAGACACAT CATCCAACAC AGCCTATCTT
301 CAGCTCAGAA GCCTGACATC TGAGGACACT GCCATCTATT ATTGTGAGAG
351 AGAGGACTAC GATGGTACCT ACACCTTTTT TCCTTACTGG GGCCAAGGGA
401 CTCTGGTCAC TGTCTCTGCA GCCAAAACGA CACCCCCATC TGTCTATCCA
451 CTGGCCCCTG GATCTGCTGC CCAAACTAAC TCCATGGTGA CCCTGGGATG
501 CCTGGTCAAG GGCTATTTCC CTGAGCCAGT GACAGTGACC TGGAACTCTG
551 GATCCCTGTC CAGCGGTGTG CACACCTTCC CAGCTGTCCT GCAGTCTGAC
601 CTCTACACTC TGAGCAGCTC AGTGACTGTC CCCTCCAGCA CCTGGCCCAG
651 CGAGACCGTC ACCTGCAACG TTGCCCACCC GGCCAGCAGC ACCAAGGTGG
701 ACAAGAAAAT TGTGCCCAGG GATTGTGGTT GTAAGCCTTG CATATGTACA
751 GTCCCAGAAG TATCATCTGT CTTCATCTTC CCCCCAAAGC CCAAGGATGT
801 GCTCACCATT ACTCTGACTC CTAAGGTCAC GTGTGTTGTG GTAGACATCA
851 GCAAGGATGA TCCCGAGGTC CAGTTCAGCT GGTTTGTAGA TGATGTGGAG
901 GTGCACACAG CTCAGACGCA ACCCCGGGAG GAGCAGTTCA ACAGCACTTT
951 CCGCTCAGTC AGTGAACTTC CCATCATGCA CCAGGACTGG CTCAATGGCA
1001 AGGAGTTCAA ATGCAGGGTC AACAGTGCAG CTTTCCCTGC CCCCATCGAG
1051 AAAACCATCT CCAAAACCAA AGGCAGACCG AAGGCTCCAC AGGTGTACAC
1101 CATTCCACCT CCCAAGGAGC AGATGGCCAA GGATAAAGTC AGTCTGACCT
1151 GCATGATAAC AGACTTCTTC CCTGAAGACA TTACTGTGGA GTGGCAGTGG
1201 AATGGGCAGC CAGCGGAGAA CTACAAGAAC ACTCAGCCCA TCATGGACAC
1251 AGATGGCTCT TACTTCATCT ACAGCAAGCT CAATGTGCAG AAGAGCAACT
1301 GGGAGGCAGG AAATACTTTC ACCTGCTCTG TGTTACATGA GGGCCTGCAC
1351 AACCACCATA CTGAGAAGAG CCTCTCCCAC TCTCCTGGTA AATGA (SEQ ID NO:124)

Ab-3

抗體3(本文亦稱為Ab-3)LC及HC之序列如下：

Ab-3輕鏈

成熟形式(移除訊號肽)Ab-3 LC之胺基酸序列：

1 EIVLTQSPAL MAASPGEKVT ITCSVSSTIS SNHLHWFQQK SDTSPKPWIY
51 GTSNLASGVP VRFSGSGSGT SYSLTISSME AEDAATYYCQ QWSSYPLTFG
101 AGTKLELR***RA DAAPTVSIFP PSSEQLTSGG ASVVCFLNNF YPKDINVKWK***
151 IDGSERQNGV LNSWTDQDSK DSTYSMSSTL TLTKDEYERH NSYTCEATHK
201 TSTSPIVKSF NRNEC (SEQ ID NO:125)

編碼成熟形式(移除訊號肽)Ab-3 LC之核酸序列：

1 GAAATTGTGC TCACCCAGTC TCCAGCACTC ATGGCTGCAT CTCCGGGGGA
51 GAAGGTCACC ATCACCTGCA GTGTCAGTTC AACTATAAGT TCCAACCACT
101 TGCACTGGTT CCAGCAGAAG TCAGACACCT CCCCCAAACC CTGGATTTAT
151 GGCACATCCA ACCTGGCTTC TGGAGTCCCT GTTCGCTTCA GTGGCAGTGG
201 ATCTGGGACC TCTTATTCTC TCACAATCAG CAGCATGGAG GCTGAGGATG
251 CTGCCACTTA TTACTGTCAA CAGTGGAGTA GTTACCCACT CACGTTCGGC
301 GCTGGGACCA AGCTGGAGCT GAGACGGGCT GATGCTGCAC CAACTGTATC
351 CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT GCCTCAGTCG
401 TGTGCTTCTT GAACAACTTC TACCCCAAAG ACATCAATGT CAAGTGGAAG
451 ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT GGACTGATCA
501 GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCTC ACGTTGACCA
551 AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC CACTCACAAG
601 ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG AGTGTTAG (SEQ ID NO:126)

包括訊號肽之Ab-3 LC之胺基酸序列：

1 MDFHVQIFSF MLISVTVILS SGEIVLTQSP ALMAASPGEK VTITCSVSST
51 ISSNHLHWFQ QKSDTSPKPW IYGTSNLASG VPVRFSGSGS GTSYSLTISS
101 MEAEDAATYY CQQWSSYPLT FGAGTKLELR RADAAPTVSI FPPSSEQLTS
151 GGASVVCFLN NFYPKDINVK WKIDGSERQN GVLNSWTDQD SKDSTYSMSS
201 TLTLTKDEYE RHNSYTCEAT HKTSTSPIVK SFNRNEC (SEQ ID NO:127)

包括訊號肽編碼序列之Ab-3 LC之核酸序列：

1 ATGGATTTTC ATGTGCAGAT TTTCAGCTTC ATGCTAATCA GTGTCACAGT
51 CATTTTGTCC AGTGGAGAAA TTGTGCTCAC CCAGTCTCCA GCACTCATGG
101 CTGCATCTCC GGGGGAGAAG GTCACCATCA CCTGCAGTGT CAGTTCAACT
151 ATAAGTTCCA ACCACTTGCA CTGGTTCCAG CAGAAGTCAG ACACCTCCCC
201 CAAACCCTGG ATTTATGGCA CATCCAACCT GGCTTCTGGA GTCCCTGTTC
251 GCTTCAGTGG CAGTGGATCT GGGACCTCTT ATTCTCTCAC AATCAGCAGC
301 ATGGAGGCTG AGGATGCTGC CACTTATTAC TGTCAACAGT GGAGTAGTTA

351 CCCACTCACG TTCGGCGCTG GGACCAAGCT GGAGCTGAGA CGGGCTGATG
401 CTGCACCAAC TGTATCCATC TTCCCACCAT CCAGTGAGCA GTTAACATCT
451 GGAGGTGCCT CAGTCGTGTG CTTCTTGAAC AACTTCTACC CCAAAGACAT
501 CAATGTCAAG TGGAAGATTG ATGGCAGTGA ACGACAAAAT GGCGTCCTGA
551 ACAGTTGGAC TGATCAGGAC AGCAAAGACA GCACCTACAG CATGAGCAGC
601 ACCCTCACGT TGACCAAGGA CGAGTATGAA CGACATAACA GCTATACCTG
651 TGAGGCCACT CACAAGACAT CAACTTCACC CATTGTCAAG AGCTTCAACA
701 GGAATGAGTG TTAG (SEQ ID NO:128)

Ab-3重鏈

成熟形式(移除訊號肽)Ab-3 HC之胺基酸序列：

1 EVQLQQSGAE LVRPGALVKL SCTASDFNIK DFYLHWMRQR PEQGLDWIGR
51 IDPENGDTLY DPKFQDKATL TTDTSSNTAY LQLSGLTSET TAVYYCSREA
101 DYFHDGTSYW YFDVWGAGTT ITVSS***AKTTP PSVYPLAPGS AAQTNSMVTL***
151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW
201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
251 DVLTITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
301 TFRSVSELPI MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIM
401 DTDGSYFIYS KLNVQKSNWE AGNTFTCSVL HEGLHNHHTE KSLSHSPGK (SEQ ID NO:129)

編碼成熟形式(移除訊號肽)Ab-3 HC之核酸序列：

1 GAGGTTCAGC TGCAGCAGTC TGGGGCTGAA CTTGTGAGGC CAGGGGCCTT
51 AGTCAAGTTG TCCTGCACAG CTTCTGACTT CAACATTAAA GACTTCTATC
101 TACACTGGAT GAGGCAGCGG CCTGAACAGG GCCTGGACTG GATTGGAAGG
151 ATTGATCCTG AGAATGGTGA TACTTTATAT GACCCGAAGT TCCAGGACAA
201 GGCCACTCTT ACAACAGACA CATCCTCCAA CACAGCCTAC CTGCAGCTCA
251 GCGGCCTGAC ATCTGAGACC ACTGCCGTCT ATTACTGTTC TAGAGAGGCG
301 GATTATTTCC ACGATGGTAC CTCCTACTGG TACTTCGATG TCTGGGGCGC
351 AGGGACCACA ATCACCGTCT CCTCAGCCAA AACGACACCC CCATCTGTCT
401 ATCCACTGGC CCCTGGATCT GCTGCCCAAA CTAACTCCAT GGTGACCCTG
451 GGATGCCTGG TCAAGGGCTA TTTCCCTGAG CCAGTGACAG TGACCTGGAA
501 CTCTGGATCC CTGTCCAGCG GTGTGCACAC CTTCCCAGCT GTCCTGCAGT
551 CTGACCTCTA CACTCTGAGC AGCTCAGTGA CTGTCCCCTC CAGCACCTGG
601 CCCAGCGAGA CCGTCACCTG CAACGTTGCC CACCCGGCCA GCAGCACCAA
651 GGTGGACAAG AAAATTGTGC CCAGGGATTG TGGTTGTAAG CCTTGCATAT
701 GTACAGTCCC AGAAGTATCA TCTGTCTTCA TCTTCCCCCC AAAGCCCAAG
751 GATGTGCTCA CCATTACTCT GACTCCTAAG GTCACGTGTG TTGTGGTAGA
801 CATCAGCAAG GATGATCCCG AGGTCCAGTT CAGCTGGTTT GTAGATGATG
851 TGGAGGTGCA CACAGCTCAG ACGCAACCCC GGGAGGAGCA GTTCAACAGC

901 ACTTTCCGCT CAGTCAGTGA ACTTCCCATC ATGCACCAGG ACTGGCTCAA
951 TGGCAAGGAG TTCAAATGCA GGGTCAACAG TGCAGCTTTC CCTGCCCCCA
1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGCA GACCGAAGGC TCCACAGGTG
1051 TACACCATTC CACCTCCCAA GGAGCAGATG GCCAAGGATA AAGTCAGTCT
1101 GACCTGCATG ATAACAGACT TCTTCCCTGA AGACATTACT GTGGAGTGGC
1151 AGTGGAATGG GCAGCCAGCG GAGAACTACA AGAACACTCA GCCCATCATG
1201 GACACAGATG GCTCTTACTT CATCTACAGC AAGCTCAATG TGCAGAAGAG
1251 CAACTGGGAG GCAGGAAATA CTTTCACCTG CTCTGTGTTA CATGAGGGCC
1301 TGCACAACCA CCATACTGAG AAGAGCCTCT CCCACTCTCC TGGTAAATGA (SEQ ID NO:130)

包括訊號肽之Ab-3 HC之胺基酸序列：

1 MKCSWVIFFL MAVVTGVNSE VQLQQSGAEL VRPGALVKLS CTASDFNIKD
51 FYLHWMRQRP EQGLDWIGRI DPENGDTLYD PKFQDKATLT TDTSSNTAYL
101 QLSGLTSETT AVYYCSREAD YFHDGTSYWY FDVWGAGTTI TVSSAKTTPP
151 SVYPLAPGSA AQTNSMVTLG CLVKGYFPEP VTVTWNSGSL SSGVHTFPAV
201 LQSDLYTLSS SVTVPSSTWP SETVTCNVAH PASSTKVDKK IVPRDCGCKP
251 CICTVPEVSS VFIFPPKPKD VLTITLTPKV TCVVVDISKD DPEVQFSWFV
301 DDVEVHTAQT QPREEQFNST FRSVSELPIM HQDWLNGKEF KCRVNSAAFP
351 APIEKTISKT KGRPKAPQVY TIPPPKEQMA KDKVSLTCMI TDFFPEDITV
401 EWQWNGQPAE NYKNTQPIMD TDGSYFIYSK LNVQKSNWEA GNTFTCSVLH
451 EGLHNHHTEK SLSHSPGK (SEQ ID NO:131)

包括訊號肽編碼序列之Ab-3 HC之核酸序列：

1 ATGAAATGCA GCTGGGTCAT CTTCTTCCTG ATGGCAGTGG TTACAGGGGT
51 CAATTCAGAG GTTCAGCTGC AGCAGTCTGG GGCTGAACTT GTGAGGCCAG
101 GGGCCTTAGT CAAGTTGTCC TGCACAGCTT CTGACTTCAA CATTAAAGAC
151 TTCTATCTAC ACTGGATGAG GCAGCGGCCT GAACAGGGCC TGGACTGGAT
201 TGGAAGGATT GATCCTGAGA ATGGTGATAC TTTATATGAC CCGAAGTTCC
251 AGGACAAGGC CACTCTTACA ACAGACACAT CCTCCAACAC AGCCTACCTG
301 CAGCTCAGCG GCCTGACATC TGAGACCACT GCCGTCTATT ACTGTTCTAG
351 AGAGGCGGAT TATTTCCACG ATGGTACCTC CTACTGGTAC TTCGATGTCT
401 GGGGCGCAGG GACCACAATC ACCGTCTCCT CAGCCAAAAC GACACCCCCA
451 TCTGTCTATC CACTGGCCCC TGGATCTGCT GCCCAAACTA ACTCCATGGT
501 GACCCTGGGA TGCCTGGTCA AGGGCTATTT CCCTGAGCCA GTGACAGTGA
551 CCTGGAACTC TGGATCCCTG TCCAGCGGTG TGCACACCTT CCCAGCTGTC
601 CTGCAGTCTG ACCTCTACAC TCTGAGCAGC TCAGTGACTG TCCCCTCCAG
651 CACCTGGCCC AGCGAGACCG TCACCTGCAA CGTTGCCCAC CCGGCCAGCA
701 GCACCAAGGT GGACAAGAAA ATTGTGCCCA GGGATTGTGG TTGTAAGCCT
751 TGCATATGTA CAGTCCCAGA AGTATCATCT GTCTTCATCT TCCCCCCAAA
801 GCCCAAGGAT GTGCTCACCA TTACTCTGAC TCCTAAGGTC ACGTGTGTTG

851 TGGTAGACAT CAGCAAGGAT GATCCCGAGG TCCAGTTCAG CTGGTTTGTA
901 GATGATGTGG AGGTGCACAC AGCTCAGACG CAACCCCGGG AGGAGCAGTT
951 CAACAGCACT TTCCGCTCAG TCAGTGAACT TCCCATCATG CACCAGGACT
1001 GGCTCAATGG CAAGGAGTTC AAATGCAGGG TCAACAGTGC AGCTTTCCCT
1051 GCCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGCAGAC CGAAGGCTCC
1101 ACAGGTGTAC ACCATTCCAC CTCCCAAGGA GCAGATGGCC AAGGATAAAG
1151 TCAGTCTGAC CTGCATGATA ACAGACTTCT TCCCTGAAGA CATTACTGTG
1201 GAGTGGCAGT GGAATGGGCA GCCAGCGGAG AACTACAAGA ACACTCAGCC
1251 CATCATGGAC ACAGATGGCT CTTACTTCAT CTACAGCAAG CTCAATGTGC
1301 AGAAGAGCAA CTGGGAGGCA GGAAATACTT TCACCTGCTC TGTGTTACAT
1351 GAGGGCCTGC ACAACCACCA TACTGAGAAG AGCCTCTCCC ACTCTCCTGG
1401 TAAATGA (SEQ ID NO:132)

Ab-4

抗體4(本文亦稱為Ab-4)LC及HC之序列如下：

Ab-4輕鏈：

成熟形式(移除訊號肽)Ab-4 LC之胺基酸序列：

1 DIQMTQITSS LSASLGDRVS ISCRASQDIS NYLNWYQQKP DGTFKLLIFY
51 TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ EDFATYFCQQ GDTLPYTFGG
101 GTKLEIK***RAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI***
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:133)

編碼成熟形式(移除訊號肽)Ab-4 LC之核酸序列：

1 GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT CTCTGGGAGA
51 CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC AATTATTTAA
101 ACTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT TATCTTCTAC
151 ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAGTG GCAGTGGGTC
201 TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA GAAGATTTTG
251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG

551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID NO:134)

包括訊號肽之Ab-4 LC之胺基酸序列：

1 MMSSAQFLGL LLLCFQGTRC DIQMTQITSS LSASLGDRVS ISCRASQDIS
51 NYLNWYQQKP DGTFKLLIFY TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ
101 EDFATYFCQQ GDTLPYTFGG GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA
151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:135)

包括訊號肽編碼序列之Ab-4 LC之核酸序列：

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TACCAGATGT GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT
101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
151 AATTATTTAA ACTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT
201 TATCTTCTAC ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAGTG
251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA
301 GAAGATTTTG CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
351 TTTCGGAGGG GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
701 GTTAG (SEQ ID NO:136)

Ab-4重鏈：

成熟形式(移除訊號肽)Ab-4 HC之胺基酸序列：

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHWVKQN QGKTLEWIGE
51 INPNSGGAGY NQKFKGKATL TVDKSSTTAY MELRSLTSED SAVYYCARLG
101 YDDIYDDWYF DVWGAGTTVT VSS***AKTTPPS VYPLAPGSAA QTNSMVTLGC***
151 LVKGYFPEPV TVTWNSGSLS SGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
301 RSVSELPIMH QDWLNGKEFK CRVNSAAFPA PIEKTISKTK GRPKAPQVYT
351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT

401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID NO:137)

編碼成熟形式(移除訊號肽)Ab-4 HC之核酸序列：

```
   1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
  51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA TACATTCACT GACTACAACA
 101 TGCACTGGGT GAAGCAGAAC CAAGGAAAGA CCCTAGAGTG GATAGGAGAA
 151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAGT TCAAGGGCAA
 201 GGCCACATTG ACTGTAGACA AGTCCTCCAC CACAGCCTAC ATGGAGCTCC
 251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
 301 TACGATGATA TCTACGACGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
 351 CACGGTCACC GTCTCCTCAG CCAAAACGAC ACCCCCATCT GTCTATCCAC
 401 TGGCCCCTGG ATCTGCTGCC CAAACTAACT CCATGGTGAC CCTGGGATGC
 451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAACTCTGG
 501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC
 551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
 601 GAGACCGTCA CCTGCAACGT TGCCCACCCG GCCAGCAGCA CCAAGGTGGA
 651 CAAGAAAATT GTGCCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
 701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAAAGCC CAAGGATGTG
 751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
 801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
 851 TGCACACAGC TCAGACGCAA CCCCGGGAGG AGCAGTTCAA CAGCACTTTC
 901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
 951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC
1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID NO:138)
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包括訊號肽之Ab-4 HC之胺基酸序列：

```
   1 MGWSWTFLFL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
  51 YNMHWVKQNQ GKTLEWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
 101 ELRSLTSEDS AVYYCARLGY DDIYDDWYFD VWGAGTTVTV SSAKTTPPSV
 151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
 201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
 251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
 301 VEVHTAQTQP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
 351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVSLTCMITD FFPEDITVEW
```

401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
451 LHNHHTEKSL SHSPGK (SEQ ID NO:139)

包括訊號肽編碼序列之Ab-4 HC之核酸序列：

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
51 CCTCTCTGAG GTCCAACTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCACTGAC
151 TACAACATGC ACTGGGTGAA GCAGAACCAA GGAAAGACCC TAGAGTGGAT
201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAGTTCA
251 AGGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
351 ATTGGGCTAC GATGATATCT ACGACGACTG GTACTTCGAT GTCTGGGGCG
401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCCTGCAG
601 TCTGACCTCT ACACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTCACGTGT GTTGTGGTAG
851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
1201 CAGTGGAATG GGCAGCCAGC GGAGAACTAC AAGAACACTC AGCCCATCAT
1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAATG
1401 A (SEQ ID NO:140)

Ab-4經人化以產生Ab-5。

Ab-5

抗體5(本文亦稱為Ab-5)LC及HC之序列如下：

Ab-5輕鏈：

成熟形式(移除訊號肽)Ab-5 LC之胺基酸序列：

1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS NYLNWYQQKP GKAPKLLIYY
51 TSRLLSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GDTLPYTFGG
101 GTKVEIK***RTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV***
151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
201 LSSPVTKSFN RGEC (SEQ ID NO:141)

編碼成熟形式(移除訊號肽)Ab-5 LC之核酸序列：

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCCGCAT CCGTAGGCGA
51 CCGCGTAACC ATAACATGTA GAGCATCTCA AGATATTTCC AACTATTTGA
101 ATTGGTACCA ACAAAAACCC GGCAAAGCAC CTAAACTCCT CATTTACTAT
151 ACATCAAGAC TCCTCTCCGG CGTTCCATCA CGATTCTCAG GCTCCGGCTC
201 CGGCACAGAT TTCACACTCA CTATTTCCTC CCTCCAACCA GAAGATTTTG
251 CAACCTATTA CTGTCAACAA GGCGATACAC TCCCATACAC ATTCGGCGGC
301 GGCACAAAAG TTGAAATTAA ACGTACGGTG GCTGCACCAT CTGTCTTCAT
351 CTTCCCGCCA TCTGATGAGC AGTTGAAATC TGGAACTGCC TCTGTTGTGT
401 GCCTGCTGAA TAACTTCTAT CCCAGAGAGG CCAAAGTACA GTGGAAGGTG
451 GATAACGCCC TCCAATCGGG TAACTCCCAG GAGAGTGTCA CAGAGCAGGA
501 CAGCAAGGAC AGCACCTACA GCCTCAGCAG CACCCTGACG CTGAGCAAAG
551 CAGACTACGA GAAACACAAA GTCTACGCCT GCGAAGTCAC CCATCAGGGC
601 CTGAGCTCGC CCGTCACAAA GAGCTTCAAC AGGGGAGAGT GT (SEQ ID NO:142)

包括訊號肽之Ab-5 LC之胺基酸序列：

1 MDMRVPAQLL GLLLLWLRGA RCDIQMTQSP SSLSASVGDR VTITCRASQD
51 ISNYLNWYQQ KPGKAPKLLI YYTSRLLSGV PSRFSGSGSG TDFTLTISSL
101 QPEDFATYYC QQGDTLPYTF GGGTKVEIKR TVAAPSVFIF PPSDEQLKSG
151 TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST
201 LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC (SEQ ID NO:143)

包括訊號肽編碼序列之Ab-5 LC之核酸序列：

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TACTCTGGCT
51 CCGAGGTGCC AGATGTGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTCT
101 CCGCATCCGT AGGCGACCGC GTAACCATAA CATGTAGAGC ATCTCAAGAT
151 ATTTCCAACT ATTTGAATTG GTACCAACAA AAACCCGGCA AAGCACCTAA
201 ACTCCTCATT TACTATACAT CAAGACTCCT CTCCGGCGTT CCATCACGAT
251 TCTCAGGCTC CGGCTCCGGC ACAGATTTCA CACTCACTAT TTCCTCCCTC
301 CAACCAGAAG ATTTTGCAAC CTATTACTGT CAACAAGGCG ATACACTCCC
351 ATACACATTC GGCGGCGGCA CAAAAGTTGA AATTAAACGT ACGGTGGCTG
401 CACCATCTGT CTTCATCTTC CCGCCATCTG ATGAGCAGTT GAAATCTGGA
451 ACTGCCTCTG TTGTGTGCCT GCTGAATAAC TTCTATCCCA GAGAGGCCAA
501 AGTACAGTGG AAGGTGGATA ACGCCCTCCA ATCGGGTAAC TCCCAGGAGA
551 GTGTCACAGA GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC
601 CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCCTGCGA
651 AGTCACCCAT CAGGGCCTGA GCTCGCCCGT CACAAAGAGC TTCAACAGGG
701 GAGAGTGT (SEQ ID NO:144)

Ab-5重鏈：

成熟形式(移除訊號肽)Ab-5 HC之胺基酸序列：

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE
51 INPNSGGAGY NQKFKGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARLG
101 YDDIYDDWYF DVWGQGTTVT VSS***ASTKGPS VFPLAPCSRS TSESTAALGC***
151 LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSNFG
201 TQTYTCNVDH KPSNTKVDKT VERKCCVECP PCPAPPVAGP SVFLFPPKPK
251 DTLMISRTPE VTCVVVDVSH EDPEVQFNWY VDGVEVHNAK TKPREEQFNS
301 TFRVVSVLTV VHQDWLNGKE YKCKVSNKGL PAPIEKTISK TKGQPREPQV
351 YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPML
401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK (SEQ ID NO:145)

無羧基末端離胺酸之成熟形式(移除訊號肽)Ab-5 HC之胺基酸序列：

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE
51 INPNSGGAGY NQKFKGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARLG
101 YDDIYDDWYF DVWGQGTTVT VSS***ASTKGPS VFPLAPCSRS TSESTAALGC***
151 LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSNFG

201 TQTYTCNVDH KPSNTKVDKT VERKCCVECP PCPAPPVAGP SVFLFPPKPK
251 DTLMISRTPE VTCVVVDVSH EDPEVQFNWY VDGVEVHNAK TKPREEQFNS
301 TFRVVSVLTV VHQDWLNGKE YKCKVSNKGL PAPIEKTISK TKGQPREPQV
351 YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPML
401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG (SEQ ID NO:392)

編碼成熟形式(移除訊號肽)Ab-5 HC之核酸序列：

1 GAGGTGCAGC TGGTGCAGAG CGGCGCCGAG GTAAAAAAAC CAGGAGCAAG
51 CGTTAAAGTT TCTTGTAAAG CAAGCGGATA TACATTTACA GATTACAACA
101 TGCATTGGGT AAGACAAGCG CCAGGACAAG GATTGGAATG GATGGGCGAA
151 ATTAACCCTA ATAGTGGAGG AGCAGGCTAC AATCAAAAAT TCAAAGGGAG
201 AGTTACAATG ACAACAGACA CAAGCACTTC AACAGCATAT ATGGAACTGC
251 GATCACTTAG AAGCGACGAT ACAGCTGTAT ACTATTGCGC ACGACTTGGG
301 TATGATGATA TATATGATGA CTGGTATTTC GATGTTTGGG GCCAGGGAAC
351 AACAGTTACC GTCTCTAGTG CCTCCACCAA GGGCCCATCG GTCTTCCCCC
401 TGGCGCCCTG CTCCAGGAGC ACCTCCGAGA GCACAGCGGC CCTGGGCTGC
451 CTGGTCAAGG ACTACTTCCC CGAACCGGTG ACGGTGTCGT GGAACTCAGG
501 CGCTCTGACC AGCGGCGTGC ACACCTTCCC AGCTGTCCTA CAGTCCTCAG
551 GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG CAACTTCGGC
601 ACCCAGACCT ACACCTGCAA CGTAGATCAC AAGCCCAGCA ACACCAAGGT
651 GGACAAGACA GTTGAGCGCA AATGTTGTGT CGAGTGCCCA CCGTGCCCAG
701 CACCACCTGT GGCAGGACCG TCAGTCTTCC TCTTCCCCCC AAAACCCAAG
751 GACACCCTCA TGATCTCCCG GACCCCTGAG GTCACGTGCG TGGTGGTGGA
801 CGTGAGCCAC GAAGACCCCG AGGTCCAGTT CAACTGGTAC GTGGACGGCG
851 TGGAGGTGCA TAATGCCAAG ACAAAGCCAC GGGAGGAGCA GTTCAACAGC
901 ACGTTCCGTG TGGTCAGCGT CCTCACCGTT GTGCACCAGG ACTGGCTGAA
951 CGGCAAGGAG TACAAGTGCA AGGTCTCCAA CAAAGGCCTC CCAGCCCCCA
1001 TCGAGAAAAC CATCTCCAAA ACCAAAGGGC AGCCCCGAGA ACCACAGGTG
1051 TACACCCTGC CCCCATCCCG GGAGGAGATG ACCAAGAACC AGGTCAGCCT
1101 GACCTGCCTG GTCAAAGGCT TCTACCCCAG CGACATCGCC GTGGAGTGGG
1151 AGAGCAATGG GCAGCCGGAG AACAACTACA AGACCACACC TCCCATGCTG
1201 GACTCCGACG GCTCCTTCTT CCTCTACAGC AAGCTCACCG TGGACAAGAG
1251 CAGGTGGCAG CAGGGGAACG TCTTCTCATG CTCCGTGATG CATGAGGCTC
1301 TGCACAACCA CTACACGCAG AAGAGCCTCT CCCTGTCTCC GGGTAAA (SEQ ID NO:146)

包括訊號肽之Ab-5 HC之胺基酸序列：

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGASVKVS CKASGYTFTD
51 YNMHWVRQAP GQGLEWMGEI NPNSGGAGYN QKFKGRVTMT TDTSTSTAYM
101 ELRSLRSDDT AVYYCARLGY DDIYDDWYFD VWGQGTTVTV SSASTKGPSV

151 FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ
201 SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVECPP
251 CPAPPVAGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVQFNWYV
301 DGVEVHNAKT KPREEQFNST FRVVSVLTVV HQDWLNGKEY KCKVSNKGLP
351 APIEKTISKT KGQPREPQVY TLPPSREEMT KNQVSLTCLV KGFYPSDIAV
401 EWESNGQPEN NYKTTPPMLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH
451 EALHNHYTQK SLSLSPGK (SEQ ID NO:147)

包括訊號肽編碼序列之Ab-5 HC之核酸序列：

1 ATGGACTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
51 CCACTCCGAG GTGCAGCTGG TGCAGAGCGG CGCCGAGGTA AAAAAACCAG
101 GAGCAAGCGT TAAAGTTTCT TGTAAAGCAA GCGGATATAC ATTTACAGAT
151 TACAACATGC ATTGGGTAAG ACAAGCGCCA GGACAAGGAT TGGAATGGAT
201 GGGCGAAATT AACCCTAATA GTGGAGGAGC AGGCTACAAT CAAAAATTCA
251 AAGGGAGAGT TACAATGACA ACAGACACAA GCACTTCAAC AGCATATATG
301 GAACTGCGAT CACTTAGAAG CGACGATACA GCTGTATACT ATTGCGCACG
351 ACTTGGGTAT GATGATATAT ATGATGACTG GTATTTCGAT GTTTGGGGCC
401 AGGGAACAAC AGTTACCGTC TCTAGTGCCT CCACCAAGGG CCCATCGGTC
451 TTCCCCCTGG CGCCCTGCTC CAGGAGCACC TCCGAGAGCA CAGCGGCCCT
501 GGGCTGCCTG GTCAAGGACT ACTTCCCCGA ACCGGTGACG GTGTCGTGGA
551 ACTCAGGCGC TCTGACCAGC GGCGTGCACA CCTTCCCAGC TGTCCTACAG
601 TCCTCAGGAC TCTACTCCCT CAGCAGCGTG GTGACCGTGC CCTCCAGCAA
651 CTTCGGCACC CAGACCTACA CCTGCAACGT AGATCACAAG CCCAGCAACA
701 CCAAGGTGGA CAAGACAGTT GAGCGCAAAT GTTGTGTCGA GTGCCCACCG
751 TGCCCAGCAC CACCTGTGGC AGGACCGTCA GTCTTCCTCT TCCCCCCAAA
801 ACCCAAGGAC ACCCTCATGA TCTCCCGGAC CCCTGAGGTC ACGTGCGTGG
851 TGGTGGACGT GAGCCACGAA GACCCCGAGG TCCAGTTCAA CTGGTACGTG
901 GACGGCGTGG AGGTGCATAA TGCCAAGACA AAGCCACGGG AGGAGCAGTT
951 CAACAGCACG TTCCGTGTGG TCAGCGTCCT CACCGTTGTG CACCAGGACT
1001 GGCTGAACGG CAAGGAGTAC AAGTGCAAGG TCTCCAACAA AGGCCTCCCA
1051 GCCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGGCAGC CCCGAGAACC
1101 ACAGGTGTAC ACCCTGCCCC CATCCCGGGA GGAGATGACC AAGAACCAGG
1151 TCAGCCTGAC CTGCCTGGTC AAAGGCTTCT ACCCCAGCGA CATCGCCGTG
1201 GAGTGGGAGA GCAATGGGCA GCCGGAGAAC AACTACAAGA CCACACCTCC
1251 CATGCTGGAC TCCGACGGCT CCTTCTTCCT CTACAGCAAG CTCACCGTGG
1301 ACAAGAGCAG GTGGCAGCAG GGGAACGTCT TCTCATGCTC CGTGATGCAT
1351 GAGGCTCTGC ACAACCACTA CACGCAGAAG AGCCTCTCCC TGTCTCCGGG
1401 TAAA (SEQ ID NO:148)

Ab-5可變結構域：

Ab-5輕鏈可變結構域胺基酸序列(無訊號序列)：

1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS NYLNWYQQKP GKAPKLLIYY
51 TSRLLSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GDTLPYTFGG
101 GTKVEIK (SEQ ID NO:376)

Ab-5輕鏈可變結構域DNA序列(無訊號序列)：

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCCGCAT CCGTAGGCGA
51 CCGCGTAACC ATAACATGTA GAGCATCTCA AGATATTTCC AACTATTTGA
101 ATTGGTACCA ACAAAAACCC GGCAAAGCAC CTAAACTCCT CATTTACTAT
151 ACATCAAGAC TCCTCTCCGG CGTTCCATCA CGATTCTCAG GCTCCGGCTC
201 CGGCACAGAT TTCACACTCA CTATTTCCTC CCTCCAACCA GAAGATTTTG
251 CAACCTATTA CTGTCAACAA GGCGATACAC TCCCATACAC ATTCGGCGGC
301 GGCACAAAAG TTGAAATTAA A (SEQ ID NO:377)

Ab-5重鏈可變結構域胺基酸序列(無訊號序列)：

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE
51 INPNSGGAGY NQKFKGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARLG
101 YDDIYDDWYF DVWGQGTTVT VSS (SEQ ID NO:378)

Ab-5重鏈可變結構域DNA序列(無訊號序列)：

1 GAGGTGCAGC TGGTGCAGAG CGGCGCCGAG GTAAAAAAAC CAGGAGCAAG
51 CGTTAAAGTT TCTTGTAAAG CAAGCGGATA TACATTTACA GATTACAACA
101 TGCATTGGGT AAGACAAGCG CCAGGACAAG GATTGGAATG GATGGGCGAA
151 ATTAACCCTA ATAGTGGAGG AGCAGGCTAC AATCAAAAAT TCAAAGGGAG
201 AGTTACAATG ACAACAGACA CAAGCACTTC AACAGCATAT ATGGAACTGC
251 GATCACTTAG AAGCGACGAT ACAGCTGTAT ACTATTGCGC ACGACTTGGG
301 TATGATGATA TATATGATGA CTGGTATTTC GATGTTTGGG GCCAGGGAAC
351 AACAGTTACC GTCTCTAGT (SEQ ID NO:379)

Ab-5重鏈可變區中之CDR(互補判定區)序列如下：

CDR-H1: DYNMH (SEQ ID NO:245)

CDR-H2: EINPNSGGAGYNQKFKG (SEQ ID NO:246)

CDR-H3: LGYDDIYDDWYFDV (SEQ ID NO:247)

Ab-5之輕鏈可變區CDR序列為：

CDR-L1: RASQDISNYLN (SEQ ID NO:78)

CDR-L2: YTSRLLS (SEQ ID NO:79)

CDR-L3: QQGDTLPYT (SEQ ID NO:80)

Ab-6

抗體6(本文亦稱為Ab-6)LC及HC之序列如下：

Ab-6輕鏈：

成熟形式(移除訊號肽)Ab-6 LC之胺基酸序列：

1 DIQMTQTTSS LSASLGDRVT ISCRASQDIS NYLNWFQQKP DGTLKLLIFY
51 TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GDTLPYTFGG
101 GTKLEIR***RAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI***
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:149)

編碼成熟形式(移除訊號肽)Ab-6 LC之核酸序列：

1 GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT CTCTGGGAGA
51 CAGAGTCACC ATCAGTTGCA GGGCAAGTCA GGACATTAGC AATTATTTAA
101 ACTGGTTTCA GCAGAAACCA GATGGAACTC TTAAACTCCT GATCTTCTAC
151 ACATCAAGAT TACACTCAGG AGTTCCATCA AGGTTCAGTG GCAGTGGGTC
201 TGGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAGCAA GAAGATATTG
251 CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC GTTCGGGGGG
301 GGGACCAAGC TGGAAATAAG ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID NO:150)

包括訊號肽之Ab-6 LC之胺基酸序列：

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTTSS LSASLGDRVT ISCRASQDIS
51 NYLNWFQQKP DGTLKLLIFY TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ
101 EDIATYFCQQ GDTLPYTFGG GTKLEIRRAD AAPTVSIFPP SSEQLTSGGA
151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:151)

包括訊號肽編碼序列之Ab-6 LC之核酸序列：

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
101 CTCTGGGAGA CAGAGTCACC ATCAGTTGCA GGGCAAGTCA GGACATTAGC
151 AATTATTTAA ACTGGTTTCA GCAGAAACCA GATGGAACTC TTAAACTCCT
201 GATCTTCTAC ACATCAAGAT TACACTCAGG AGTTCCATCA AGGTTCAGTG
251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAGCAA
301 GAAGATATTG CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC
351 GTTCGGGGGG GGGACCAAGC TGGAAATAAG ACGGGCTGAT GCTGCACCAA
401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
701 GTTAG (SEQ ID NO:152)

Ab-6重鏈：

成熟形式(移除訊號肽)Ab-6 HC之胺基酸序列：

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHWVKQN QGKSLEWIGE
51 INPNSGGSGY NQKFKGKATL TVDKSSSTAY MELRSLTSED SAVYYCARLV
101 YDGSYEDWYF DVWGAGTTVT VSS***AKTTPPS VYPLAPGSAA QTNSMVTLGC***
151 LVKGYFPEPV TVTWNSGSLS SGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
301 RSVSELPIMH QDWLNGKEFK CRVNSAAFPA PIEKTISKTK GRPKAPQVYT
351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID NO:153)

編碼成熟形式(移除訊號肽)Ab-6 HC之核酸序列：

1 GAGGTCCAGC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA CACATTCACT GACTACAACA
101 TGCACTGGGT GAAACAGAAC CAAGGAAAGA GCCTAGAGTG GATAGGAGAA
151 ATTAATCCTA ACAGTGGTGG TAGTGGCTAC AACCAAAAGT TCAAAGGCAA
201 GGCCACATTG ACTGTAGACA AGTCTTCCAG CACAGCCTAC ATGGAGCTCC
251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGTC
301 TACGATGGCA GCTACGAGGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
351 CACGGTCACC GTCTCCTCAG CCAAAACGAC ACCCCCATCT GTCTATCCAC
401 TGGCCCCTGG ATCTGCTGCC CAAACTAACT CCATGGTGAC CCTGGGATGC
451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAACTCTGG
501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC

551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
601 GAGACCGTCA CCTGCAACGT TGCCCACCCG GCCAGCAGCA CCAAGGTGGA
651 CAAGAAAATT GTGCCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAAAGCC CAAGGATGTG
751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
851 TGCACACAGC TCAGACGCAA CCCCGGGAGG AGCAGTTCAA CAGCACTTTC
901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC
1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID NO:154)

包括訊號肽之Ab-6 HC之胺基酸序列：

1 MGWSWTFLFL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
51 YNMHWVKQNQ GKSLEWIGEI NPNSGGSGYN QKFKGKATLT VDKSSSTAYM
101 ELRSLTSEDS AVYYCARLVY DGSYEDWYFD VWGAGTTVTV SSAKTTPPSV
151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
301 VEVHTAQTQP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVSLTCMITD FFPEDITVEW
401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
451 LHNHHTEKSL SHSPGK (SEQ ID NO:155)

包括訊號肽編碼序列之Ab-6 HC之核酸序列：

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
51 CCTCTCTGAG GTCCAGCTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATACAC ATTCACTGAC
151 TACAACATGC ACTGGGTGAA ACAGAACCAA GGAAAGAGCC TAGAGTGGAT
201 AGGAGAAATT AATCCTAACA GTGGTGGTAG TGGCTACAAC CAAAAGTTCA
251 AAGGCAAGGC CACATTGACT GTAGACAAGT CTTCCAGCAC AGCCTACATG
301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
351 ATTGGTCTAC GATGGCAGCT ACGAGGACTG GTACTTCGAT GTCTGGGGCG
401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT

501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCCTGCAG
601 TCTGACCTCT ACACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTCACGTGT GTTGTGGTAG
851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
1201 CAGTGGAATG GGCAGCCAGC GGAGAACTAC AAGAACACTC AGCCCATCAT
1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAATG
1401 A (SEQ ID NO:156)

Ab-7

抗體7(本文亦稱為Ab-7)LC及HC之序列如下：

Ab-7輕鏈：

成熟形式(移除訊號肽)Ab-7 LC之胺基酸序列：

1 DIQMTQTTSS LSASLGDRVT ICCRASQVIT NYLYWYQQKP DGTFKLLIYY
51 TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GDTLPYTFGG
101 GTKLEIK***RAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI***
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:157)

編碼成熟形式(移除訊號肽)Ab-7 LC之核酸序列：

1 GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT CTCTGGGAGA
51 CAGAGTCACC ATCTGTTGCA GGGCAAGTCA GGTCATTACC AATTATTTAT
101 ACTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT GATCTACTAC
151 ACATCAAGAT TACACTCAGG AGTCCCATCA AGGTTCAGTG GCAGTGGGTC
201 TGGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAACAG GAAGATATTG
251 CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC GTTCGGAGGG
301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT

401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GT (SEQ ID NO:158)

包括訊號肽之Ab-7 LC之胺基酸序列：

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTTSS LSASLGDRVT ICCRASQVIT
51 NYLYWYQQKP DGTFKLLIYY TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ
101 EDIATYFCQQ GDTLPYTFGG GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA
151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:159)

包括訊號肽編碼序列之Ab-7 LC之核酸序列：

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
101 CTCTGGGAGA CAGAGTCACC ATCTGTTGCA GGGCAAGTCA GGTCATTACC
151 AATTATTTAT ACTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT
201 GATCTACTAC ACATCAAGAT TACACTCAGG AGTCCCATCA AGGTTCAGTG
251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTAGCAA CCTGGAACAG
301 GAAGATATTG CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC
351 GTTCGGAGGG GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
701 GT (SEQ ID NO:160)

Ab-7重鏈：

成熟形式(移除訊號肽)Ab-7 HC之胺基酸序列：

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHWMKQN QGKSLEWIGE
51 INPNSGGAGY NQQFKGKATL TVDKSSRTAY MELRSLTSED SAVYYCARLG
101 YVGNYEDWYF DVWGAGTTVT VSS***AKTTPPS VYPLAPGSAA QTNSMVTLGC***
151 LVKGYFPEPV TVTWNSGSLS SGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
301 RSVSELPIMH QDWLNGKEFK CRVNSAAFPA PIEKTISKTK GRPKAPQVYT
351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT

401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID NO:161)

編碼成熟形式(移除訊號肽)Ab-7 HC之核酸序列：

1 GAGGTCCAGC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA CACATTCACT GACTACAACA
101 TGCACTGGAT GAAGCAGAAC CAAGGAAAGA GCCTAGAATG GATAGGAGAA
151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGCAGT TCAAAGGCAA
201 GGCCACATTG ACTGTAGACA AGTCCTCCAG GACAGCCTAC ATGGAGCTCC
251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
301 TACGTTGGTA ATTACGAGGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
351 CACGGTCACC GTCTCCTCAG CCAAAACGAC ACCCCCATCT GTCTATCCAC
401 TGGCCCCTGG ATCTGCTGCC CAAACTAACT CCATGGTGAC CCTGGGATGC
451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAACTCTGG
501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC
551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
601 GAGACCGTCA CCTGCAACGT TGCCCACCCG GCCAGCAGCA CCAAGGTGGA
651 CAAGAAAATT GTGCCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAAAGCC CAAGGATGTG
751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
851 TGCACACAGC TCAGACGCAA CCCCGGGAGG AGCAGTTCAA CAGCACTTTC
901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC
1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA A (SEQ ID NO:162)

包括訊號肽之Ab-7 HC之胺基酸序列：

1 MGWSWTFLFL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
51 YNMHWMKQNQ GKSLEWIGEI NPNSGGAGYN QQFKGKATLT VDKSSRTAYM
101 ELRSLTSEDS AVYYCARLGY VGNYEDWYFD VWGAGTTVTV SSAKTTPPSV
151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
301 VEVHTAQTQP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVSLTCMITD FFPEDITVEW

401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
451 LHNHHTEKSL SHSPGK (SEQ ID NO:163)

包括訊號肽編碼序列之Ab-7 HC之核酸序列：

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
51 CCTCTCTGAG GTCCAGCTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATACAC ATTCACTGAC
151 TACAACATGC ACTGGATGAA GCAGAACCAA GGAAAGAGCC TAGAATGGAT
201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGCAGTTCA
251 AAGGCAAGGC CACATTGACT GTAGACAAGT CCTCCAGGAC AGCCTACATG
301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
351 ATTGGGCTAC GTTGGTAATT ACGAGGACTG GTACTTCGAT GTCTGGGGCG
401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCCTGCAG
601 TCTGACCTCT ACACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTCACGTGT GTTGTGGTAG
851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
1201 CAGTGGAATG GGCAGCCAGC GGAGAACTAC AAGAACACTC AGCCCATCAT
1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAA (SEQ ID NO:164)

Ab-8

抗體8(本文亦稱為Ab-8)LC及HC之序列如下：

Ab-8輕鏈：

成熟形式(移除訊號肽)Ab-8 LC之胺基酸序列：

1 DIQMTQTTSS LSASLGDRVS ISCRASQDIS NYLNWYQQKP DGTFKLLIFY

51 TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ EDFATYFCQQ GDTLPYTFGG
101 GTKLEIK***RAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI***
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:165)

編碼成熟形式(移除訊號肽)Ab-8 LC之核酸序列：

1 GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT CTCTGGGAGA
51 CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC AATTATTTAA
101 ACTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT TATCTTCTAC
151 ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAGTG GCAGTGGGTC
201 TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA GAAGATTTTG
251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
301 GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID NO:166)

包括訊號肽之Ab-8 LC之胺基酸序列：

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTTSS LSASLGDRVS ISCRASQDIS
51 NYLNWYQQKP DGTFKLLIFY TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ
101 EDFATYFCQQ GDTLPYTFGG GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA
151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:167)

包括訊號肽編碼序列之Ab-8 LC之核酸序列：

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
151 AATTATTTAA ACTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT
201 TATCTTCTAC ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAGTG
251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA
301 GAAGATTTTG CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
351 TTTCGGAGGG GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG

601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
701 GTTAG (SEQ ID NO:168)

Ab-8重鏈：

成熟形式(移除訊號肽)Ab-8 HC之胺基酸序列：

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHWVKQN QGKTLDWIGE
51 INPNSGGAGY NQKFKGKATL TVDKSSTTAY MELRSLTSED SAVYYCARLG
101 YDDIYDDWYF DVWGAGTTVT VSS***AKTTPPS VYPLAPGSAA QTNSMVTLGC***
151 LVKGYFPEPV TVTWNSGSLS SGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
301 RSVSELPIMH QDWLNGKEFK CRVNSAAFPA PIEKTISKTK GRPKAPQVYT
351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID NO:169)

編碼成熟形式(移除訊號肽)Ab-8 HC之核酸序列：

1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA TACATTCACT GACTACAACA
101 TGCACTGGGT GAAGCAGAAC CAAGGAAAGA CCCTAGACTG GATAGGAGAA
151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAGT TCAAGGGCAA
201 GGCCACATTG ACTGTAGACA AGTCCTCCAC CACAGCCTAC ATGGAGCTCC
251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
301 TACGATGATA TCTACGACGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
351 CACGGTCACC GTCTCCTCAG CCAAAACGAC ACCCCCATCT GTCTATCCAC
401 TGGCCCCTGG ATCTGCTGCC CAAACTAACT CCATGGTGAC CCTGGGATGC
451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAACTCTGG
501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC
551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
601 GAGACCGTCA CCTGCAACGT TGCCCACCCG GCCAGCAGCA CCAAGGTGGA
651 CAAGAAAATT GTGCCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAAAGCC CAAGGATGTG
751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
851 TGCACACAGC TCAGACGCAA CCCCGGGAGG AGCAGTTCAA CAGCACTTTC
901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC
1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA

1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID NO:170)

包括訊號肽之Ab-8 HC之胺基酸序列：

1 MGWSWTFLFL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
51 YNMHWVKQNQ GKTLDWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
101 ELRSLTSEDS AVYYCARLGY DDIYDDWYFD VWGAGTTVTV SSAKTTPPSV
151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
301 VEVHTAQTQP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVSLTCMITD FFPEDITVEW
401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
451 LHNHHTEKSL SHSPGK (SEQ ID NO:171)

包括訊號肽編碼序列之Ab-8 HC之核酸序列：

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
51 CCTCTCTGAG GTCCAACTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCACTGAC
151 TACAACATGC ACTGGGTGAA GCAGAACCAA GGAAAGACCC TAGACTGGAT
201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAGTTCA
251 AGGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
351 ATTGGGCTAC GATGATATCT ACGACGACTG GTACTTCGAT GTCTGGGGCG
401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCCTGCAG
601 TCTGACCTCT ACACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTCACGTGT GTTGTGGTAG
851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT

1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
1201 CAGTGGAATG GGCAGCCAGC GGAGAACTAC AAGAACACTC AGCCCATCAT
1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAATG
1401 A (SEQ ID NO:172)

Ab-9

抗體9(本文亦稱為Ab-9)LC及HC之序列如下：

Ab-9輕鏈：

成熟形式(移除訊號肽)Ab-9 LC之胺基酸序列：

1 DIQMTQITSS LSASLGDRVS ISCRASQDIS NYLNWYQQKP DGTFKLLIFY
51 TSRLFSGVPS RFSGSGSGTD YSLTIYNLEQ EDFATYFCQQ GDTLPYTFGG
101 GTKVEIK***RAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI***
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:173)

編碼成熟形式(移除訊號肽)Ab-9 LC之核酸序列：

1 GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT CTCTGGGAGA
51 CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC AATTATTTAA
101 ATTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT TATCTTCTAC
151 ACATCAAGAT TATTTTCAGG AGTCCCATCA AGGTTCAGTG GCAGTGGGTC
201 TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA GAAGATTTTG
251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
301 GGGACCAAGG TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GT (SEQ ID NO:174)

包括訊號肽之Ab-9 LC之胺基酸序列：

1 MMSSAQFLGL LLLCFQGTRC DIQMTQITSS LSASLGDRVS ISCRASQDIS
51 NYLNWYQQKP DGTFKLLIFY TSRLFSGVPS RFSGSGSGTD YSLTIYNLEQ
101 EDFATYFCQQ GDTLPYTFGG GTKVEIKRAD AAPTVSIFPP SSEQLTSGGA

151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:175)

包括訊號肽編碼序列之Ab-9 LC之核酸序列：

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TACCAGATGT GATATCCAGA TGACACAGAT TACATCCTCC CTGTCTGCCT
101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
151 AATTATTTAA ATTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT
201 TATCTTCTAC ACATCAAGAT TATTTTCAGG AGTCCCATCA AGGTTCAGTG
251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA
301 GAAGATTTTG CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
351 TTTCGGAGGG GGGACCAAGG TGGAAATAAA ACGGGCTGAT GCTGCACCAA
401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
701 GT (SEQ ID NO:176)

Ab-9重鏈：

成熟形式(移除訊號肽)Ab-9 HC之胺基酸序列：

1 EVQLQQSGPE LMKPGTSVKM SCKASGYTFT DYNMHWVKQT QGKTLEWIGE
51 INPNSGGAGY NQKFKGKATL TVDKSSTTAY MELRSLTSED SAVYYCAKLG
101 YDDIYDDWYF DVWGAGTTVT VSS***AKTTAPS VYPLAPVCGD TTGSSVTLGC***
151 LVKGYFPEPV TLTWNSGSLS SDVHTFPALL QSGLYTLSSS VTVTTWPSQT
201 ITCNVAHPAS STKVDKKIEP RGSPTHKPCP PCPAPNLLGG PSVFIFPPKI
251 KDVLMISLSP MVTCVVVDVS EDDPDVHVSW FVNNVEVHTA QTQTHREDYN
301 STIRVVSALP IQHQDWMSGK EFKCKVNNKA LPAPIERTIS KPKGPVRAPQ
351 VYVLPPPEEE MTKKQVTLTC MITDFMPEDI YVEWTNNGQT ELNYKNTEPV
401 LDSDGSYFMY SKLRVEKKNW VERNSYSCSV VHEGLHNHHT TKSFSRTPGK (SEQ ID NO:177)

編碼成熟形式(移除訊號肽)Ab-9 HC之核酸序列：

1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGACTTC
51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA TACATTCACT GACTACAACA
101 TGCACTGGGT GAAGCAGACC CAAGGAAAGA CCCTAGAGTG GATAGGAGAA
151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAGT TCAAGGGCAA
201 GGCCACATTG ACTGTAGACA AGTCCTCCAC CACAGCCTAC ATGGAGCTCC
251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAAATTGGGC

301 TACGATGATA TCTACGACGA CTGGTATTTC GATGTCTGGG GCGCAGGGAC
351 CACGGTCACC GTCTCCTCAG CCAAAACAAC AGCCCCATCG GTCTATCCAC
401 TGGCCCCTGT GTGTGGAGAT ACAACTGGCT CCTCGGTGAC TCTAGGATGC
451 CTGGTCAAGG GTTATTTCCC TGAGCCAGTG ACCTTGACCT GGAACTCTGG
501 ATCCCTGTCC AGTGATGTGC ACACCTTCCC AGCTCTCCTG CAGTCTGGCC
551 TCTACACCCT CAGCAGCTCA GTGACTGTAA CCACCTGGCC CAGCCAGACC
601 ATCACCTGCA ATGTGGCCCA CCCGGCAAGC AGCACCAAAG TGGACAAGAA
651 AATTGAGCCC AGAGGGTCCC CAACACATAA ACCCTGTCCT CCATGCCCAG
701 CTCCTAACCT CTTGGGTGGA CCATCCGTCT TCATCTTCCC TCCAAAGATC
751 AAGGATGTAC TCATGATCTC CCTGAGCCCC ATGGTCACGT GTGTGGTGGT
801 GGATGTGAGC GAGGATGACC CAGATGTCCA TGTCAGCTGG TTCGTGAACA
851 ACGTGGAAGT ACACACAGCT CAGACACAAA CCCATAGAGA GGATTACAAC
901 AGTACTATCC GGGTGGTCAG TGCCCTCCCC ATCCAGCACC AGGACTGGAT
951 GAGTGGCAAG GAGTTCAAAT GCAAGGTCAA CAACAAAGCC CTCCCAGCGC
1001 CCATCGAGAG AACCATCTCA AAACCCAAAG GGCCAGTAAG AGCTCCACAG
1051 GTATATGTCT TGCCTCCACC AGAAGAAGAG ATGACTAAGA AACAGGTCAC
1101 TCTGACCTGC ATGATCACAG ACTTCATGCC TGAAGACATT TACGTGGAGT
1151 GGACCAACAA CGGGCAAACA GAGCTAAACT ACAAGAACAC TGAACCAGTC
1201 CTGGACTCTG ATGGTTCTTA CTTCATGTAC AGCAAGCTGA GAGTGGAAAA
1251 GAAGAACTGG GTGGAAAGAA ATAGCTACTC CTGTTCAGTG GTCCACGAGG
1301 GTCTGCACAA TCACCACACG ACTAAGAGCT TCTCCCGGAC TCCGGGTAAA
(SEQ ID NO:178)

包括訊號肽之Ab-9 HC之胺基酸序列：

1 MGWSWTFLFL LSGTAGVLSE VQLQQSGPEL MKPGTSVKMS CKASGYTFTD
51 YNMHWVKQTQ GKTLEWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
101 ELRSLTSEDS AVYYCAKLGY DDIYDDWYFD VWGAGTTVTV SSAKTTAPSV
151 YPLAPVCGDT TGSSVTLGCL VKGYFPEPVT LTWNSGSLSS DVHTFPALLQ
201 SGLYTLSSSV TVTTWPSQTI TCNVAHPASS TKVDKKIEPR GSPTHKPCPP
251 CPAPNLLGGP SVFIFPPKIK DVLMISLSPM VTCVVVDVSE DDPDVHVSWF
301 VNNVEVHTAQ TQTHREDYNS TIRVVSALPI QHQDWMSGKE FKCKVNNKAL
351 PAPIERTISK PKGPVRAPQV YVLPPPEEEM TKKQVTLTCM ITDFMPEDIY
401 VEWTNNGQTE LNYKNTEPVL DSDGSYFMYS KLRVEKKNWV ERNSYSCSVV
451 HEGLHNHHTT KSFSRTPGK (SEQ ID NO:179)

包括訊號肽編碼序列之Ab-9 HC之核酸序列：

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
51 CCTCTCTGAG GTCCAACTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
101 GGACTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCACTGAC
151 TACAACATGC ACTGGGTGAA GCAGACCCAA GGAAAGACCC TAGAGTGGAT
201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAGTTCA

251 AGGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAA
351 ATTGGGCTAC GATGATATCT ACGACGACTG GTATTTCGAT GTCTGGGGCG
401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACAACAGC CCCATCGGTC
451 TATCCACTGG CCCCTGTGTG TGGAGATACA ACTGGCTCCT CGGTGACTCT
501 AGGATGCCTG GTCAAGGGTT ATTTCCCTGA GCCAGTGACC TTGACCTGGA
551 ACTCTGGATC CCTGTCCAGT GATGTGCACA CCTTCCCAGC TCTCCTGCAG
601 TCTGGCCTCT ACACCCTCAG CAGCTCAGTG ACTGTAACCA CCTGGCCCAG
651 CCAGACCATC ACCTGCAATG TGGCCCACCC GGCAAGCAGC ACCAAAGTGG
701 ACAAGAAAAT TGAGCCCAGA GGGTCCCCAA CACATAAACC CTGTCCTCCA
751 TGCCCAGCTC CTAACCTCTT GGGTGGACCA TCCGTCTTCA TCTTCCCTCC
801 AAAGATCAAG GATGTACTCA TGATCTCCCT GAGCCCCATG GTCACGTGTG
851 TGGTGGTGGA TGTGAGCGAG GATGACCCAG ATGTCCATGT CAGCTGGTTC
901 GTGAACAACG TGGAAGTACA CACAGCTCAG ACACAAACCC ATAGAGAGGA
951 TTACAACAGT ACTATCCGGG TGGTCAGTGC CCTCCCCATC CAGCACCAGG
1001 ACTGGATGAG TGGCAAGGAG TTCAAATGCA AGGTCAACAA CAAAGCCCTC
1051 CCAGCGCCCA TCGAGAGAAC CATCTCAAAA CCCAAAGGGC CAGTAAGAGC
1101 TCCACAGGTA TATGTCTTGC CTCCACCAGA AGAAGAGATG ACTAAGAAAC
1151 AGGTCACTCT GACCTGCATG ATCACAGACT TCATGCCTGA AGACATTTAC
1201 GTGGAGTGGA CCAACAACGG GCAAACAGAG CTAAACTACA AGAACACTGA
1251 ACCAGTCCTG GACTCTGATG GTTCTTACTT CATGTACAGC AAGCTGAGAG
1301 TGGAAAAGAA GAACTGGGTG GAAAGAAATA GCTACTCCTG TTCAGTGGTC
1351 CACGAGGGTC TGCACAATCA CCACACGACT AAGAGCTTCT CCCGGACTCC
1401 GGGTAAA (SEQ ID NO:180)

Ab-10

抗體10(本文亦稱為Ab-10)LC及HC之序列如下：

Ab-10輕鏈：

成熟形式(移除訊號肽)Ab-10 LC之胺基酸序列：

1 DIQMTQTTSS LSASLGDRVS ISCRASQDIS NYLNWYQQKP DGTFKLLIFY
51 TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ EDFATYFCQQ GDTLPYTFGG
101 GTKLEIK***RAD AAPTVSIFPL SSEQLTSGGA SVVCFLNNFY PKDINVKWKI***
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:181)

編碼成熟形式(移除訊號肽)Ab-10 LC之核酸序列：

1 GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT CTCTGGGAGA
51 CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC AATTATTTAA
101 ACTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT TATCTTCTAC

151 ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAGTG GCAGTGGGTC
201 TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA GAAGATTTTG
251 CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC TTTCGGAGGG
301 GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCCACTA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID NO:182)

包括訊號肽之Ab-10 LC的胺基酸序列：

1 MMSSAQFLGL LLLCFQGTRC DIQMTQTTSS LSASLGDRVS ISCRASQDIS
51 NYLNWYQQKP DGTFKLLIFY TSRLLSGVPS RFSGSGSGTD YSLTIYNLEQ
101 EDFATYFCQQ GDTLPYTFGG GTKLEIKRAD AAPTVSIFPL SSEQLTSGGA
151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:183)

包括訊號肽編碼序列之Ab-10 LC之核酸序列：

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TACCAGATGT GATATCCAGA TGACACAGAC TACATCCTCC CTGTCTGCCT
101 CTCTGGGAGA CAGGGTCTCC ATCAGTTGCA GGGCAAGTCA AGACATTAGC
151 AATTATTTAA ACTGGTATCA GCAGAAACCA GATGGAACTT TTAAACTCCT
201 TATCTTCTAC ACATCAAGAT TACTCTCAGG AGTCCCATCA AGGTTCAGTG
251 GCAGTGGGTC TGGAACAGAT TATTCTCTCA CCATTTACAA CCTGGAGCAA
301 GAAGATTTTG CCACTTACTT TTGCCAACAG GGAGATACGC TTCCGTACAC
351 TTTCGGAGGG GGGACCAAAC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
401 CTGTATCCAT CTTCCCACTA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
701 GTTAG (SEQ ID NO:184)

Ab-10重鏈：

成熟形式(移除訊號肽)Ab-10 HC之胺基酸序列：

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHWVKQN QGKTLEWIGE
51 INPNSGGAGY NQKFKGKATL TVDKSSTTAY MELRSLTSED SAVYYCARLG
101 YDDIYDDWYF DVWGAGTTVT VSS***AKTTPPS VYPLAPGSAA QTNSMVTLGC***
151 LVKGYFPEPV TVTWNSGSLS SGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
301 RSVSELPIMH QDWLNGKEFK CRVNSAAFPA PIEKTISKTK GRPKAPQVYT
351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID NO:185)

編碼成熟形式(移除訊號肽)Ab-10 HC之核酸序列：

1 GAGGTCCAAC TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA TACATTCACT GACTACAACA
101 TGCACTGGGT GAAGCAGAAC CAAGGAAAGA CCCTAGAATG GATAGGAGAA
151 ATTAATCCTA ACAGTGGTGG TGCTGGCTAC AACCAGAAGT TCAAGGGCAA
201 GGCCACATTG ACTGTAGACA AGTCCTCCAC CACAGCCTAC ATGGAGCTCC
251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
301 TACGATGATA TCTACGACGA CTGGTACTTC GATGTCTGGG GCGCAGGGAC
351 CACGGTCACC GTCTCCTCAG CCAAAACGAC ACCCCCATCT GTCTATCCAC
401 TGGCCCCTGG ATCTGCTGCC CAAACTAACT CCATGGTGAC CCTGGGATGC
451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAACTCTGG
501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC
551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
601 GAGACCGTCA CCTGCAACGT TGCCCACCCG GCCAGCAGCA CCAAGGTGGA
651 CAAGAAAATT GTGCCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAAAGCC CAAGGATGTG
751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
851 TGCACACAGC TCAGACGCAA CCCCGGGAGG AGCAGTTCAA CAGCACTTTC
901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC
1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA

1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID NO:186)

包括訊號肽之Ab-10 HC之胺基酸序列：

1 MGWSWTFLFL LSGTAGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
51 YNMHWVKQNQ GKTLEWIGEI NPNSGGAGYN QKFKGKATLT VDKSSTTAYM
101 ELRSLTSEDS AVYYCARLGY DDIYDDWYFD VWGAGTTVTV SSAKTTPPSV
151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
301 VEVHTAQTQP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVSLTCMITD FFPEDITVEW
401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
451 LHNHHTEKSL SHSPGK (SEQ ID NO:187)

包括訊號肽編碼序列之Ab-10 HC之核酸序列：

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTGCAGGTGT
51 CCTCTCTGAG GTCCAACTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATATAC ATTCACTGAC
151 TACAACATGC ACTGGGTGAA GCAGAACCAA GGAAAGACCC TAGAATGGAT
201 AGGAGAAATT AATCCTAACA GTGGTGGTGC TGGCTACAAC CAGAAGTTCA
251 AGGGCAAGGC CACATTGACT GTAGACAAGT CCTCCACCAC AGCCTACATG
301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
351 ATTGGGCTAC GATGATATCT ACGACGACTG GTACTTCGAT GTCTGGGGCG
401 CAGGGACCAC GGTCACCGTC TCCTCAGCCA AAACGACACC CCCATCTGTC
451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCCTGCAG
601 TCTGACCTCT ACACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTCACGTGT GTTGTGGTAG
851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT

1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
1201 CAGTGGAATG GGCAGCCAGC GGAGAACTAC AAGAACACTC AGCCCATCAT
1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAATG
1401 A (SEQ ID NO:188)

Ab-11

抗體11(本文亦稱為Ab-11)LC及HC之序列如下：

Ab-11輕鏈：

成熟形式(移除訊號肽)Ab-11 LC之胺基酸序列：

1 QIVLSQSPAF LSVSPGDKVT MTCRASSSIS YIHWFQQKPG SSPRSWIYAT
51 SNLASGVPGR FSGSGSGTSY SLTISRVEAE DAATYYCQQW SSDPLTFGAG
101 TKLELK***RADA APTVSIFPPS SEQLTSGGAS VVCFLNNFYP KDINVKWKID***
151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
201 TSPIVKSFNR NEC (SEQ ID NO:189)

編碼成熟形式(移除訊號肽)Ab-11 LC之核酸序列：

1 CAAATTGTTC TCTCCCAGTC TCCAGCATTC CTGTCTGTAT CTCCAGGGGA
51 TAAGGTCACA ATGACTTGCA GGGCCAGCTC AAGTATAAGT TACATACACT
101 GGTTTCAGCA GAAGCCAGGA TCCTCCCCCA GATCCTGGAT TTATGCCACA
151 TCCAACCTGG CTTCTGGAGT CCCTGGTCGC TTCAGTGGCA GTGGGTCTGG
201 GACCTCTTAC TCTCTCACAA TCAGCAGAGT GGAGGCTGAG GATGCTGCCA
251 CTTATTACTG CCAGCAGTGG AGTAGTGACC CACTCACGTT CGGTGCTGGG
301 ACCAAGCTGG AGCTGAAACG GGCTGATGCT GCACCAACTG TATCCATCTT
351 CCCACCATCC AGTGAGCAGT TAACATCTGG AGGTGCCTCA GTCGTGTGCT
401 TCTTGAACAA CTTCTACCCC AAAGACATCA ATGTCAAGTG GAAGATTGAT
451 GGCAGTGAAC GACAAAATGG CGTCCTGAAC AGTTGGACTG ATCAGGACAG
501 CAAAGACAGC ACCTACAGCA TGAGCAGCAC CCTCACGTTG ACCAAGGACG
551 AGTATGAACG ACATAACAGC TATACCTGTG AGGCCACTCA CAAGACATCA
601 ACTTCACCCA TTGTCAAGAG CTTCAACAGG AATGAGTGTT AG (SEQ ID NO:190)

包括訊號肽之Ab-11 LC之胺基酸序列：

1 MDFQVQIFSF LLISASVIMS RGQIVLSQSP AFLSVSPGDK VTMTCRASSS
51 ISYIHWFQQK PGSSPRSWIY ATSNLASGVP GRFSGSGSGT SYSLTISRVE

101 AEDAATYYCQ QWSSDPLTFG AGTKLELKRA DAAPTVSIFP PSSEQLTSGG
151 ASVVCFLNNF YPKDINVKWK IDGSERQNGV LNSWTDQDSK DSTYSMSSTL
201 TLTKDEYERH NSYTCEATHK TSTSPIVKSF NRNEC (SEQ ID NO:191)

包括訊號肽編碼序列之Ab-11 LC之核酸序列：

1 ATGGATTTTC AAGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCTTCAGT
51 CATAATGTCC AGAGGACAAA TTGTTCTCTC CCAGTCTCCA GCATTCCTGT
101 CTGTATCTCC AGGGGATAAG GTCACAATGA CTTGCAGGGC CAGCTCAAGT
151 ATAAGTTACA TACACTGGTT TCAGCAGAAG CCAGGATCCT CCCCCAGATC
201 CTGGATTTAT GCCACATCCA ACCTGGCTTC TGGAGTCCCT GGTCGCTTCA
251 GTGGCAGTGG GTCTGGGACC TCTTACTCTC TCACAATCAG CAGAGTGGAG
301 GCTGAGGATG CTGCCACTTA TTACTGCCAG CAGTGGAGTA GTGACCCACT
351 CACGTTCGGT GCTGGGACCA AGCTGGAGCT GAAACGGGCT GATGCTGCAC
401 CAACTGTATC CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT
451 GCCTCAGTCG TGTGCTTCTT GAACAACTTC TACCCCAAAG ACATCAATGT
501 CAAGTGGAAG ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT
551 GGACTGATCA GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCTC
601 ACGTTGACCA AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC
651 CACTCACAAG ACATCAACTT CACCCATTGT CAAGAGCTTC AACAGGAATG
701 AGTGTTAG (SEQ ID NO:192)

Ab-11重鏈：

成熟形式(移除訊號肽)Ab-11 HC之胺基酸序列：

1 EVQLQQSGAD LVQPGASVKV SCTASGFDIK DYYIHWMKQR PDQGLEWIGR
51 VDPDNGETEF APKFPGKATF TTDTSSNTAY LQLRGLTSED TAIYYCGRED
101 YDGTYTWFPY WGQGTLVTVS A***AKTTPPSVY PLAPGSAAQT NSMVTLGCLV***
151 KGYFPEPVTV TWNSGSLSSG VHTFPAVLQS DLYTLSSSVT VPSSTWPSET
201 VTCNVAHPAS STKVDKKIVP RDCGCKPCIC TVPEVSSVFI FPPKPKDVLT
251 ITLTPKVTCV VVDISKDDPE VQFSWFVDDV EVHTAQTQPR EEQFNSTFRS
301 VSELPIMHQD WLNGKEFKCR VNSAAFPAPI EKTISKTKGR PKAPQVYTIP
351 PPKEQMAKDK VSLTCMITDF FPEDITVEWQ WNGQPAENYK NTQPIMDTDG
401 SYFIYSKLNV QKSNWEAGNT FTCSVLHEGL HNHHTEKSLS HSPGK (SEQ ID NO:193)

編碼成熟形式(移除訊號肽)Ab-11 HC之核酸序列：

1 GAAGTTCAGC TGCAACAGTC TGGGGCAGAC CTTGTGCAGC CAGGGGCCTC
51 AGTCAAGGTG TCCTGCACAG CTTCTGGCTT CGACATTAAG GACTACTATA
101 TACACTGGAT GAAACAGAGG CCTGACCAGG GCCTGGAGTG GATTGGAAGG
151 GTTGATCCTG ACAATGGTGA GACTGAATTT GCCCCGAAGT TCCCGGGCAA
201 GGCCACTTTT ACAACAGACA CATCCTCCAA CACAGCCTAC CTACAACTCA

251 GAGGCCTGAC ATCTGAGGAC ACTGCCATCT ATTACTGTGG GAGAGAAGAC
301 TACGATGGTA CCTACACCTG GTTTCCTTAT TGGGGCCAAG GGACTCTGGT
351 CACTGTCTCT GCAGCCAAAA CGACACCCCC ATCTGTCTAT CCACTGGCCC
401 CTGGATCTGC TGCCCAAACT AACTCCATGG TGACCCTGGG ATGCCTGGTC
451 AAGGGCTATT TCCCTGAGCC AGTGACAGTG ACCTGGAACT CTGGATCCCT
501 GTCCAGCGGT GTGCACACCT TCCCAGCTGT CCTGCAGTCT GACCTCTACA
551 CTCTGAGCAG CTCAGTGACT GTCCCCTCCA GCACCTGGCC CAGCGAGACC
601 GTCACCTGCA ACGTTGCCCA CCCGGCCAGC AGCACCAAGG TGGACAAGAA
651 AATTGTGCCC AGGGATTGTG GTTGTAAGCC TTGCATATGT ACAGTCCCAG
701 AAGTATCATC TGTCTTCATC TTCCCCCCAA AGCCCAAGGA TGTGCTCACC
751 ATTACTCTGA CTCCTAAGGT CACGTGTGTT GTGGTAGACA TCAGCAAGGA
801 TGATCCCGAG GTCCAGTTCA GCTGGTTTGT AGATGATGTG GAGGTGCACA
851 CAGCTCAGAC GCAACCCCGG GAGGAGCAGT TCAACAGCAC TTTCCGCTCA
901 GTCAGTGAAC TTCCCATCAT GCACCAGGAC TGGCTCAATG GCAAGGAGTT
951 CAAATGCAGG GTCAACAGTG CAGCTTTCCC TGCCCCCATC GAGAAAACCA
1001 TCTCCAAAAC CAAAGGCAGA CCGAAGGCTC CACAGGTGTA CACCATTCCA
1051 CCTCCCAAGG AGCAGATGGC CAAGGATAAA GTCAGTCTGA CCTGCATGAT
1101 AACAGACTTC TTCCCTGAAG ACATTACTGT GGAGTGGCAG TGGAATGGGC
1151 AGCCAGCGGA GAACTACAAG AACACTCAGC CCATCATGGA CACAGATGGC
1201 TCTTACTTCA TCTACAGCAA GCTCAATGTG CAGAAGAGCA ACTGGGAGGC
1251 AGGAAATACT TTCACCTGCT CTGTGTTACA TGAGGGCCTG CACAACCACC
1301 ATACTGAGAA GAGCCTCTCC CACTCTCCTG GTAAATGA (SEQ ID NO:194)

包括訊號肽之Ab-11 HC之胺基酸序列：

1 MKCSWVIFFL MAVVTGVNSE VQLQQSGADL VQPGASVKVS CTASGFDIKD
51 YYIHWMKQRP DQGLEWIGRV DPDNGETEFA PKFPGKATFT TDTSSNTAYL
101 QLRGLTSEDT AIYYCGREDY DGTYTWFPYW GQGTLVTVSA AKTTPPSVYP
151 LAPGSAAQTN SMVTLGCLVK GYFPEPVTVT WNSGSLSSGV HTFPAVLQSD
201 LYTLSSSVTV PSSTWPSETV TCNVAHPASS TKVDKKIVPR DCGCKPCICT
251 VPEVSSVFIF PPKPKDVLTI TLTPKVTCVV VDISKDDPEV QFSWFVDDVE
301 VHTAQTQPRE EQFNSTFRSV SELPIMHQDW LNGKEFKCRV NSAAFPAPIE
351 KTISKTKGRP KAPQVYTIPP PKEQMAKDKV SLTCMITDFF PEDITVEWQW
401 NGQPAENYKN TQPIMDTDGS YFIYSKLNVQ KSNWEAGNTF TCSVLHEGLH
451 NHHTEKSLSH SPGK (SEQ ID NO:195)

包括訊號肽編碼序列之Ab-11 HC之核酸序列：

1 ATGAAATGCA GCTGGGTCAT CTTCTTCCTG ATGGCAGTGG TTACAGGGGT
51 CAATTCAGAA GTTCAGCTGC AACAGTCTGG GGCAGACCTT GTGCAGCCAG
101 GGGCCTCAGT CAAGGTGTCC TGCACAGCTT CTGGCTTCGA CATTAAGGAC
151 TACTATATAC ACTGGATGAA ACAGAGGCCT GACCAGGGCC TGGAGTGGAT
201 TGGAAGGGTT GATCCTGACA ATGGTGAGAC TGAATTTGCC CCGAAGTTCC

251 CGGGCAAGGC CACTTTTACA ACAGACACAT CCTCCAACAC AGCCTACCTA
301 CAACTCAGAG GCCTGACATC TGAGGACACT GCCATCTATT ACTGTGGGAG
351 AGAAGACTAC GATGGTACCT ACACCTGGTT TCCTTATTGG GGCCAAGGGA
401 CTCTGGTCAC TGTCTCTGCA GCCAAAACGA CACCCCCATC TGTCTATCCA
451 CTGGCCCCTG GATCTGCTGC CCAAACTAAC TCCATGGTGA CCCTGGGATG
501 CCTGGTCAAG GGCTATTTCC CTGAGCCAGT GACAGTGACC TGGAACTCTG
551 GATCCCTGTC CAGCGGTGTG CACACCTTCC CAGCTGTCCT GCAGTCTGAC
601 CTCTACACTC TGAGCAGCTC AGTGACTGTC CCCTCCAGCA CCTGGCCCAG
651 CGAGACCGTC ACCTGCAACG TTGCCCACCC GGCCAGCAGC ACCAAGGTGG
701 ACAAGAAAAT TGTGCCCAGG GATTGTGGTT GTAAGCCTTG CATATGTACA
751 GTCCCAGAAG TATCATCTGT CTTCATCTTC CCCCCAAAGC CCAAGGATGT
801 GCTCACCATT ACTCTGACTC CTAAGGTCAC GTGTGTTGTG GTAGACATCA
851 GCAAGGATGA TCCCGAGGTC CAGTTCAGCT GGTTTGTAGA TGATGTGGAG
901 GTGCACACAG CTCAGACGCA ACCCCGGGAG GAGCAGTTCA ACAGCACTTT
951 CCGCTCAGTC AGTGAACTTC CCATCATGCA CCAGGACTGG CTCAATGGCA
1001 AGGAGTTCAA ATGCAGGGTC AACAGTGCAG CTTTCCCTGC CCCCATCGAG
1051 AAAACCATCT CCAAAACCAA AGGCAGACCG AAGGCTCCAC AGGTGTACAC
1101 CATTCCACCT CCCAAGGAGC AGATGGCCAA GGATAAAGTC AGTCTGACCT
1151 GCATGATAAC AGACTTCTTC CCTGAAGACA TTACTGTGGA GTGGCAGTGG
1201 AATGGGCAGC CAGCGGAGAA CTACAAGAAC ACTCAGCCCA TCATGGACAC
1251 AGATGGCTCT TACTTCATCT ACAGCAAGCT CAATGTGCAG AAGAGCAACT
1301 GGGAGGCAGG AAATACTTTC ACCTGCTCTG TGTTACATGA GGGCCTGCAC
1351 AACCACCATA CTGAGAAGAG CCTCTCCCAC TCTCCTGGTA AATGA (SEQ ID NO:196)

Ab-12

抗體12(本文亦稱為Ab-12)LC及HC之序列如下：

Ab-12輕鏈：

成熟形式(移除訊號肽)Ab-12 LC之胺基酸序列：

1 DLQMTQTTSS LSASLGDRVT ISCRASQDIS NYLNWYQQKP DGTVKLLIFY
51 TSTLQSGVPS RFSGSGSGTN YSLTITNLEQ DDAATYFCQQ GDTLPYTFGG
101 GTKLEIK***RAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI***
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC (SEQ ID NO:197)

編碼成熟形式(移除訊號肽)Ab-12 LC之核酸序列：

1 GATCTCCAGA TGACACAGAC TACTTCCTCC CTGTCTGCCT CTCTGGGAGA
51 CAGAGTCACC ATCAGTTGCA GGGCAAGTCA GGACATTAGC AATTATTTAA

101 ACTGGTATCA GCAGAAACCA GATGGAACTG TTAAGCTCCT GATCTTCTAC
151 ACATCAACAT TACAGTCAGG AGTCCCATCG AGGTTCAGTG GCAGTGGGTC
201 TGGAACAAAT TATTCTCTCA CCATTACCAA CCTGGAGCAA GATGATGCTG
251 CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC GTTCGGAGGG
301 GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA CTGTATCCAT
351 CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC TCAGTCGTGT
401 GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA GTGGAAGATT
451 GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA CTGATCAGGA
501 CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG TTGACCAAGG
551 ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC TCACAAGACA
601 TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT GTTAG (SEQ ID NO:198)

包括訊號肽之Ab-12 LC之胺基酸序列：

1 MMSSAQFLGL LLLCFQGSRC DLQMTQTTSS LSASLGDRVT ISCRASQDIS
51 NYLNWYQQKP DGTVKLLIFY TSTLQSGVPS RFSGSGSGTN YSLTITNLEQ
101 DDAATYFCQQ GDTLPYTFGG GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA
151 SVVCFLNNFY PKDINVKWKI DGSERQNGVL NSWTDQDSKD STYSMSSTLT
201 LTKDEYERHN SYTCEATHKT STSPIVKSFN RNEC (SEQ ID NO:199)

包括訊號肽編碼序列之Ab-12 LC之核酸序列：

1 ATGATGTCCT CTGCTCAGTT CCTTGGTCTC CTGTTGCTCT GTTTTCAAGG
51 TTCCAGATGT GATCTCCAGA TGACACAGAC TACTTCCTCC CTGTCTGCCT
101 CTCTGGGAGA CAGAGTCACC ATCAGTTGCA GGGCAAGTCA GGACATTAGC
151 AATTATTTAA ACTGGTATCA GCAGAAACCA GATGGAACTG TTAAGCTCCT
201 GATCTTCTAC ACATCAACAT TACAGTCAGG AGTCCCATCG AGGTTCAGTG
251 GCAGTGGGTC TGGAACAAAT TATTCTCTCA CCATTACCAA CCTGGAGCAA
301 GATGATGCTG CCACTTACTT TTGCCAACAG GGTGATACGC TTCCGTACAC
351 GTTCGGAGGG GGGACCAAGC TGGAAATAAA ACGGGCTGAT GCTGCACCAA
401 CTGTATCCAT CTTCCCACCA TCCAGTGAGC AGTTAACATC TGGAGGTGCC
451 TCAGTCGTGT GCTTCTTGAA CAACTTCTAC CCCAAAGACA TCAATGTCAA
501 GTGGAAGATT GATGGCAGTG AACGACAAAA TGGCGTCCTG AACAGTTGGA
551 CTGATCAGGA CAGCAAAGAC AGCACCTACA GCATGAGCAG CACCCTCACG
601 TTGACCAAGG ACGAGTATGA ACGACATAAC AGCTATACCT GTGAGGCCAC
651 TCACAAGACA TCAACTTCAC CCATTGTCAA GAGCTTCAAC AGGAATGAGT
701 GTTAG (SEQ ID NO:200)

Ab-12重鏈：

成熟形式(移除訊號肽)Ab-12 HC之胺基酸序列：

1 EVQLQQSGPE LMKPGASVKM SCKASGYTFT DYNMHWMKQN QGKSLEWIGE
51 INPNSGGSGY NQKFKGKATL TVDKSSSTAY MELRSLTSED SAVYYCARLG
101 YYGNYEDWYF DVWGAGTTVT VSS***AKTTPPS VYPLAPGSAA QTNSMVTLGC***
151 LVKGYFPEPV TVTWNSGSLS SGVHTFPAVL QSDLYTLSSS VTVPSSTWPS
201 ETVTCNVAHP ASSTKVDKKI VPRDCGCKPC ICTVPEVSSV FIFPPKPKDV
251 LTITLTPKVT CVVVDISKDD PEVQFSWFVD DVEVHTAQTQ PREEQFNSTF
301 RSVSELPIMH QDWLNGKEFK CRVNSAAFPA PIEKTISKTK GRPKAPQVYT
351 IPPPKEQMAK DKVSLTCMIT DFFPEDITVE WQWNGQPAEN YKNTQPIMDT
401 DGSYFIYSKL NVQKSNWEAG NTFTCSVLHE GLHNHHTEKS LSHSPGK (SEQ ID NO:201)

編碼成熟形式(移除訊號肽)Ab-12 HC之核酸序列：

1 GAGGTCCAGT TGCAACAGTC TGGACCTGAA CTAATGAAGC CTGGGGCTTC
51 AGTGAAGATG TCCTGCAAGG CTTCTGGATA CACATTCACT GACTACAACA
101 TGCACTGGAT GAAGCAGAAC CAAGGAAAGA GCCTAGAGTG GATAGGAGAG
151 ATTAATCCTA ACAGTGGTGG TTCTGGTTAC AACCAGAAGT TCAAAGGCAA
201 GGCCACATTG ACTGTAGACA AGTCCTCCAG CACAGCCTAC ATGGAGCTCC
251 GCAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGATTGGGC
301 TACTATGGTA ACTACGAGGA CTGGTATTTC GATGTCTGGG GCGCAGGGAC
351 CACGGTCACC GTCTCCTCTG CCAAAACGAC ACCCCCATCT GTCTATCCAC
401 TGGCCCCTGG ATCTGCTGCC CAAACTAACT CCATGGTGAC CCTGGGATGC
451 CTGGTCAAGG GCTATTTCCC TGAGCCAGTG ACAGTGACCT GGAACTCTGG
501 ATCCCTGTCC AGCGGTGTGC ACACCTTCCC AGCTGTCCTG CAGTCTGACC
551 TCTACACTCT GAGCAGCTCA GTGACTGTCC CCTCCAGCAC CTGGCCCAGC
601 GAGACCGTCA CCTGCAACGT TGCCCACCCG GCCAGCAGCA CCAAGGTGGA
651 CAAGAAAATT GTGCCCAGGG ATTGTGGTTG TAAGCCTTGC ATATGTACAG
701 TCCCAGAAGT ATCATCTGTC TTCATCTTCC CCCCAAAGCC CAAGGATGTG
751 CTCACCATTA CTCTGACTCC TAAGGTCACG TGTGTTGTGG TAGACATCAG
801 CAAGGATGAT CCCGAGGTCC AGTTCAGCTG GTTTGTAGAT GATGTGGAGG
851 TGCACACAGC TCAGACGCAA CCCCGGGAGG AGCAGTTCAA CAGCACTTTC
901 CGCTCAGTCA GTGAACTTCC CATCATGCAC CAGGACTGGC TCAATGGCAA
951 GGAGTTCAAA TGCAGGGTCA ACAGTGCAGC TTTCCCTGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGCAGACCGA AGGCTCCACA GGTGTACACC
1051 ATTCCACCTC CCAAGGAGCA GATGGCCAAG GATAAAGTCA GTCTGACCTG
1101 CATGATAACA GACTTCTTCC CTGAAGACAT TACTGTGGAG TGGCAGTGGA
1151 ATGGGCAGCC AGCGGAGAAC TACAAGAACA CTCAGCCCAT CATGGACACA
1201 GATGGCTCTT ACTTCATCTA CAGCAAGCTC AATGTGCAGA AGAGCAACTG
1251 GGAGGCAGGA AATACTTTCA CCTGCTCTGT GTTACATGAG GGCCTGCACA
1301 ACCACCATAC TGAGAAGAGC CTCTCCCACT CTCCTGGTAA ATGA (SEQ ID NO:202)

包括訊號肽之Ab-12 HC之胺基酸序列：

1 MGWSWTFLFL LSGTSGVLSE VQLQQSGPEL MKPGASVKMS CKASGYTFTD
51 YNMHWMKQNQ GKSLEWIGEI NPNSGGSGYN QKFKGKATLT VDKSSSTAYM
101 ELRSLTSEDS AVYYCARLGY YGNYEDWYFD VWGAGTTVTV SSAKTTPPSV
151 YPLAPGSAAQ TNSMVTLGCL VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ
201 SDLYTLSSSV TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
251 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP EVQFSWFVDD
301 VEVHTAQTQP REEQFNSTFR SVSELPIMHQ DWLNGKEFKC RVNSAAFPAP
351 IEKTISKTKG RPKAPQVYTI PPPKEQMAKD KVSLTCMITD FFPEDITVEW
401 QWNGQPAENY KNTQPIMDTD GSYFIYSKLN VQKSNWEAGN TFTCSVLHEG
451 LHNHHTEKSL SHSPGK (SEQ ID NO:203)

包括訊號肽編碼序列之Ab-12 HC之核酸序列：

1 ATGGGATGGA GCTGGACCTT TCTCTTCCTC CTGTCAGGAA CTTCGGGTGT
51 CCTCTCTGAG GTCCAGTTGC AACAGTCTGG ACCTGAACTA ATGAAGCCTG
101 GGGCTTCAGT GAAGATGTCC TGCAAGGCTT CTGGATACAC ATTCACTGAC
151 TACAACATGC ACTGGATGAA GCAGAACCAA GGAAAGAGCC TAGAGTGGAT
201 AGGAGAGATT AATCCTAACA GTGGTGGTTC TGGTTACAAC CAGAAGTTCA
251 AAGGCAAGGC CACATTGACT GTAGACAAGT CCTCCAGCAC AGCCTACATG
301 GAGCTCCGCA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
351 ATTGGGCTAC TATGGTAACT ACGAGGACTG GTATTTCGAT GTCTGGGGCG
401 CAGGGACCAC GGTCACCGTC TCCTCTGCCA AAACGACACC CCCATCTGTC
451 TATCCACTGG CCCCTGGATC TGCTGCCCAA ACTAACTCCA TGGTGACCCT
501 GGGATGCCTG GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
551 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC TGTCCTGCAG
601 TCTGACCTCT ACACTCTGAG CAGCTCAGTG ACTGTCCCCT CCAGCACCTG
651 GCCCAGCGAG ACCGTCACCT GCAACGTTGC CCACCCGGCC AGCAGCACCA
701 AGGTGGACAA GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
751 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC CAAAGCCCAA
801 GGATGTGCTC ACCATTACTC TGACTCCTAA GGTCACGTGT GTTGTGGTAG
851 ACATCAGCAA GGATGATCCC GAGGTCCAGT TCAGCTGGTT TGTAGATGAT
901 GTGGAGGTGC ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
951 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG GACTGGCTCA
1001 ATGGCAAGGA GTTCAAATGC AGGGTCAACA GTGCAGCTTT CCCTGCCCCC
1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGC AGACCGAAGG CTCCACAGGT
1101 GTACACCATT CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
1151 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC TGTGGAGTGG
1201 CAGTGGAATG GGCAGCCAGC GGAGAACTAC AAGAACACTC AGCCCATCAT
1251 GGACACAGAT GGCTCTTACT TCATCTACAG CAAGCTCAAT GTGCAGAAGA
1301 GCAACTGGGA GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
1351 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC CTGGTAAATG
1401 A (SEQ ID NO:204)

Ab-13

抗體13(本文亦稱為Ab-13)LC及HC之序列如下：

Ab-13輕鏈：

成熟形式(移除訊號肽)Ab-13 LC之胺基酸序列：

1 QIVLTQSPAI MSASPGEKVT MTCRASSSVT SSYLNWYQQK PGSSPKLWIY
51 STSNLASGVP ARFSGSGSGT SYSLTISSVE AEDAATYYCQ QYDFFPSTFG
101 GGTKLEIK***RA DAAPTVSIFP PSSEQLTSGG ASVVCFLNNF YPKDINVKWK***
151 IDGSERQNGV LNSWTDQDSK DSTYSMSSTL TLTKDEYERH NSYTCEATHK
201 TSTSPIVKSF NRNEC (SEQ ID NO:205)

編碼成熟形式(移除訊號肽)Ab-13 LC之核酸序列：

1 CAGATTGTTC TCACCCAGTC TCCAGCAATC ATGTCTGCAT CTCCAGGGGA
51 GAAGGTCACC ATGACCTGCA GGGCCAGCTC AAGTGTAACT TCCAGTTACT
101 TGAACTGGTA CCAGCAGAAG CCAGGATCTT CCCCCAAACT CTGGATTTAT
151 AGCACATCCA ACCTGGCTTC AGGAGTCCCA GCTCGCTTCA GTGGCAGTGG
201 GTCTGGGACC TCTTACTCTC TCACAATCAG CAGTGTGGAG GCTGAGGATG
251 CTGCCACTTA TTACTGCCAG CAGTATGATT TTTTCCCATC GACGTTCGGT
301 GGAGGCACCA AGCTGGAAAT CAAGCGGGCT GATGCTGCAC CAACTGTATC
351 CATCTTCCCA CCATCCAGTG AGCAGTTAAC ATCTGGAGGT GCCTCAGTCG
401 TGTGCTTCTT GAACAACTTC TACCCCAAAG ACATCAATGT CAAGTGGAAG
451 ATTGATGGCA GTGAACGACA AAATGGCGTC CTGAACAGTT GGACTGATCA
501 GGACAGCAAA GACAGCACCT ACAGCATGAG CAGCACCCTC ACGTTGACCA
551 AGGACGAGTA TGAACGACAT AACAGCTATA CCTGTGAGGC CACTCACAAG
601 ACATCAACTT CACCCATCGT CAAGAGCTTC AACAGGAATG AGTGT (SEQ ID NO:206)

包括訊號肽之Ab-13 LC之胺基酸序列：

1 MDSQVQIFSF LLISALVKMS RGQIVLTQSP AIMSASPGEK VTMTCRASSS
51 VTSSYLNWYQ QKPGSSPKLW IYSTSNLASG VPARFSGSGS GTSYSLTISS
101 VEAEDAATYY CQQYDFFPST FGGGTKLEIK RADAAPTVSI FPPSSEQLTS
151 GGASVVCFLN NFYPKDINVK WKIDGSERQN GVLNSWTDQD SKDSTYSMSS
201 TLTLTKDEYE RHNSYTCEAT HKTSTSPIVK SFNRNEC (SEQ ID NO:207)

包括訊號肽編碼序列之Ab-13 LC之核酸序列：

1 ATGGATTCTC AAGTGCAGAT TTTCAGCTTC CTTCTAATCA GTGCCTTAGT
51 CAAAATGTCC AGAGGACAGA TTGTTCTCAC CCAGTCTCCA GCAATCATGT

101 CTGCATCTCC AGGGGAGAAG GTCACCATGA CCTGCAGGGC CAGCTCAAGT
151 GTAACTTCCA GTTACTTGAA CTGGTACCAG CAGAAGCCAG GATCTTCCCC
201 CAAACTCTGG ATTTATAGCA CATCCAACCT GGCTTCAGGA GTCCCAGCTC
251 GCTTCAGTGG CAGTGGGTCT GGGACCTCTT ACTCTCTCAC AATCAGCAGT
301 GTGGAGGCTG AGGATGCTGC CACTTATTAC TGCCAGCAGT ATGATTTTTT
351 CCCATCGACG TTCGGTGGAG GCACCAAGCT GGAAATCAAG CGGGCTGATG
401 CTGCACCAAC TGTATCCATC TTCCCACCAT CCAGTGAGCA GTTAACATCT
451 GGAGGTGCCT CAGTCGTGTG CTTCTTGAAC AACTTCTACC CCAAAGACAT
501 CAATGTCAAG TGGAAGATTG ATGGCAGTGA ACGACAAAAT GGCGTCCTGA
551 ACAGTTGGAC TGATCAGGAC AGCAAAGACA GCACCTACAG CATGAGCAGC
601 ACCCTCACGT TGACCAAGGA CGAGTATGAA CGACATAACA GCTATACCTG
651 TGAGGCCACT CACAAGACAT CAACTTCACC CATCGTCAAG AGCTTCAACA
701 GGAATGAGTG T (SEQ ID NO:208)

Ab-13重鏈：

成熟形式(移除訊號肽)Ab-13 HC之胺基酸序列：

1 EVQLQQSGPE LVKPGASVKM SCKASGYTFT DYYMNWVKQS HGESLEWIGD
51 INPYNDDTTY NHKFKGKATL TVDKSSNTAY MQLNSLTSED SAVYYCARET
101 AVITTNAMDY WGQGTSVTVS S***AKTTPPSVY PLAPGSAAQT NSMVTLGCLV***
151 KGYFPEPVTV TWNSGSLSSG VHTFPAVLQS DLYTLSSSVT VPSSTWPSET
201 VTCNVAHPAS STKVDKKIVP RDCGCKPCIC TVPEVSSVFI FPPKPKDVLT
251 ITLTPKVTCV VVDISKDDPE VQFSWFVDDV EVHTAQTQPR EEQFNSTFRS
301 VSELPIMHQD WLNGKEFKCR VNSAAFPAPI EKTISKTKGR PKAPQVYTIP
351 PPKEQMAKDK VSLTCMITDF FPEDITVEWQ WNGQPAENYK NTQPIMDTDG
401 SYFIYSKLNV QKSNWEAGNT FTCSVLHEGL HNHHTEKSLS HSPGK (SEQ ID NO:209)

編碼成熟形式(移除訊號肽)Ab-13 HC之核酸序列：

1 GAGGTCCAGC TGCAACAATC TGGACCTGAG CTGGTGAAGC CTGGGGCTTC
51 AGTGAAGATG TCCTGTAAGG CTTCTGGATA CACATTCACT GACTACTACA
101 TGAACTGGGT GAAGCAGAGC CATGGAGAGA GCCTTGAGTG GATTGGAGAT
151 ATTAATCCTT ACAACGATGA TACTACCTAC AACCACAAGT TCAAGGGCAA
201 GGCCACATTG ACTGTAGACA AATCCTCCAA CACAGCCTAC ATGCAGCTCA
251 ACAGCCTGAC ATCTGAGGAC TCTGCAGTCT ATTACTGTGC AAGAGAGACG
301 GCCGTTATTA CTACGAATGC TATGGACTAC TGGGGTCAAG GAACCTCAGT
351 CACCGTCTCC TCAGCCAAAA CGACACCCCC ATCTGTCTAT CCACTGGCCC
401 CTGGATCTGC TGCCCAAACT AACTCCATGG TGACCCTGGG ATGCCTGGTC
451 AAGGGCTATT TCCCTGAGCC AGTGACAGTG ACCTGGAACT CTGGATCCCT
501 GTCCAGCGGT GTGCACACCT TCCCAGCTGT CCTGCAGTCT GACCTCTACA
551 CTCTGAGCAG CTCAGTGACT GTCCCCTCCA GCACCTGGCC CAGCGAGACC
601 GTCACCTGCA ACGTTGCCCA CCCGGCCAGC AGCACCAAGG TGGACAAGAA
651 AATTGTGCCC AGGGATTGTG GTTGTAAGCC TTGCATATGT ACAGTCCCAG

701 AAGTATCATC TGTCTTCATC TTCCCCCCAA AGCCCAAGGA TGTGCTCACC
751 ATTACTCTGA CTCCTAAGGT CACGTGTGTT GTGGTAGACA TCAGCAAGGA
801 TGATCCCGAG GTCCAGTTCA GCTGGTTTGT AGATGATGTG GAGGTGCACA
851 CAGCTCAGAC GCAACCCCGG GAGGAGCAGT TCAACAGCAC TTTCCGCTCA
901 GTCAGTGAAC TTCCCATCAT GCACCAGGAC TGGCTCAATG GCAAGGAGTT
951 CAAATGCAGG GTCAACAGTG CAGCTTTCCC TGCCCCCATC GAGAAAACCA
1001 TCTCCAAAAC CAAAGGCAGA CCGAAGGCTC CACAGGTGTA CACCATTCCA
1051 CCTCCCAAGG AGCAGATGGC CAAGGATAAA GTCAGTCTGA CCTGCATGAT
1101 AACAGACTTC TTCCCTGAAG ACATTACTGT GGAGTGGCAG TGGAATGGGC
1151 AGCCAGCGGA GAACTACAAG AACACTCAGC CCATCATGGA CACAGATGGC
1201 TCTTACTTCA TCTACAGCAA GCTCAATGTG CAGAAGAGCA ACTGGGAGGC
1251 AGGAAATACT TTCACCTGCT CTGTGTTACA TGAGGGCCTG CACAACCACC
1301 ATACTGAGAA GAGCCTCTCC CACTCTCCTG GTAAA (SEQ ID NO:210)

包括訊號肽之Ab-13 HC之胺基酸序列：

1 MGWNWIFLFL LSGTAGVYSE VQLQQSGPEL VKPGASVKMS CKASGYTFTD
51 YYMNWVKQSH GESLEWIGDI NPYNDDTTYN HKFKGKATLT VDKSSNTAYM
101 QLNSLTSEDS AVYYCARETA VITTNAMDYW GQGTSVTVSS AKTTPPSVYP
151 LAPGSAAQTN SMVTLGCLVK GYFPEPVTVT WNSGSLSSGV HTFPAVLQSD
201 LYTLSSSVTV PSSTWPSETV TCNVAHPASS TKVDKKIVPR DCGCKPCICT
251 VPEVSSVFIF PPKPKDVLTI TLTPKVTCVV VDISKDDPEV QFSWFVDDVE
301 VHTAQTQPRE EQFNSTFRSV SELPIMHQDW LNGKEFKCRV NSAAFPAPIE
351 KTISKTKGRP KAPQVYTIPP PKEQMAKDKV SLTCMITDFF PEDITVEWQW
401 NGQPAENYKN TQPIMDTDGS YFIYSKLNVQ KSNWEAGNTF TCSVLHEGLH
451 NHHTEKSLSH SPGK (SEQ ID NO:211)

包括訊號肽編碼序列之Ab-13 HC之核酸序列：

1 ATGGGATGGA ACTGGATCTT TCTCTTCCTC TTGTCAGGAA CTGCAGGTGT
51 CTACTCTGAG GTCCAGCTGC AACAATCTGG ACCTGAGCTG GTGAAGCCTG
101 GGGCTTCAGT GAAGATGTCC TGTAAGGCTT CTGGATACAC ATTCACTGAC
151 TACTACATGA ACTGGGTGAA GCAGAGCCAT GGAGAGAGCC TTGAGTGGAT
201 TGGAGATATT AATCCTTACA ACGATGATAC TACCTACAAC CACAAGTTCA
251 AGGGCAAGGC CACATTGACT GTAGACAAAT CCTCCAACAC AGCCTACATG
301 CAGCTCAACA GCCTGACATC TGAGGACTCT GCAGTCTATT ACTGTGCAAG
351 AGAGACGGCC GTTATTACTA CGAATGCTAT GGACTACTGG GGTCAAGGAA
401 CCTCAGTCAC CGTCTCCTCA GCCAAAACGA CACCCCCATC TGTCTATCCA
451 CTGGCCCCTG GATCTGCTGC CCAAACTAAC TCCATGGTGA CCCTGGGATG
501 CCTGGTCAAG GGCTATTTCC CTGAGCCAGT GACAGTGACC TGGAACTCTG
551 GATCCCTGTC CAGCGGTGTG CACACCTTCC CAGCTGTCCT GCAGTCTGAC
601 CTCTACACTC TGAGCAGCTC AGTGACTGTC CCCTCCAGCA CCTGGCCCAG
651 CGAGACCGTC ACCTGCAACG TTGCCCACCC GGCCAGCAGC ACCAAGGTGG
701 ACAAGAAAAT TGTGCCCAGG GATTGTGGTT GTAAGCCTTG CATATGTACA
751 GTCCCAGAAG TATCATCTGT CTTCATCTTC CCCCCAAAGC CCAAGGATGT

801 GCTCACCATT ACTCTGACTC CTAAGGTCAC GTGTGTTGTG GTAGACATCA
851 GCAAGGATGA TCCCGAGGTC CAGTTCAGCT GGTTTGTAGA TGATGTGGAG
901 GTGCACACAG CTCAGACGCA ACCCCGGGAG GAGCAGTTCA ACAGCACTTT
951 CCGCTCAGTC AGTGAACTTC CCATCATGCA CCAGGACTGG CTCAATGGCA
1001 AGGAGTTCAA ATGCAGGGTC AACAGTGCAG CTTTCCCTGC CCCCATCGAG
1051 AAAACCATCT CCAAAACCAA AGGCAGACCG AAGGCTCCAC AGGTGTACAC
1101 CATTCCACCT CCCAAGGAGC AGATGGCCAA GGATAAAGTC AGTCTGACCT
1151 GCATGATAAC AGACTTCTTC CCTGAAGACA TTACTGTGGA GTGGCAGTGG
1201 AATGGGCAGC CAGCGGAGAA CTACAAGAAC ACTCAGCCCA TCATGGACAC
1251 AGATGGCTCT TACTTCATCT ACAGCAAGCT CAATGTGCAG AAGAGCAACT
1301 GGGAGGCAGG AAATACTTTC ACCTGCTCTG TGTTACATGA GGGCCTGCAC
1351 AACCACCATA CTGAGAAGAG CCTCTCCCAC TCTCCTGGTA AA (SEQ ID NO:212)

Ab-13經人化以產生Ab-14。

抗體14(本文亦稱為Ab-14)LC及HC之序列如下：

Ab-14輕鏈：

成熟形式(移除訊號肽)Ab-14 LC之胺基酸序列：

1 DIQLTQSPSF LSASVGDRVT ITCRASSSVT SSYLNWYQQK PGKAPKLLIY
51 STSNLASGVP SRFSGSGSGT EFTLTISSLQ PEDFATYYCQ QYDFFPSTFG
101 GGTKVEIK***RT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK***
151 VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ
201 GLSSPVTKSF NRGEC (SEQ ID NO:213)

編碼成熟形式(移除訊號肽)Ab-14 LC之核酸序列：

1 GACATCCAGC TGACCCAGAG CCCCAGCTTC CTTTCCGCAT CCGTTGGTGA
51 CCGAGTAACA ATCACATGCC GCGCCTCATC TTCAGTTACA TCTTCTTATC
101 TTAATTGGTA TCAACAAAAA CCAGGAAAAG CACCTAAACT TCTTATATAC
151 TCTACATCTA ATCTCGCATC AGGAGTTCCC TCTCGATTTT CAGGATCTGG
201 ATCAGGCACA GAATTTACAC TTACTATATC ATCACTCCAA CCAGAAGACT
251 TCGCCACTTA TTACTGCCAA CAATACGATT TTTTTCCAAG CACATTCGGA
301 GGAGGTACAA AAGTAGAAAT CAAGCGTACG GTGGCTGCAC CATCTGTCTT
351 CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAACT GCCTCTGTTG
401 TGTGCCTGCT GAATAACTTC TATCCCAGAG AGGCCAAAGT ACAGTGGAAG
451 GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG TCACAGAGCA
501 GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCCTG ACGCTGAGCA
551 AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT CACCCATCAG
601 GGCCTGAGCT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG AGTGT (SEQ ID NO:214)

包括訊號肽之Ab-14 LC之胺基酸序列：

1 MDMRVPAQLL GLLLLWLPGA RCDIQLTQSP SFLSASVGDR VTITCRASSS
51 VTSSYLNWYQ QKPGKAPKLL IYSTSNLASG VPSRFSGSGS GTEFTLTISS
101 LQPEDFATYY CQQYDFFPST FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS
151 GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS
201 TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC (SEQ ID NO:215)

包括訊號肽編碼序列之Ab-14 LC之核酸序列：

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TACTCTGGCT
51 CCCAGGTGCC AGATGTGACA TCCAGCTGAC CCAGAGCCCC AGCTTCCTTT
101 CCGCATCCGT TGGTGACCGA GTAACAATCA CATGCCGCGC CTCATCTTCA
151 GTTACATCTT CTTATCTTAA TTGGTATCAA CAAAAACCAG GAAAAGCACC
201 TAAACTTCTT ATATACTCTA CATCTAATCT CGCATCAGGA GTTCCCTCTC
251 GATTTTCAGG ATCTGGATCA GGCACAGAAT TTACACTTAC TATATCATCA
301 CTCCAACCAG AAGACTTCGC CACTTATTAC TGCCAACAAT ACGATTTTTT
351 TCCAAGCACA TTCGGAGGAG GTACAAAAGT AGAAATCAAG CGTACGGTGG
401 CTGCACCATC TGTCTTCATC TTCCCGCCAT CTGATGAGCA GTTGAAATCT
451 GGAACTGCCT CTGTTGTGTG CCTGCTGAAT AACTTCTATC CCAGAGAGGC
501 CAAAGTACAG TGGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCCAGG
551 AGAGTGTCAC AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC
601 ACCCTGACGC TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG
651 CGAAGTCACC CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA
701 GGGGAGAGTG T (SEQ ID NO:216)

Ab-14重鏈：

成熟形式(移除訊號肽)Ab-14 HC之胺基酸序列：

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYYMNWVRQA PGQRLEWMGD
51 INPYNDDTTY NHKFKGRVTI TRDTSASTAY MELSSLRSED TAVYYCARET
101 AVITTNAMDY WGQGTTVTVS S***ASTKGPSVF PLAPCSRSTS ESTAALGCLV***
151 KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ
201 TYTCNVDHKP SNTKVDKTVE RKCCVECPPC PAPPVAGPSV FLFPPKPKDT
251 LMISRTPEVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF
301 RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT
351 LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPMLDS
401 DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK (SEQ ID NO:217)

無羧基末端離胺酸之成熟形式(移除訊號肽)Ab-14 HC之胺基酸序

列：

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYYMNWVRQA PGQRLEWMGD
51 INPYNDDTTY NHKFKGRVTI TRDTSASTAY MELSSLRSED TAVYYCARET
101 AVITTNAMDY WGQGTTVTVS S***ASTKGPSVF PLAPCSRSTS ESTAALGCLV***
151 KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ
201 TYTCNVDHKP SNTKVDKTVE RKCCVECPPC PAPPVAGPSV FLFPPKPKDT
251 LMISRTPEVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF
301 RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT
351 LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPMLDS
401 DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG (SEQ ID NO:393)

編碼成熟形式(移除訊號肽)Ab-14 HC之核酸序列：

1 GAGGTGCAGC TGGTGCAGAG CGGCGCCGAG GTCAAGAAAC CTGGAGCAAG
51 CGTAAAGGTT AGTTGCAAAG CATCTGGATA CACATTTACC GACTACTACA
101 TGAATTGGGT ACGACAAGCC CCTGGACAAA GACTTGAATG GATGGGAGAC
151 ATTAACCCTT ATAACGACGA CACTACATAC AATCATAAAT TTAAAGGAAG
201 AGTTACAATT ACAAGAGATA CATCCGCATC AACCGCCTAT ATGGAACTTT
251 CCTCATTGAG ATCTGAAGAC ACTGCTGTTT ATTACTGTGC AAGAGAAACT
301 GCCGTTATTA CTACTAACGC TATGGATTAC TGGGGTCAAG GAACCACTGT
351 TACCGTCTCT AGTGCCTCCA CCAAGGGCCC ATCGGTCTTC CCCCTGGCGC
401 CCTGCTCCAG GAGCACCTCC GAGAGCACAG CGGCCCTGGG CTGCCTGGTC
451 AAGGACTACT TCCCCGAACC GGTGACGGTG TCGTGGAACT CAGGCGCTCT
501 GACCAGCGGC GTGCACACCT TCCCAGCTGT CCTACAGTCC TCAGGACTCT
551 ACTCCCTCAG CAGCGTGGTG ACCGTGCCCT CCAGCAACTT CGGCACCCAG
601 ACCTACACCT GCAACGTAGA TCACAAGCCC AGCAACACCA AGGTGGACAA
651 GACAGTTGAG CGCAAATGTT GTGTCGAGTG CCCACCGTGC CCAGCACCAC
701 CTGTGGCAGG ACCGTCAGTC TTCCTCTTCC CCCCAAAACC CAAGGACACC
751 CTCATGATCT CCCGGACCCC TGAGGTCACG TGCGTGGTGG TGGACGTGAG
801 CCACGAAGAC CCCGAGGTCC AGTTCAACTG GTACGTGGAC GGCGTGGAGG
851 TGCATAATGC CAAGACAAAG CCACGGGAGG AGCAGTTCAA CAGCACGTTC
901 CGTGTGGTCA GCGTCCTCAC CGTTGTGCAC CAGGACTGGC TGAACGGCAA
951 GGAGTACAAG TGCAAGGTCT CCAACAAAGG CCTCCCAGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGGCAGCCCC GAGAACCACA GGTGTACACC
1051 CTGCCCCCAT CCCGGGAGGA GATGACCAAG AACCAGGTCA GCCTGACCTG
1101 CCTGGTCAAA GGCTTCTACC CCAGCGACAT CGCCGTGGAG TGGGAGAGCA
1151 ATGGGCAGCC GGAGAACAAC TACAAGACCA CACCTCCCAT GCTGGACTCC
1201 GACGGCTCCT TCTTCCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG
1251 GCAGCAGGGG AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA
1301 ACCACTACAC GCAGAAGAGC CTCTCCCTGT CTCCGGGTAA A (SEQ ID NO:218)

包括訊號肽之Ab-14 HC之胺基酸序列：

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGASVKVS CKASGYTFTD
51 YYMNWVRQAP GQRLEWMGDI NPYNDDTTYN HKFKGRVTIT RDTSASTAYM
101 ELSSLRSEDT AVYYCARETA VITTNAMDYW GQGTTVTVSS ASTKGPSVFP
151 LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
201 GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP
251 APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG
301 VEVHNAKTKP REEQFNSTFR VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP
351 IEKTISKTKG QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSDIAVEW
401 ESNGQPENNY KTTPPMLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA
451 LHNHYTQKSL SLSPGK (SEQ ID NO:219)

包括訊號肽編碼序列之Ab-14 HC之核酸序列：

1 ATGGACTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
51 CCACTCCGAG GTGCAGCTGG TGCAGAGCGG CGCCGAGGTC AAGAAACCTG
101 GAGCAAGCGT AAAGGTTAGT TGCAAAGCAT CTGGATACAC ATTTACCGAC
151 TACTACATGA ATTGGGTACG ACAAGCCCCT GGACAAAGAC TTGAATGGAT
201 GGGAGACATT AACCCTTATA ACGACGACAC TACATACAAT CATAAATTTA
251 AAGGAAGAGT TACAATTACA AGAGATACAT CCGCATCAAC CGCCTATATG
301 GAACTTTCCT CATTGAGATC TGAAGACACT GCTGTTTATT ACTGTGCAAG
351 AGAAACTGCC GTTATTACTA CTAACGCTAT GGATTACTGG GGTCAAGGAA
401 CCACTGTTAC CGTCTCTAGT GCCTCCACCA AGGGCCCATC GGTCTTCCCC
451 CTGGCGCCCT GCTCCAGGAG CACCTCCGAG AGCACAGCGG CCCTGGGCTG
501 CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCG TGGAACTCAG
551 GCGCTCTGAC CAGCGGCGTG CACACCTTCC CAGCTGTCCT ACAGTCCTCA
601 GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAACTTCGG
651 CACCCAGACC TACACCTGCA ACGTAGATCA CAAGCCCAGC AACACCAAGG
701 TGGACAAGAC AGTTGAGCGC AAATGTTGTG TCGAGTGCCC ACCGTGCCCA
751 GCACCACCTG TGGCAGGACC GTCAGTCTTC CTCTTCCCCC CAAAACCCAA
801 GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACGTGC GTGGTGGTGG
851 ACGTGAGCCA CGAAGACCCC GAGGTCCAGT TCAACTGGTA CGTGGACGGC
901 GTGGAGGTGC ATAATGCCAA GACAAAGCCA CGGGAGGAGC AGTTCAACAG
951 CACGTTCCGT GTGGTCAGCG TCCTCACCGT TGTGCACCAG GACTGGCTGA
1001 ACGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAAGGCCT CCCAGCCCCC
1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGG CAGCCCCGAG AACCACAGGT
1101 GTACACCCTG CCCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTCAGCC
1151 TGACCTGCCT GGTCAAAGGC TTCTACCCCA GCGACATCGC CGTGGAGTGG
1201 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACAC CTCCCATGCT
1251 GGACTCCGAC GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA
1301 GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT

1351 CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTAAA (SEQ ID NO:220)

Ab-14之重鏈可變區中之CDR序列為：

CDR-H1: DYYMN (SEQ ID NO:296)

CDR-H2: DINPYNDDTTYNHKFKG (SEQ ID NO:297)

CDR-H3: ETAVITTNAMD (SEQ ID NO:298)

Ab-14之輕鏈可變區CDR序列為：

CDR-L1: RASSSVTSSYLN (SEQ ID NO:284)

CDR-L2: STSNLAS (SEQ ID NO:285)

CDR-L3: QQYDFFPST (SEQ ID NO:286)

Ab-14可變結構域：

Ab-14輕鏈可變結構域胺基酸序列(無訊號序列)：

1 DIQLTQSPSF LSASVGDRVT ITCRASSSVT SSYLNWYQQK PGKAPKLLIY
51 STSNLASGVP SRFSGSGSGT EFTLTISSLQ PEDFATYYCQ QYDFFPSTFG
101 GGTKVEIK (SEQ ID NO:380)

Ab-14輕鏈可變結構域DNA序列(無訊號序列)：

1 GACATCCAGC TGACCCAGAG CCCCAGCTTC CTTTCCGCAT CCGTTGGTGA
51 CCGAGTAACA ATCACATGCC GCGCCTCATC TTCAGTTACA TCTTCTTATC
101 TTAATTGGTA TCAACAAAAA CCAGGAAAAG CACCTAAACT TCTTATATAC
151 TCTACATCTA ATCTCGCATC AGGAGTTCCC TCTCGATTTT CAGGATCTGG
201 ATCAGGCACA GAATTTACAC TTACTATATC ATCACTCCAA CCAGAAGACT
251 TCGCCACTTA TTACTGCCAA CAATACGATT TTTTTCCAAG CACATTCGGA
301 GGAGGTACAA AAGTAGAAAT CAAG (SEQ ID NO:381)

Ab-14重鏈可變結構域胺基酸序列(無訊號序列)：

1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYYMNWVRQA PGQRLEWMGD
51 INPYNDDTTY NHKFKGRVTI TRDTSASTAY MELSSLRSED TAVYYCARET
101 AVITTNAMDY WGQGTTVTVS S (SEQ ID NO:382)

Ab-14重鏈可變結構域DNA序列(無訊號序列)：

1 GAGGTGCAGC TGGTGCAGAG CGGCGCCGAG GTCAAGAAAC CTGGAGCAAG

51 CGTAAAGGTT AGTTGCAAAG CATCTGGATA CACATTTACC GACTACTACA
101 TGAATTGGGT ACGACAAGCC CCTGGACAAA GACTTGAATG GATGGGAGAC
151 ATTAACCCTT ATAACGACGA CACTACATAC AATCATAAAT TTAAAGGAAG
201 AGTTACAATT ACAAGAGATA CATCCGCATC AACCGCCTAT ATGGAACTTT
251 CCTCATTGAG ATCTGAAGAC ACTGCTGTTT ATTACTGTGC AAGAGAAACT
301 GCCGTTATTA CTACTAACGC TATGGATTAC TGGGGTCAAG GAACCACTGT
351 TACCGTCTCT AGT (SEQ ID NO:383)

Ab-3經人化以產生Ab-15。

Ab-15

抗體15(本文亦稱為Ab-15)LC及HC之序列如下：

Ab-15輕鏈：

成熟形式(移除訊號肽)Ab-15 LC之胺基酸序列：

1 DIQMTQSPSS LSASVGDRVT ITCSVSSTIS SNHLHWFQQK PGKAPKSLIY
51 GTSNLASGVP SRFSGSGSGT DFTLTISSLQ PEDFATYYCQ QWSSYPLTFG
101 GGTKVEIK***RT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK***
151 VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ
201 GLSSPVTKSF NRGEC (SEQ ID NO:221)

編碼成熟形式(移除訊號肽)Ab-15 LC之核酸序列：

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCAGCAT CCGTAGGCGA
51 TAGAGTTACA ATAACATGCA GCGTATCATC AACTATATCA TCAAATCATC
101 TTCATTGGTT CCAACAGAAA CCCGGCAAAG CACCTAAATC ACTTATATAC
151 GGCACATCAA ATCTCGCATC AGGCGTTCCT TCAAGATTTT CAGGCTCTGG
201 CTCAGGCACC GACTTTACTC TTACAATATC CTCCCTCCAA CCCGAAGACT
251 TCGCAACCTA TTACTGTCAA CAATGGTCCT CATATCCACT CACATTTGGC
301 GGCGGCACAA AAGTAGAAAT TAAACGTACG GTGGCTGCAC CATCTGTCTT
351 CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAACT GCCTCTGTTG
401 TGTGCCTGCT GAATAACTTC TATCCCAGAG AGGCCAAAGT ACAGTGGAAG
451 GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG TCACAGAGCA
501 GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCCTG ACGCTGAGCA
551 AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT CACCCATCAG
601 GGCCTGAGCT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG AGTGT (SEQ ID NO:222)

包括訊號肽之Ab-15 LC之胺基酸序列：

1 MDMRVPAQLL GLLLLWLRGA RCDIQMTQSP SSLSASVGDR VTITCSVSST

51 ISSNHLHWFQ QKPGKAPKSL IYGTSNLASG VPSRFSGSGS GTDFTLTISS
101 LQPEDFATYY CQQWSSYPLT FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS
151 GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS
201 TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC (SEQ ID NO:223)

包括訊號肽編碼序列之Ab-15 LC之核酸序列：

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TACTCTGGCT
51 CCGAGGTGCC AGATGTGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTCT
101 CAGCATCCGT AGGCGATAGA GTTACAATAA CATGCAGCGT ATCATCAACT
151 ATATCATCAA ATCATCTTCA TTGGTTCCAA CAGAAACCCG GCAAAGCACC
201 TAAATCACTT ATATACGGCA CATCAAATCT CGCATCAGGC GTTCCTTCAA
251 GATTTTCAGG CTCTGGCTCA GGCACCGACT TTACTCTTAC AATATCCTCC
301 CTCCAACCCG AAGACTTCGC AACCTATTAC TGTCAACAAT GGTCCTCATA
351 TCCACTCACA TTTGGCGGCG GCACAAAAGT AGAAATTAAA CGTACGGTGG
401 CTGCACCATC TGTCTTCATC TTCCCGCCAT CTGATGAGCA GTTGAAATCT
451 GGAACTGCCT CTGTTGTGTG CCTGCTGAAT AACTTCTATC CCAGAGAGGC
501 CAAAGTACAG TGGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCCAGG
551 AGAGTGTCAC AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC
601 ACCCTGACGC TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG
651 CGAAGTCACC CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA
701 GGGGAGAGTG T (SEQ ID NO:224)

Ab-15重鏈

成熟形式(移除訊號肽)Ab-15 HC之胺基酸序列：

1 EVQLVQSGAE VKKPGASVKV SCKASDFNIK DFYLHWVRQA PGQGLEWIGR
51 IDPENGDTLY DPKFQDKVTM TTDTSTSTAY MELRSLRSDD TAVYYCAREA
101 DYFHDGTSYW YFDVWGRGTL VTVSS***ASTKG PSVFPLAPCS RSTSESTAAL***
151 GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSN
201 FGTQTYTCNV DHKPSNTKVD KTVERKCCVE CPPCPAPPVA GPSVFLFPPK
251 PKDTLMISRT PEVTCVVVDV SHEDPEVQFN WYVDGVEVHN AKTKPREEQF
301 NSTFRVVSVL TVVHQDWLNG KEYKCKVSNK GLPAPIEKTI SKTKGQPREP
351 QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP
401 MLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG
451 K (SEQ ID NO:225)

無羧基末端離胺酸之成熟形式(移除訊號肽)Ab-15 HC之胺基酸序列：

1 EVQLVQSGAE VKKPGASVKV SCKASDFNIK DFYLHWVRQA PGQGLEWIGR
51 IDPENGDTLY DPKFQDKVTM TTDTSTSTAY MELRSLRSDD TAVYYCAREA

101 DYFHDGTSYW YFDVWGRGTL VTVSS*ASTKG PSVFPLAPCS RSTSESTAAL*
151 GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSN
201 FGTQTYTCNV DHKPSNTKVD KTVERKCCVE CPPCPAPPVA GPSVFLFPPK
251 PKDTLMISRT PEVTCVVVDV SHEDPEVQFN WYVDGVEVHN AKTKPREEQF
301 NSTFRVVSVL TVVHQDWLNG KEYKCKVSNK GLPAPIEKTI SKTKGQPREP
351 QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP
401 MLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG
451 (SEQ ID NO:394)

編碼成熟形式(移除訊號肽)Ab-15 HC之核酸序列：

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGGCCTC
51 AGTGAAGGTC TCCTGCAAGG CTTCTGACTT CAACATTAAA GACTTCTATC
101 TACACTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG GATTGGAAGG
151 ATTGATCCTG AGAATGGTGA TACTTTATAT GACCCGAAGT TCCAGGACAA
201 GGTCACCATG ACCACAGACA CGTCCACCAG CACAGCCTAC ATGGAGCTGA
251 GGAGCCTGAG ATCTGACGAC ACGGCCGTGT ATTACTGTGC GAGAGAGGCG
301 GATTATTTCC ACGATGGTAC CTCCTACTGG TACTTCGATG TCTGGGGCCG
351 TGGCACCCTG GTCACCGTCT CTAGTGCCTC CACCAAGGGC CCATCGGTCT
401 TCCCCCTGGC GCCCTGCTCC AGGAGCACCT CCGAGAGCAC AGCGGCCCTG
451 GGCTGCCTGG TCAAGGACTA CTTCCCCGAA CCGGTGACGG TGTCGTGGAA
501 CTCAGGCGCT CTGACCAGCG GCGTGCACAC CTTCCCAGCT GTCCTACAGT
551 CCTCAGGACT CTACTCCCTC AGCAGCGTGG TGACCGTGCC CTCCAGCAAC
601 TTCGGCACCC AGACCTACAC CTGCAACGTA GATCACAAGC CCAGCAACAC
651 CAAGGTGGAC AAGACAGTTG AGCGCAAATG TTGTGTCGAG TGCCCACCGT
701 GCCCAGCACC ACCTGTGGCA GGACCGTCAG TCTTCCTCTT CCCCCCAAAA
751 CCCAAGGACA CCCTCATGAT CTCCCGGACC CCTGAGGTCA CGTGCGTGGT
801 GGTGGACGTG AGCCACGAAG ACCCCGAGGT CCAGTTCAAC TGGTACGTGG
851 ACGGCGTGGA GGTGCATAAT GCCAAGACAA AGCCACGGGA GGAGCAGTTC
901 AACAGCACGT TCCGTGTGGT CAGCGTCCTC ACCGTTGTGC ACCAGGACTG
951 GCTGAACGGC AAGGAGTACA AGTGCAAGGT CTCCAACAAA GGCCTCCCAG
1001 CCCCCATCGA GAAAACCATC TCCAAAACCA AAGGGCAGCC CCGAGAACCA
1051 CAGGTGTACA CCCTGCCCCC ATCCCGGGAG GAGATGACCA AGAACCAGGT
1101 CAGCCTGACC TGCCTGGTCA AAGGCTTCTA CCCCAGCGAC ATCGCCGTGG
1151 AGTGGGAGAG CAATGGGCAG CCGGAGAACA ACTACAAGAC CACACCTCCC
1201 ATGCTGGACT CCGACGGCTC CTTCTTCCTC TACAGCAAGC TCACCGTGGA
1251 CAAGAGCAGG TGGCAGCAGG GGAACGTCTT CTCATGCTCC GTGATGCATG
1301 AGGCTCTGCA CAACCACTAC ACGCAGAAGA GCCTCTCCCT GTCTCCGGGT
1351 AAA (SEQ ID NO:226)

包括訊號肽之Ab-15 HC之胺基酸序列：

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGASVKVS CKASDFNIKD
51 FYLHWVRQAP GQGLEWIGRI DPENGDTLYD PKFQDKVTMT TDTSTSTAYM

101 ELRSLRSDDT AVYYCAREAD YFHDGTSYWY FDVWGRGTLV TVSSASTKGP
151 SVFPLAPCSR STSESTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV
201 LQSSGLYSLS SVVTVPSSNF GTQTYTCNVD HKPSNTKVDK TVERKCCVEC
251 PPCPAPPVAG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVQFNW
301 YVDGVEVHNA KTKPREEQFN STFRVVSVLT VVHQDWLNGK EYKCKVSNKG
351 LPAPIEKTIS KTKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI
401 AVEWESNGQP ENNYKTTPPM LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV
451 MHEALHNHYT QKSLSLSPGK (SEQ ID NO:227)

包括訊號肽編碼序列之Ab-15 HC之核酸序列：

1 ATGGACTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
51 CCACTCCGAG GTGCAGCTGG TGCAGTCTGG GGCTGAGGTG AAGAAGCCTG
101 GGGCCTCAGT GAAGGTCTCC TGCAAGGCTT CTGACTTCAA CATTAAAGAC
151 TTCTATCTAC ACTGGGTGCG ACAGGCCCCT GGACAAGGGC TTGAGTGGAT
201 TGGAAGGATT GATCCTGAGA ATGGTGATAC TTTATATGAC CCGAAGTTCC
251 AGGACAAGGT CACCATGACC ACAGACACGT CCACCAGCAC AGCCTACATG
301 GAGCTGAGGA GCCTGAGATC TGACGACACG GCCGTGTATT ACTGTGCGAG
351 AGAGGCGGAT TATTTCCACG ATGGTACCTC CTACTGGTAC TTCGATGTCT
401 GGGGCCGTGG CACCCTGGTC ACCGTCTCTA GTGCCTCCAC CAAGGGCCCA
451 TCGGTCTTCC CCCTGGCGCC CTGCTCCAGG AGCACCTCCG AGAGCACAGC
501 GGCCCTGGGC TGCCTGGTCA AGGACTACTT CCCCGAACCG GTGACGGTGT
551 CGTGGAACTC AGGCGCTCTG ACCAGCGGCG TGCACACCTT CCCAGCTGTC
601 CTACAGTCCT CAGGACTCTA CTCCCTCAGC AGCGTGGTGA CCGTGCCCTC
651 CAGCAACTTC GGCACCCAGA CCTACACCTG CAACGTAGAT CACAAGCCCA
701 GCAACACCAA GGTGGACAAG ACAGTTGAGC GCAAATGTTG TGTCGAGTGC
751 CCACCGTGCC CAGCACCACC TGTGGCAGGA CCGTCAGTCT TCCTCTTCCC
801 CCCAAAACCC AAGGACACCC TCATGATCTC CCGGACCCCT GAGGTCACGT
851 GCGTGGTGGT GGACGTGAGC CACGAAGACC CCGAGGTCCA GTTCAACTGG
901 TACGTGGACG GCGTGGAGGT GCATAATGCC AAGACAAAGC CACGGGAGGA
951 GCAGTTCAAC AGCACGTTCC GTGTGGTCAG CGTCCTCACC GTTGTGCACC
1001 AGGACTGGCT GAACGGCAAG GAGTACAAGT GCAAGGTCTC CAACAAAGGC
1051 CTCCCAGCCC CCATCGAGAA AACCATCTCC AAAACCAAAG GGCAGCCCCG
1101 AGAACCACAG GTGTACACCC TGCCCCCATC CCGGGAGGAG ATGACCAAGA
1151 ACCAGGTCAG CCTGACCTGC CTGGTCAAAG GCTTCTACCC CAGCGACATC
1201 GCCGTGGAGT GGGAGAGCAA TGGGCAGCCG GAGAACAACT ACAAGACCAC
1251 ACCTCCCATG CTGGACTCCG ACGGCTCCTT CTTCCTCTAC AGCAAGCTCA
1301 CCGTGGACAA GAGCAGGTGG CAGCAGGGGA ACGTCTTCTC ATGCTCCGTG
1351 ATGCATGAGG CTCTGCACAA CCACTACACG CAGAAGAGCC TCTCCCTGTC
1401 TCCGGGTAAA (SEQ ID NO:228)

Ab-15重鏈可變區中之CDR序列為：

CDR-H1: DFYLH (SEQ ID NO:290)

CDR-H2: RIDPENGDTLYDPKFQD (SEQ ID NO:291)

CDR-H3: EADYFHDGTSYWYFDV (SEQ ID NO:292)

Ab-15之輕鏈可變區CDR序列為：

CDR-L1: SVSSTISSNHLH (SEQ ID NO:278)

CDR-L2: GTSNLAS (SEQ ID NO:279)

CDR-L3: QQWSSYPLT (SEQ ID NO:280)

Ab-15可變結構域：

Ab-15輕鏈可變結構域胺基酸序列(無訊號序列)：

1 DIQMTQSPSS LSASVGDRVT ITCSVSSTIS SNHLHWFQQK PGKAPKSLIY
51 GTSNLASGVP SRFSGSGSGT DFTLTISSLQ PEDFATYYCQ QWSSYPLTFG
101 GGTKVEIK (SEQ ID NO:384)

Ab-15輕鏈可變結構域DNA序列(無訊號序列)：

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTCTCAGCAT CCGTAGGCGA
51 TAGAGTTACA ATAACATGCA GCGTATCATC AACTATATCA TCAAATCATC
101 TTCATTGGTT CCAACAGAAA CCCGGCAAAG CACCTAAATC ACTTATATAC
151 GGCACATCAA ATCTCGCATC AGGCGTTCCT TCAAGATTTT CAGGCTCTGG
201 CTCAGGCACC GACTTTACTC TTACAATATC CTCCCTCCAA CCCGAAGACT
251 TCGCAACCTA TTACTGTCAA CAATGGTCCT CATATCCACT CACATTTGGC
301 GGCGGCACAA AAGTAGAAAT TAAA (SEQ ID NO:385)

Ab-15重鏈可變結構域胺基酸序列(無訊號序列)：

1 EVQLVQSGAE VKKPGASVKV SCKASDFNIK DFYLHWVRQA PGQGLEWIGR
51 IDPENGDTLY DPKFQDKVTM TTDTSTSTAY MELRSLRSDD TAVYYCAREA
101 DYFHDGTSYW YFDVWGRGTL VTVSS (SEQ ID NO:386)

Ab-15重鏈可變結構域DNA序列(無訊號序列)：

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGGCCTC
51 AGTGAAGGTC TCCTGCAAGG CTTCTGACTT CAACATTAAA GACTTCTATC
101 TACACTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG GATTGGAAGG
151 ATTGATCCTG AGAATGGTGA TACTTTATAT GACCCGAAGT TCCAGGACAA
201 GGTCACCATG ACCACAGACA CGTCCACCAG CACAGCCTAC ATGGAGCTGA
251 GGAGCCTGAG ATCTGACGAC ACGGCCGTGT ATTACTGTGC GAGAGAGGCG

301 GATTATTTCC ACGATGGTAC CTCCTACTGG TACTTCGATG TCTGGGGCCG
351 TGGCACCCTG GTCACCGTCT CTAGT (SEQ ID NO:387)

Ab-11經人化以產生Ab-16。

Ab-16

抗體16(本文亦稱為Ab-16)LC及HC之序列如下：

Ab-16輕鏈：

成熟形式(移除訊號肽)Ab-16 LC之胺基酸序列：

1 DIQLTQSPSF LSASVGDRVT ITCRASSSIS YIHWYQQKPG KAPKLLIYAT
51 SNLASGVPSR FSGSGSGTEF TLTISSLQPE DFATYYCQQW SSDPLTFGGG
101 TKVEIK***RTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD***
151 NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL
201 SSPVTKSFNR GEC (SEQ ID NO:229)

編碼成熟形式(移除訊號肽)Ab-16 LC之核酸序列：

1 GACATCCAGT TGACCCAGTC TCCATCCTTC CTGTCTGCAT CTGTAGGAGA
51 CAGAGTCACC ATCACTTGCA GGGCCAGCTC AAGTATAAGT TACATACACT
101 GGTATCAGCA AAAACCAGGG AAAGCCCCTA AGCTCCTGAT CTATGCCACA
151 TCCAACCTGG CTTCTGGGGT CCCATCAAGG TTCAGCGGCA GTGGATCTGG
201 GACAGAATTC ACTCTCACAA TCAGCAGCCT GCAGCCTGAA GATTTTGCAA
251 CTTATTACTG TCAGCAGTGG AGTAGTGACC CACTCACGTT CGGCGGAGGG
301 ACCAAGGTGG AGATCAAACG TACGGTGGCT GCACCATCTG TCTTCATCTT
351 CCCGCCATCT GATGAGCAGT TGAAATCTGG AACTGCCTCT GTTGTGTGCC
401 TGCTGAATAA CTTCTATCCC AGAGAGGCCA AAGTACAGTG GAAGGTGGAT
451 AACGCCCTCC AATCGGGTAA CTCCCAGGAG AGTGTCACAG AGCAGGACAG
501 CAAGGACAGC ACCTACAGCC TCAGCAGCAC CCTGACGCTG AGCAAAGCAG
551 ACTACGAGAA ACACAAAGTC TACGCCTGCG AAGTCACCCA TCAGGGCCTG
601 AGCTCGCCCG TCACAAAGAG CTTCAACAGG GGAGAGTGT (SEQ ID NO:230)

包括訊號肽之Ab-16 LC之胺基酸序列：

1 MDMRVPAQLL GLLLLWLPGA RCDIQLTQSP SFLSASVGDR VTITCRASSS
51 ISYIHWYQQK PGKAPKLLIY ATSNLASGVP SRFSGSGSGT EFTLTISSLQ
101 PEDFATYYCQ QWSSDPLTFG GGTKVEIKRT VAAPSVFIFP PSDEQLKSGT
151 ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL
201 TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC (SEQ ID NO:231)

包括訊號肽編碼序列之Ab-16 LC之核酸序列：

1 ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TGCTCTGGCT
51 CCCAGGTGCC AGATGTGACA TCCAGTTGAC CCAGTCTCCA TCCTTCCTGT
101 CTGCATCTGT AGGAGACAGA GTCACCATCA CTTGCAGGGC CAGCTCAAGT
151 ATAAGTTACA TACACTGGTA TCAGCAAAAA CCAGGGAAAG CCCCTAAGCT
201 CCTGATCTAT GCCACATCCA ACCTGGCTTC TGGGGTCCCA TCAAGGTTCA
251 GCGGCAGTGG ATCTGGGACA GAATTCACTC TCACAATCAG CAGCCTGCAG
301 CCTGAAGATT TTGCAACTTA TTACTGTCAG CAGTGGAGTA GTGACCCACT
351 CACGTTCGGC GGAGGGACCA AGGTGGAGAT CAAACGTACG GTGGCTGCAC
401 CATCTGTCTT CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAACT
451 GCCTCTGTTG TGTGCCTGCT GAATAACTTC TATCCCAGAG AGGCCAAAGT
501 ACAGTGGAAG GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG
551 TCACAGAGCA GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCCTG
601 ACGCTGAGCA AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT
651 CACCCATCAG GGCCTGAGCT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG
701 AGTGT (SEQ ID NO:232)

Ab-16重鏈：

成熟形式(移除訊號肽)Ab-16 HC之胺基酸序列：

1 EVQLVQSGAE VKKPGASVKV SCKASGFDIKDYYIHWVRQA PGQGLEWIGR
51 VDPDNGETEF APKFPGKVTM TTDTSISTAY MELSRLRSDD TAVYYCARED
101 YDGTYTWFPY WGQGTLVTVS S***ASTKGPSVF PLAPCSRSTS ESTAALGCLV***
151 KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ
201 TYTCNVDHKP SNTKVDKTVE RKCCVECPPC PAPPVAGPSV FLFPPKPKDT
251 LMISRTPEVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF
301 RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT
351 LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPMLDS
401 DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK (SEQ ID NO:233)

無羧基末端離胺酸之成熟形式(移除訊號肽)Ab-16 HC之胺基酸序列：

1 EVQLVQSGAE VKKPGASVKV SCKASGFDIKDYYIHWVRQA PGQGLEWIGR
51 VDPDNGETEF APKFPGKVTM TTDTSISTAY MELSRLRSDD TAVYYCARED
101 YDGTYTWFPY WGQGTLVTVS S***ASTKGPSVF PLAPCSRSTS ESTAALGCLV***
151 KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ
201 TYTCNVDHKP SNTKVDKTVE RKCCVECPPC PAPPVAGPSV FLFPPKPKDT
251 LMISRTPEVT CVVVDVSHED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF
301 RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT
351 LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPMLDS
401 DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG (SEQ ID

NO:395)

編碼成熟形式(移除訊號肽)Ab-16 HC之核酸序列：

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGGCCTC
51 AGTGAAGGTC TCCTGCAAGG CTTCTGGATT CGACATTAAG GACTACTATA
101 TACACTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG GATCGGAAGG
151 GTTGATCCTG ACAATGGTGA GACTGAATTT GCCCCGAAGT TCCCGGGCAA
201 GGTCACCATG ACCACAGACA CGTCCATCAG CACAGCCTAC ATGGAGCTGA
251 GCAGGCTGAG ATCTGACGAC ACGGCCGTGT ATTACTGTGC GAGAGAAGAC
301 TACGATGGTA CCTACACCTG GTTTCCTTAT TGGGGCCAAG GGACTCTGGT
351 CACCGTCTCT AGTGCCTCCA CCAAGGGCCC ATCGGTCTTC CCCCTGGCGC
401 CCTGCTCCAG GAGCACCTCC GAGAGCACAG CGGCCCTGGG CTGCCTGGTC
451 AAGGACTACT TCCCCGAACC GGTGACGGTG TCGTGGAACT CAGGCGCTCT
501 GACCAGCGGC GTGCACACCT TCCCAGCTGT CCTACAGTCC TCAGGACTCT
551 ACTCCCTCAG CAGCGTGGTG ACCGTGCCCT CCAGCAACTT CGGCACCCAG
601 ACCTACACCT GCAACGTAGA TCACAAGCCC AGCAACACCA AGGTGGACAA
651 GACAGTTGAG CGCAAATGTT GTGTCGAGTG CCCACCGTGC CCAGCACCAC
701 CTGTGGCAGG ACCGTCAGTC TTCCTCTTCC CCCCAAAACC CAAGGACACC
751 CTCATGATCT CCCGGACCCC TGAGGTCACG TGCGTGGTGG TGGACGTGAG
801 CCACGAAGAC CCCGAGGTCC AGTTCAACTG GTACGTGGAC GGCGTGGAGG
851 TGCATAATGC CAAGACAAAG CCACGGGAGG AGCAGTTCAA CAGCACGTTC
901 CGTGTGGTCA GCGTCCTCAC CGTTGTGCAC CAGGACTGGC TGAACGGCAA
951 GGAGTACAAG TGCAAGGTCT CCAACAAAGG CCTCCCAGCC CCCATCGAGA
1001 AAACCATCTC CAAAACCAAA GGGCAGCCCC GAGAACCACA GGTGTACACC
1051 CTGCCCCCAT CCCGGGAGGA GATGACCAAG AACCAGGTCA GCCTGACCTG
1101 CCTGGTCAAA GGCTTCTACC CCAGCGACAT CGCCGTGGAG TGGGAGAGCA
1151 ATGGGCAGCC GGAGAACAAC TACAAGACCA CACCTCCCAT GCTGGACTCC
1201 GACGGCTCCT TCTTCCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG
1251 GCAGCAGGGG AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA
1301 ACCACTACAC GCAGAAGAGC CTCTCCCTGT CTCCGGGTAA A (SEQ ID NO:234)

包括訊號肽之Ab-16 HC之胺基酸序列：

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGASVKVS CKASGFDIKD
51 YYIHWVRQAP GQGLEWIGRV DPDNGETEFA PKFPGKVTMT TDTSISTAYM
101 ELSRLRSDDT AVYYCAREDY DGTYTWFPYW GQGTLVTVSS ASTKGPSVFP
151 LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
201 GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP
251 APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG
301 VEVHNAKTKP REEQFNSTFR VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP
351 IEKTISKTKG QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSDIAVEW
401 ESNGQPENNY KTTPPMLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA

451 LHNHYTQKSL SLSPGK (SEQ ID NO:235)

包括訊號肽編碼序列之Ab-16 HC之核酸序列：

1 ATGGACTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
51 CCACTCCGAG GTGCAGCTGG TGCAGTCTGG GGCTGAGGTG AAGAAGCCTG
101 GGGCCTCAGT GAAGGTCTCC TGCAAGGCTT CTGGATTCGA CATTAAGGAC
151 TACTATATAC ACTGGGTGCG ACAGGCCCCT GGACAAGGGC TTGAGTGGAT
201 CGGAAGGGTT GATCCTGACA ATGGTGAGAC TGAATTTGCC CCGAAGTTCC
251 CGGGCAAGGT CACCATGACC ACAGACACGT CCATCAGCAC AGCCTACATG
301 GAGCTGAGCA GGCTGAGATC TGACGACACG GCCGTGTATT ACTGTGCGAG
351 AGAAGACTAC GATGGTACCT ACACCTGGTT TCCTTATTGG GGCCAAGGGA
401 CTCTGGTCAC CGTCTCTAGT GCCTCCACCA AGGGCCCATC GGTCTTCCCC
451 CTGGCGCCCT GCTCCAGGAG CACCTCCGAG AGCACAGCGG CCCTGGGCTG
501 CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCG TGGAACTCAG
551 GCGCTCTGAC CAGCGGCGTG CACACCTTCC CAGCTGTCCT ACAGTCCTCA
601 GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAACTTCGG
651 CACCCAGACC TACACCTGCA ACGTAGATCA CAAGCCCAGC AACACCAAGG
701 TGGACAAGAC AGTTGAGCGC AAATGTTGTG TCGAGTGCCC ACCGTGCCCA
751 GCACCACCTG TGGCAGGACC GTCAGTCTTC CTCTTCCCCC CAAAACCCAA
801 GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACGTGC GTGGTGGTGG
851 ACGTGAGCCA CGAAGACCCC GAGGTCCAGT TCAACTGGTA CGTGGACGGC
901 GTGGAGGTGC ATAATGCCAA GACAAAGCCA CGGGAGGAGC AGTTCAACAG
951 CACGTTCCGT GTGGTCAGCG TCCTCACCGT TGTGCACCAG GACTGGCTGA
1001 ACGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAAGGCCT CCCAGCCCCC
1051 ATCGAGAAAA CCATCTCCAA AACCAAAGGG CAGCCCCGAG AACCACAGGT
1101 GTACACCCTG CCCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTCAGCC
1151 TGACCTGCCT GGTCAAAGGC TTCTACCCCA GCGACATCGC CGTGGAGTGG
1201 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACAC CTCCCATGCT
1251 GGACTCCGAC GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA
1301 GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT
1351 CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTAAA (SEQ ID NO:236)

Ab-16重鏈可變區中之CDR序列為：

CDR-H1: DYYIH (SEQ ID NO:293)

CDR-H2: RVDPDNGETEFAPKFPG (SEQ ID NO:294)

CDR-H3: EDYDGTYTWFPY (SEQ ID NO:295)

Ab-16之輕鏈可變區CDR序列為：

CDR-L1: RASSSISYIH (SEQ ID NO:281)

CDR-L2: ATSNLAS (SEQ ID NO:282)

CDR-L3: QQWSSDPLT (SEQ ID NO:283)

Ab-16可變結構域：

Ab-16輕鏈可變結構域胺基酸序列(無訊號序列)：

1 DIQLTQSPSF LSASVGDRVT ITCRASSSIS YIHWYQQKPG KAPKLLIYAT
51 SNLASGVPSR FSGSGSGTEF TLTISSLQPE DFATYYCQQW SSDPLTFGGG
101 TKVEIK (SEQ ID NO:388)

Ab-16輕鏈可變結構域DNA序列(無訊號序列)：

1 GACATCCAGT TGACCCAGTC TCCATCCTTC CTGTCTGCAT CTGTAGGAGA
51 CAGAGTCACC ATCACTTGCA GGGCCAGCTC AAGTATAAGT TACATACACT
101 GGTATCAGCA AAAACCAGGG AAAGCCCCTA AGCTCCTGAT CTATGCCACA
151 TCCAACCTGG CTTCTGGGGT CCCATCAAGG TTCAGCGGCA GTGGATCTGG
201 GACAGAATTC ACTCTCACAA TCAGCAGCCT GCAGCCTGAA GATTTTGCAA
251 CTTATTACTG TCAGCAGTGG AGTAGTGACC CACTCACGTT CGGCGGAGGG
301 ACCAAGGTGG AGATCAAA (SEQ ID NO:389)

Ab-16重鏈可變結構域胺基酸序列(無訊號序列)：

1 EVQLVQSGAE VKKPGASVKV SCKASGFDIKDYYIHWVRQA PGQGLEWIGR
51 VDPDNGETEF APKFPGKVTM TTDTSISTAY MELSRLRSDD TAVYYCARED
101 YDGTYTWFPY WGQGTLVTVS S (SEQ ID NO:390)

Ab-16重鏈可變結構域DNA序列(無訊號序列)：

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGGCCTC
51 AGTGAAGGTC TCCTGCAAGG CTTCTGGATT CGACATTAAG GACTACTATA
101 TACACTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG GATCGGAAGG
151 GTTGATCCTG ACAATGGTGA GACTGAATTT GCCCCGAAGT TCCCGGGCAA
201 GGTCACCATG ACCACAGACA CGTCCATCAG CACAGCCTAC ATGGAGCTGA
251 GCAGGCTGAG ATCTGACGAC ACGGCCGTGT ATTACTGTGC GAGAGAAGAC
301 TACGATGGTA CCTACACCTG GTTTCCTTAT TGGGGCCAAG GGACTCTGGT
351 CACCGTCTCT AGT (SEQ ID NO:391)

額外之抗體在本文中稱為抗體17-22(本文亦稱為Ab-17、Ab-18、Ab-19、Ab-20、Ab-21及Ab-22)。Ab-17、Ab-19及Ab-21之所有VK區

之κ恆定區如下：

TDAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSK
DSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC (SEQ ID NO:323)

抗體17、19及21之所有VH區之重鏈恆定區如下：

AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDL
YTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKP
KDVLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSVSELPIM
HQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMIT
DFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTCSVLH
EGLHNHHTEKSLSHSPGK (SEQ ID NO:324)

在以下抗體胺基酸序列中，陰影框之胺基酸代表互補判定區(CDR)且下劃線胺基酸代表訊號肽。

Ab-17

包括訊號肽之Ab-17 LC之胺基酸序列：

MDFQVQIFSFMLISVTVILSSGEIVLTQSPALMAASPGEKVTITCSVSSSISSSNLHWSQQKSG
TSPKLWIYGTSNLASGVPVRFSGSGSGTSYSLTISSMEAEDAATYYCQQWTTTYTFGSGTKL
ELKR (SEQ ID NO:299)

包括訊號肽之Ab-17 LC之核酸序列：

ATGGATTTTCAGGTGCAGATTTTCAGCTTCATGCTAATCAGTGTCACAGTCATATTGTCC
AGTGGAGAAATTGTGCTCACCCAGTCTCCAGCACTCATGGCTGCATCTCCAGGGGAGA
AGGTCACCATCACCTGCAGTGTCAGCTCGAGTATAAGTTCCAGCAACTTACACTGGTCC
CAGCAGAAGTCAGGAACCTCCCCCAAACTCTGGATTTATGGCACATCCAACCTTGCTTC
TGGAGTCCCTGTTCGCTTCAGTGGCAGTGGATCTGGGACCTCTTATTCTCTCACAATCAG
CAGCATGGAGGCTGAAGATGCTGCCACTTATTACTGTCAACAGTGGACTACTACGTATAC
GTTCGGATCGGGGACCAAGCTGGAGCTGAAACGT (SEQ ID NO:300)

包括訊號肽之Ab-17 HC之胺基酸序列：

**MGWNWIIFFLMAVVTGVNSEVQLRQSGADLVKPGASVKLSCTASGFNIKDYYIHW
VKQRPEQGLEWIGRIDPDNGESTYVPKFQGKATITADTSSNTAYLQLRSLTSEDTAI
YYCGREGLDYGDYYAVDYWGQGTSVTVSS (SEQ ID NO:301)**

包括訊號肽之Ab-17 HC之核酸序列：

ATGGGATGGAACTGGATCATCTTCTTCCTGATGGCAGTGGTTACAGGGGTCAATTCAG
AGGTGCAGTTGCGGCAGTCTGGGGCAGACCTTGTGAAGCCAGGGGCCTCAGTCAAG
TTGTCCTGCACAGCTTCTGGCTTCAACATTAAAGACTACTATATACACTGGGTGAAGC
AGAGGCCTGAACAGGGCCTGGAGTGGATTGGAAGGATTGATCCTGATAATGGTGAAA
GTACATATGTCCCGAAGTTCCAGGGCAAGGCCACTATAACAGCAGACACATCATCCA
ACACAGCCTACCTACAACTCAGAAGCCTGACATCTGAGGACACTGCCATCTATTATTG
TGGGAGAGAGGGGCTCGACTATGGTGACTACTATGCTGTGGACTACTGGGGTCAAGG
AACCTCGGTCACAGTCTCGAGC (SEQ ID NO:302)

Ab-17經人化以產生Ab-18。

Ab-18

包括訊號肽之Ab-18 LC之胺基酸序列：

MDMRVPAQLLGLLLLWLPGARCDIQLTQSPSFLSASVGDRVTITCSVSSSISSSNLHWYQ
QKPGKAPKLLIYGTSNLASGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQWTTTYTFG
QGTKLEIKR (SEQ ID NO:303)

包括訊號肽之Ab-18 LC之核酸序列：

ATGGATATGCGCGTGCCGGCGCAGCTGCTGGGCCTGCTGCTGCTGTGGCTGCCGGGC
GCGCGCTGCGATATTCAGCTGACCCAGAGCCCGAGCTTTCTGAGCGCGAGCGTGGGC
GATCGCGTGACCATTACCTGCAGCGTGAGCAGCAGCATTAGCAGCAGCAACCTGCAT
TGGTATCAGCAGAAACCGGGCAAAGCGCCGAAACTGCTGATTTATGGCACCAGCAAC
CTGGCGAGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGCAGCGGCACCGAATTTACC
CTGACCATTAGCAGCCTGCAGCCGGAAGATTTTGCGACCTATTATTGCCAGCAGTGGA
CCACCACCTATACCTTTGGCCAGGGCACCAAACTGGAAATTAAACGT (SEQ ID NO:304)

包括訊號肽之Ab-18 HC之胺基酸序列：

MDWTWSILFLVAAPTGAHSEVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYIHWVRQ
APGQGLEWMGRIDPDNGESTYVPKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCA
REGLDYGDYYAVDYWGQGTLVTVSS (SEQ ID NO:305)

包括訊號肽之Ab-18 HC之核酸序列：

ATGGATTGGACCTGGAGCATTCTGTTTCTGGTGGCGGCGCCGACCGGCGCGCATAGC
GAAGTGCAGCTGGTGCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAGCGTGA
AAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATTCATTGGGTGCG
CCAGGCGCCGGGCCAGGGCCTGGAATGGATGGGCCGCATTGATCCGGATAACGGCGA
AAGCACCTATGTGCCGAAATTTCAGGGCCGCGTGACCATGACCACCGATACCAGCAC
CAGCACCGCGTATATGGAACTGCGCAGCCTGCGCAGCGATGATACCGCGGTGTATTAT
TGCGCGCGCGAAGGCCTGGATTATGGCGATTATTATGCGGTGGATTATTGGGGCCAGG

GCACCCTGGTGACCGTCTCGAGC (SEQ ID NO:306)

Ab-18輕鏈可變結構域胺基酸序列(無訊號序列)：

DIQLTQSPSFLSASVGDRVTITCSVSSSISSSNLHWYQQKPGKAPKLLIYGTSNLASGVPSR
FSGSGSGTEFTLTISSLQPEDFATYYCQQWTTTYTFGQGTKLEIKR (SEQ ID NO:368)

Ab-18輕鏈可變結構域DNA序列(無訊號序列)：

GATATTCAGCTGACCCAGAGCCCGAGCTTTCTGAGCGCGAGCGTGGGCGATCGCGTG
ACCATTACCTGCAGCGTGAGCAGCAGCATTAGCAGCAGCAACCTGCATTGGTATCAGC
AGAAACCGGGCAAAGCGCCGAAACTGCTGATTTATGGCACCAGCAACCTGGCGAGC
GGCGTGCCGAGCCGCTTTAGCGGCAGCGGCAGCGGCACCGAATTTACCCTGACCATT
AGCAGCCTGCAGCCGGAAGATTTTGCGACCTATTATTGCCAGCAGTGGACCACCACCT
ATACCTTTGGCCAGGGCACCAAACTGGAAATTAAACGT (SEQ ID NO:369)

Ab-18重鏈可變結構域胺基酸序列(無訊號序列)：

EVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYIHWVRQAPGQGLEWMGRIDPDNGES
TYVPKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAREGLDYGDYYAVDYWGQGT
LVTVSS (SEQ ID NO:370)

Ab-18重鏈可變結構域DNA序列(無訊號序列)：

GAAGTGCAGCTGGTGCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAGCGTGAA
AGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATTCATTGGGTGCGCC
AGGCGCCGGGCCAGGGCCTGGAATGGATGGGCCGCATTGATCCGGATAACGGCGAAA
GCACCTATGTGCCGAAATTTCAGGGCCGCGTGACCATGACCACCGATACCAGCACCAG
CACCGCGTATATGGAACTGCGCAGCCTGCGCAGCGATGATACCGCGGTGTATTATTGCG
CGCGCGAAGGCCTGGATTATGGCGATTATTATGCGGTGGATTATTGGGGCCAGGGCACC
CTGGTGACCGTCTCGAGC (SEQ ID NO:371)

Ab-19

包括訊號肽之Ab-19 LC之胺基酸序列：

MMSSAQFLGLLLLCFQGTRCDIQMTQTTSSLSASLGDRVNISCRASQDISSYLNWYQQKPD
GTVKLLIYSTSRLNSGVPSRFSGSGSGTDYSLTISNLAQEDIATYFCQQDIKHPTFGGGTKLEL
KR (SEQ ID NO:307)

包括訊號肽之Ab-19 LC之核酸序列：

ATGATGTCCTCTGCTCAGTTCCTTGGTCTCCTGTTGCTCTGTTTTCAAGGTACCAGATG
TGATATCCAGATGACACAGACTACATCCTCCCTGTCTGCCTCTCTGGGAGACAGAGTC

AACATCAGCTGCAGGGCAAGTCAGGACATTAGCAGTTATTTAAACTGGTATCAGCAGA
AACCAGATGGAACTGTTAAACTCCTGATCTACTCCACATCAAGATTAAACTCAGGAGT
CCCATCAAGGTTCAGTGGCAGTGGGTCTGGGACAGATTATTCTCTCACTATTAGCAAC
CTGGCACAAGAAGATATTGCCACTTACTTTTGCCAACAGGATATTAAGCATCCGACGTT
CGGTGGAGGCACCAAGTTGGAGCTGAAACGT (SEQ ID NO:308)

包括訊號肽之Ab-19 HC之胺基酸序列：

MEWIWIFLFLLSGTAGVHSEVQLQQSGPELVKPGASVKMSCKASGFTFTDYIMHWVKQ
KPGQGLEWIGYINPYNDDTEYNEKFKGKATLTSDKSSSTAYMDLSSLTSEGSAVYYCARS
IYYYDAPFAYWGQGTLVTVSS (SEQ ID NO:309)

包括訊號肽之Ab-19 HC之核酸序列：

ATGGAATGGATCTGGATATTTCTCTTCCTCCTGTCAGGAACTGCAGGTGTCCACTCTGA
GGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCAGTGAAGAT
GTCCTGCAAGGCTTCTGGGTTCACATTCACTGACTACATTATGCACTGGGTGAAGCAG
AAGCCTGGGCAGGGCCTTGAGTGGATTGGATATATTAATCCTTACAATGATGATACTGA
ATACAATGAGAAGTTCAAAGGCAAGGCCACACTGACTTCAGACAAATCCTCCAGCAC
AGCCTACATGGATCTCAGCAGTCTGACCTCTGAGGGCTCTGCGGTCTATTACTGTGCA
AGATCGATTTATTACTACGATGCCCCGTTTGCTTACTGGGGCCAAGGGACTCTGGTCAC
AGTCTCGAGC (SEQ ID NO:310)

Ab-19經人化以抗體20(本文亦稱為Ab-20)及抗體23(本文亦稱為Ab-23)。

Ab-20

IgG4變體

包括訊號肽之Ab-20 LC之胺基酸序列：

MMSSAQFLGLLLLCFQGTRCDIQMTQSPSSLSASVGDRVTITCRASQDISSYLNWYQQKP
GKAPKLLIYSTSRLNSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDIKHPTFGQGTK
VEIKR (SEQ ID NO:311)

包括訊號肽之Ab-20 LC之核酸序列：

ATGATGTCCTCTGCTCAGTTCCTTGGTCTCCTGTTGCTCTGTTTTCAAGGTACCAGATG
TGATATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGTGACCGTGTCA
CCATCACTTGCCGCGCAAGTCAGGATATTAGCAGCTATTTAAATTGGTATCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCTATTCTACTTCCCGTTTGAATAGTGGGGTC
CCATCACGCTTCAGTGGCAGTGGCTCTGGGACAGATTTCACTCTCACCATCAGCAGTC
TGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGGATATTAAACACCCTACGTT

CGGTCAAGGCACCAAGGTGGAGATCAAACGT (SEQ ID NO:312)

包括訊號肽之Ab-20 HC之胺基酸序列：

MEWIWIFLFLLSGTAGVHSEVQLVQSGAEVKKPGSSVKVSCKASGFTFTDYIMHWVRQA
PGQGLEWMGYINPYNDDTEYNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARSI
YYYDAPFAYWGQGTLVTVSS (SEQ ID NO:313)

包括訊號肽之Ab-20 HC之核酸序列：

ATGGAATGGATCTGGATATTTCTCTTCCTCCTGTCAGGAACTGCAGGTGTCCACTCTG
AGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAG
GTCTCCTGCAAGGCTTCTGGTTTTACCTTCACCGACTATATTATGCACTGGGTGCGTCA
GGCCCCTGGTCAAGGGCTTGAGTGGATGGGCTATATCAACCCTTATAATGATGACACC
GAATACAACGAGAAGTTCAAGGGCCGTGTCACGATTACCGCGGACAAATCCACGAGC
ACAGCCTACATGGAGCTGAGCAGCCTGCGCTCTGAGGACACGGCCGTGTATTACTGT
GCGCGTTCGATTTATTACTACGATGCCCCGTTTGCTTACTGGGGCCAAGGGACTCTGG
TCACAGTCTCGAGC (SEQ ID NO:349)

Ab-23

IgG2變體

輕鏈：

成熟形式(移除訊號肽)Ab-23 LC之胺基酸序列：

1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYS
51 TSRLNSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ DIKHPTFGQG
101 TKVEIK***RTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD***
151 NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL
201 SSPVTKSFNR GEC (SEQ ID NO:341)

編碼成熟形式(移除訊號肽)Ab-23 LC之核酸序列：

1 GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGTGA
51 CCGTGTCACC ATCACTTGCC GCGCAAGTCA GGATATTAGC AGCTATTTAA
101 ATTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTATTCT
151 ACTTCCCGTT TGAATAGTGG GGTCCCATCA CGCTTCAGTG GCAGTGGCTC
201 TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG
251 CAACTTACTA CTGTCAACAG GATATTAAAC ACCCTACGTT CGGTCAAGGC
301 ACCAAGGTGG AGATCAAACG TACGGTGGCT GCACCATCTG TCTTCATCTT
351 CCCGCCATCT GATGAGCAGT TGAAATCTGG AACTGCCTCT GTTGTGTGCC
401 TGCTGAATAA CTTCTATCCC AGAGAGGCCA AAGTACAGTG GAAGGTGGAT

451 AACGCCCTCC AATCGGGTAA CTCCCAGGAG AGTGTCACAG AGCAGGACAG
501 CAAGGACAGC ACCTACAGCC TCAGCAGCAC CCTGACGCTG AGCAAAGCAG
551 ACTACGAGAA ACACAAAGTC TACGCCTGCG AAGTCACCCA TCAGGGCCTG
601 AGCTCGCCCG TCACAAAGAG CTTCAACAGG GGAGAGTGT (SEQ ID NO:342)

包括訊號肽之Ab-23 LC之胺基酸序列：

1 MDMRVPAQLL GLLLLWLRGA RCDIQMTQSP SSLSASVGDR VTITCRASQD
51 ISSYLNWYQQ KPGKAPKLLI YSTSRLNSGV PSRFSGSGSG TDFTLTISSL
101 QPEDFATYYC QQDIKHPTFG QGTKVEIKRT VAAPSVFIFP PSDEQLKSGT
151 ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL
201 TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC (SEQ ID NO:343)

包括訊號肽編碼序列之Ab-23 LC之核酸序列：

1 ATGGACATGA GGGTGCCCGC TCAGCTCCTG GGGCTCCTGC TGCTGTGGCT
51 GAGAGGTGCC AGATGTGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTGT
101 CTGCATCTGT AGGTGACCGT GTCACCATCA CTTGCCGCGC AAGTCAGGAT
151 ATTAGCAGCT ATTTAAATTG GTATCAGCAG AAACCAGGGA AAGCCCCTAA
201 GCTCCTGATC TATTCTACTT CCCGTTTGAA TAGTGGGGTC CCATCACGCT
251 TCAGTGGCAG TGGCTCTGGG ACAGATTTCA CTCTCACCAT CAGCAGTCTG
301 CAACCTGAAG ATTTTGCAAC TTACTACTGT CAACAGGATA TTAAACACCC
351 TACGTTCGGT CAAGGCACCA AGGTGGAGAT CAAACGTACG GTGGCTGCAC
401 CATCTGTCTT CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAACT
451 GCCTCTGTTG TGTGCCTGCT GAATAACTTC TATCCCAGAG AGGCCAAAGT
501 ACAGTGGAAG GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG
551 TCACAGAGCA GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCCTG
601 ACGCTGAGCA AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT
651 CACCCATCAG GGCCTGAGCT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG
701 AGTGT (SEQ ID NO:344)

重鏈：

成熟形式(移除訊號肽)Ab-23 HC之胺基酸序列：

1 EVQLVQSGAE VKKPGSSVKV SCKASGFTFT DYIMHWVRQA PGQGLEWMGY
51 INPYNDDTEY NEKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARSI
101 YYYDAPFAYW GQGTLVTVSS ***ASTKGPSVFP LAPCSRSTSE STAALGCLVK***
151 DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT
201 YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF LFPPKPKDTL
251 MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR
301 VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP IEKTISKTKG QPREPQVYTL
351 PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPMLDSD
401 GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK (SEQ ID

NO:345)

無羧基末端離胺酸之成熟形式(移除訊號肽)Ab-23 HC之胺基酸序列：

1 EVQLVQSGAE VKKPGSSVKV SCKASGFTFT DYIMHWVRQA PGQGLEWMGY
51 INPYNDDTEY NEKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARSI
101 YYYDAPFAYW GQGTLVTVSS ***ASTKGPSVFP LAPCSRSTSE STAALGCLVK***
151 DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT
201 YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF LFPPKPKDTL
251 MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR
301 VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP IEKTISKTKG QPREPQVYTL
351 PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPMLDSD
401 GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPG (SEQ ID NO:396)

編碼成熟形式(移除訊號肽)Ab-23 HC之核酸序列：

1 GAGGTGCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGTCCTC
51 GGTGAAGGTC TCCTGCAAGG CTTCTGGTTT TACCTTCACC GACTATATTA
101 TGCACTGGGT GCGTCAGGCC CCTGGTCAAG GGCTTGAGTG GATGGGCTAT
151 ATCAACCCTT ATAATGATGA CACCGAATAC AACGAGAAGT TCAAGGGCCG
201 TGTCACGATT ACCGCGGACA AATCCACGAG CACAGCCTAC ATGGAGCTGA
251 GCAGCCTGCG CTCTGAGGAC ACGGCCGTGT ATTACTGTGC GCGTTCGATT
301 TATTACTACG ATGCCCCGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC
351 CGTCTCTAGT GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCGCCCT
401 GCTCCAGGAG CACCTCCGAG AGCACAGCGG CCCTGGGCTG CCTGGTCAAG
451 GACTACTTCC CCGAACCGGT GACGGTGTCG TGGAACTCAG GCGCTCTGAC
501 CAGCGGCGTG CACACCTTCC CAGCTGTCCT ACAGTCCTCA GGACTCTACT
551 CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAACTTCGG CACCCAGACC
601 TACACCTGCA ACGTAGATCA CAAGCCCAGC AACACCAAGG TGGACAAGAC
651 AGTTGAGCGC AAATGTTGTG TCGAGTGCCC ACCGTGCCCA GCACCACCTG
701 TGGCAGGACC GTCAGTCTTC CTCTTCCCCC CAAAACCCAA GGACACCCTC
751 ATGATCTCCC GGACCCCTGA GGTCACGTGC GTGGTGGTGG ACGTGAGCCA
801 CGAAGACCCC GAGGTCCAGT TCAACTGGTA CGTGGACGGC GTGGAGGTGC
851 ATAATGCCAA GACAAAGCCA CGGGAGGAGC AGTTCAACAG CACGTTCCGT
901 GTGGTCAGCG TCCTCACCGT TGTGCACCAG GACTGGCTGA ACGGCAAGGA
951 GTACAAGTGC AAGGTCTCCA ACAAAGGCCT CCCAGCCCCC ATCGAGAAAA
1001 CCATCTCCAA AACCAAAGGG CAGCCCCGAG AACCACAGGT GTACACCCTG
1051 CCCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTCAGCC TGACCTGCCT
1101 GGTCAAAGGC TTCTACCCCA GCGACATCGC CGTGGAGTGG GAGAGCAATG
1151 GGCAGCCGGA GAACAACTAC AAGACCACAC CTCCCATGCT GGACTCCGAC
1201 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA

1251 GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC
1301 ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTAAA (SEQ ID NO:346)

包括訊號肽之Ab-23 HC之胺基酸序列：

1 MDWTWRILFL VAAATGAHSE VQLVQSGAEV KKPGSSVKVS CKASGFTFTD
51 YIMHWVRQAP GQGLEWMGYI NPYNDDTEYN EKFKGRVTIT ADKSTSTAYM
101 ELSSLRSEDT AVYYCARSIY YYDAPFAYWG QGTLVTVSSA STKGPSVFPL
151 APCSRSTSES TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG
201 LYSLSSVVTV PSSNFGTQTY TCNVDHKPSN TKVDKTVERK CCVECPPCPA
251 PPVAGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV
301 EVHNAKTKPR EEQFNSTFRV VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI
351 EKTISKTKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE
401 SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL
451 HNHYTQKSLS LSPGK (SEQ ID NO:347)

包括訊號肽編碼序列之Ab-23 HC之核酸序列：

1 ATGGACTGGA CCTGGAGGAT CCTCTTCTTG GTGGCAGCAG CCACAGGAGC
51 CCACTCCGAG GTGCAGCTGG TGCAGTCTGG GGCTGAGGTG AAGAAGCCTG
101 GGTCCTCGGT GAAGGTCTCC TGCAAGGCTT CTGGTTTTAC CTTCACCGAC
151 TATATTATGC ACTGGGTGCG TCAGGCCCCT GGTCAAGGGC TTGAGTGGAT
201 GGGCTATATC AACCCTTATA ATGATGACAC CGAATACAAC GAGAAGTTCA
251 AGGGCCGTGT CACGATTACC GCGGACAAAT CCACGAGCAC AGCCTACATG
301 GAGCTGAGCA GCCTGCGCTC TGAGGACACG GCCGTGTATT ACTGTGCGCG
351 TTCGATTTAT TACTACGATG CCCCGTTTGC TTACTGGGGC CAAGGGACTC
401 TGGTCACCGT CTCTAGTGCC TCCACCAAGG GCCCATCGGT CTTCCCCCTG
451 GCGCCCTGCT CCAGGAGCAC CTCCGAGAGC ACAGCGGCCC TGGGCTGCCT
501 GGTCAAGGAC TACTTCCCCG AACCGGTGAC GGTGTCGTGG AACTCAGGCG
551 CTCTGACCAG CGGCGTGCAC ACCTTCCCAG CTGTCCTACA GTCCTCAGGA
601 CTCTACTCCC TCAGCAGCGT GGTGACCGTG CCCTCCAGCA ACTTCGGCAC
651 CCAGACCTAC ACCTGCAACG TAGATCACAA GCCCAGCAAC ACCAAGGTGG
701 ACAAGACAGT TGAGCGCAAA TGTTGTGTCG AGTGCCCACC GTGCCCAGCA
751 CCACCTGTGG CAGGACCGTC AGTCTTCCTC TTCCCCCCAA AACCCAAGGA
801 CACCCTCATG ATCTCCCGGA CCCCTGAGGT CACGTGCGTG GTGGTGGACG
851 TGAGCCACGA AGACCCCGAG GTCCAGTTCA ACTGGTACGT GGACGGCGTG
901 GAGGTGCATA ATGCCAAGAC AAAGCCACGG GAGGAGCAGT TCAACAGCAC
951 GTTCCGTGTG GTCAGCGTCC TCACCGTTGT GCACCAGGAC TGGCTGAACG
1001 GCAAGGAGTA CAAGTGCAAG GTCTCCAACA AAGGCCTCCC AGCCCCCATC
1051 GAGAAAACCA TCTCCAAAAC CAAAGGGCAG CCCCGAGAAC CACAGGTGTA
1101 CACCCTGCCC CCATCCCGGG AGGAGATGAC CAAGAACCAG GTCAGCCTGA
1151 CCTGCCTGGT CAAAGGCTTC TACCCCAGCG ACATCGCCGT GGAGTGGGAG
1201 AGCAATGGGC AGCCGGAGAA CAACTACAAG ACCACACCTC CCATGCTGGA

1251 CTCCGACGGC TCCTTCTTCC TCTACAGCAA GCTCACCGTG GACAAGAGCA
1301 GGTGGCAGCA GGGGAACGTC TTCTCATGCT CCGTGATGCA TGAGGCTCTG
1351 CACAACCACT ACACGCAGAA GAGCCTCTCC CTGTCTCCGG GTAAA (SEQ ID NO:348)

Ab-23重鏈可變區中之CDR(互補判定區)序列如下：

CDR-H1: DYIMH (SEQ ID NO:269)

CDR-H2: YINPYNDDTEYNEKFKG (SEQ ID NO:270)

CDR-H3: SIYYYDAPFAY (SEQ ID NO:271)

Ab-23之輕鏈可變區CDR序列為：

CDR-L1: RASQDISSYLN (SEQ ID NO:239)

CDR-L2: STSRLNS (SEQ ID NO:240)

CDR-L3: QQDIKHPT (SEQ ID NO:241)

Ab-23可變結構域：

Ab-23輕鏈可變結構域胺基酸序列(無訊號序列)：

DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYS TSRLNSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ DIKHPTFGQG TKVEIK (SEQ ID NO:364)

Ab-23輕鏈可變結構域DNA序列(無訊號序列)：

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGTGACCGTGTCACC ATCACTTGCC GCGCAAGTCA GGATATTAGC AGCTATTTAAATTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTATTCTACTTCCCGTT TGAATAGTGG GGTCCCATCA CGCTTCAGTG GCAGTGGCTCTGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTGCAACTTACTA CTGTCAACAG GATATTAAAC ACCCTACGTT CGGTCAAGGCACCAAGGTGG AGATCAAA (SEQ ID NO:365)

Ab-23重鏈可變結構域胺基酸序列(無訊號序列)：

EVQLVQSGAE VKKPGSSVKV SCKASGFTFT DYIMHWVRQA PGQGLEWMGYINPYNDDTEY NEKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARSIYYYDAPFAYW GQGTLVTVSS (SEQ ID NO:366)

Ab-23重鏈可變結構域DNA序列(無訊號序列)：

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAA
GGTC TCCTGCAAGG CTTCTGGTTT TACCTTCACC GACTATATTATGCACTGGGT
GCGTCAGGCC CCTGGTCAAG GGCTTGAGTG GATGGGCTATATCAACCCTT
ATAATGATGA CACCGAATAC AACGAGAAGT TCAAGGGCCGTGTCACGATT
ACCGCGGACA AATCCACGAG CACAGCCTAC ATGGAGCTGAGCAGCCTGCG
CTCTGAGGAC ACGGCCGTGT ATTACTGTGC GCGTTCGATTTATTACTACG
ATGCCCCGTT TGCTTACTGG GGCCAAGGGACTCTGGTCACCGTCTCTAGT (SEQ ID
NO:367)

Ab-21

包括訊號肽之Ab-21 LC之胺基酸序列：

MKSQTQVFVYMLLWLSGVEGDIVMTQSHKFMSTSVGDRVTITCKASQDVFTAVAWYQQ
KPGQSPKLLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPLTFG
AGTKLELKR (SEQ ID NO:315)

包括訊號肽之Ab-21 LC之核酸序列：

ATGAAGTCACAGACCCAGGTCTTTGTATACATGTTGCTGTGGTTGTCTGGTGTTGAAG
GAGACATTGTGATGACCCAGTCTCACAAATTCATGTCCACGTCAGTAGGAGACAGGG
TCACCATCACCTGCAAGGCCAGTCAGGATGTCTTTACTGCTGTAGCCTGGTATCAACA
GAAACCAGGACAATCTCCTAAACTACTGATTTACTGGGCATCCACCCGGCACACTGG
AGTCCCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATTAGC
AATGTGCAGTCTGAAGACTTGGCAGATTATTTCTGTCAACAATATAGCAGCTATCCTCT
CACGTTCGGTGCTGGGACCAAGTTGGAGCTGAAACGT (SEQ ID NO:316)

包括訊號肽之Ab-21 HC之胺基酸序列：

MGWNWIIFFLMAVVTGVNSEVQLQQSGAELVRPGALVKLSCKASGFNIKDYYMHWVK
QRPEQGLEWIGRIDPENGDIIYDPKFQGKASITTDTSSNTAYLQLSSLTSEDTAVYYCAYD
AGDPAWFTYWGQGTLVTVSS (SEQ ID NO:317)

包括訊號肽之Ab-21 HC之核酸序列：

ATGGGATGGAACTGGATCATCTTCTTCCTGATGGCAGTGGTTACAGGGGTCAATTCAG
AGGTTCAGCTGCAGCAGTCTGGGGCTGAGCTTGTGAGGCCAGGGGCCTTAGTCAAGT
TGTCCTGCAAAGCTTCTGGCTTCAATATTAAAGACTACTATATGCACTGGGTGAAGCA
GAGGCCTGAACAGGGCCTGGAGTGGATTGGAAGGATTGATCCTGAGAATGGTGATAT
TATATATGACCCGAAGTTCCAGGGCAAGGCCAGTATAACAACAGACACATCCTCCAAC
ACAGCCTACCTGCAGCTCAGCAGCCTGACGTCTGAGGACACTGCCGTCTATTACTGT
GCTTACGATGCTGGTGACCCCGCCTGGTTTACTTACTGGGGCCAAGGGACTCTGGTCA
CCGTCTCGAGC (SEQ ID NO:318)

Ab-21經人化以產生Ab-22。

Ab-22

包括訊號肽之Ab-22 LC之胺基酸序列：

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCKASQDVFTAVAWYQ
QKPGKAPKLLIYWASTRHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSSYPLTF
GGGTKVEIKR (SEQ ID NO:319)

包括訊號肽之Ab-22 LC之核酸序列：

ATGGATATGCGCGTGCCGGCGCAGCTGCTGGGCCTGCTGCTGCTGTGGCTGCGCGGC
GCGCGCTGCGATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCGAGCGTGGGC
GATCGCGTGACCATTACCTGCAAAGCGAGCCAGGATGTGTTTACCGCGGTGGCGTGG
TATCAGCAGAAACCGGGCAAAGCGCCGAAACTGCTGATTTATTGGGCGAGCACCCGC
CATACCGGCGTGCCGAGTCGCTTTAGCGGCAGCGGCAGCGGCACCGATTTTACCCTG
ACCATTAGCAGCCTGCAGCCGGAAGATTTTGCGACCTATTATTGCCAGCAGTATAGCA
GCTATCCGCTGACCTTTGGCGGCGGCACCAAAGTGGAAATTAAACGT (SEQ ID NO:320)

包括訊號肽之Ab-22 HC之胺基酸序列：

MDWTWSILFLVAAPTGAHSEVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYMHWVR
QAPGQGLEWIGRIDPENGDIIYDPKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAY
DAGDPAWFTYWGQGTLVTVSS (SEQ ID NO:321)

包括訊號肽之Ab-22 HC之核酸序列：

ATGGATTGGACCTGGAGCATTCTGTTTCTGGTGGCGGCGCCGACCGGCGCGCATAGC
GAAGTGCAGCTGGTGCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAGCGTGA
AAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATGCATTGGGTGCG
CCAGGCGCCGGGCCAGGGCCTGGAATGGATCGGCCGCATTGATCCGGAAAACGGCG
ATATTATTTATGATCCGAAATTTCAGGGCCGCGTGACCATGACCACCGATACCAGCACC
AGCACCGCGTATATGGAACTGCGCAGCCTGCGCAGCGATGATACCGCGGTGTATTATT
GCGCGTATGATGCGGGCGATCCGGCGTGGTTTACCTATTGGGGCCAGGGCACCCTGGT
GACCGTCTCGAGC (SEQ ID NO:322)

Ab-22輕鏈可變結構域胺基酸序列(無訊號序列)：

DIQMTQSPSS LSASVGDRVT ITCKASQDVF TAVAWYQQKP GKAPKLLIYW
ASTRHTGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSSYPLTFGG
GTKVEIKR (SEQ ID NO:336)

Ab-22輕鏈可變結構域DNA序列(無訊號序列)：

GATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCGAGCGTGGGCGATCGCGTG
ACCATTACCTGCAAAGCGAGCCAGGATGTGTTTACCGCGGTGGCGTGGTATCAGCAG
AAACCGGGCAAAGCGCCGAAACTGCTGATTTATTGGGCGAGCACCCGCCATACCGGC
GTGCCGAGTCGCTTTAGCGGCAGCGGCAGCGGCACCGATTTTACCCTGACCATTAGC
AGCCTGCAGCCGGAAGATTTTGCGACCTATTATTGCCAGCAGTATAGCAGCTATCCGC
TGACCTTTGGCGGCGGCACCAAAGTGGAAATTAAACGT (SEQ ID NO:337)

Ab-22重鏈可變結構域胺基酸序列(無訊號序列)：

EVQLVQSGAE VKKPGASVKV SCKASGFNIK DYYMHWVRQA
PGQGLEWIGRIDPENGDIIY DPKFQGRVTM TTDTSTSTAY MELRSLRSDD
TAVYYCAYDAGDPAWFTYWG QGTLVTVSS (SEQ ID NO:338)

Ab-22重鏈可變結構域DNA序列(無訊號序列)：

GAAGTGCAGCTGGTGCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAGCGTGA
AAGTGAGCTGCAAAGCGAGCGGCTTTAACATTAAAGATTATTATATGCATTGGGTGCG
CCAGGCGCCGGGCCAGGGCCTGGAATGGATCGGCCGCATTGATCCGGAAAACGGCG
ATATTATTTATGATCCGAAATTTCAGGGCCGCGTGACCATGACCACCGATACCAGCACC
AGCACCGCGTATATGGAACTGCGCAGCCTGCGCAGCGATGATACCGCGGTGTATTATT
GCGCGTATGATGCGGGCGATCCGGCGTGGTTTACCTATTGGGGCCAGGGCACCCTGGT
GACCGTCTCGAGC (SEQ ID NO:339).

對於Ab-18、Ab-20及Ab-22而言，輕鏈人類κ恆定區如下：

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:325)

且重鏈人類γ-4恆定區如下：

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLSLGK* (SEQ ID NO:326)

鉸鏈區含有Ser-241-Pro突變以改良鉸鏈穩定性(Angal S等人，(1993), Mol Immunol, 30(1), 105-108)。

Ab-24

抗體24(本文亦稱為Ab-24)LC及HC之序列如下：

輕鏈：

成熟形式(移除訊號肽)Ab-24 LC之胺基酸序列：

1 DIVLTQSPAS LAVSLGQRAT IACKASQSVD YDGTSYMNWY QQKPGQPPKL
51 LIYAASNLES EIPARFSGTG SGTDFTLNIH PVEEEDITTY YCQQSNEDPF
101 TFGGGTKLEI K***RADAAPTVS IFPPSSEQLT SGGASVVCFL NNFYPKDINV***
151 KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS STLTLTKDEY ERHNSYTCEA
201 THKTSTSPIV KSFNRNEC (SEQ ID NO:350)

編碼成熟形式(移除訊號肽)Ab-24 LC之核酸序列：

1 GACATTGTGT TGACCCAGTC TCCAGCTTCT TTGGCTGTGT CTCTAGGGCA
51 GAGGGCCACC ATCGCCTGCA AGGCCAGCCA AGTGTTGAT TATGATGGTA
101 CTAGTTATAT GAATTGGTAC CAACAGAAAC CAGGACAGCC ACCCAAACTC
151 CTCATCTATG CTGCATCCAA TCTAGAATCT GAGATCCCAG CCAGGTTTAG
201 TGGCACTGGG TCTGGGACAG ACTTCACCCT CAACATCCAT CCTGTGGAGG
251 AGGAGGATAT CACAACCTAT TACTGTCAGC AAAGTAATGA GGATCCGTTC
301 ACGTTCGGAG GGGGGACCAA GTTGGAAATA AAACGGGCTG ATGCTGCACC
351 AACTGTATCC ATCTTCCCAC CATCCAGTGA GCAGTTAACA TCTGGAGGTG
401 CCTCAGTCGT GTGCTTCTTG AACAACTTCT ACCCCAAAGA CATCAATGTC
451 AAGTGGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC TGAACAGTTG
501 GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC AGCACCCTCA
551 CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC CTGTGAGGCC
601 ACTCACAAGA CATCAACTTC ACCCATTGTC AAGAGCTTCA ACAGGAATGA
651 GTGTTAG (SEQ ID NO:354)

包括訊號肽之Ab-24 LC之胺基酸序列：

1 METDTILLWV LLLWVPGSTG DIVLTQSPAS LAVSLGQRAT IACKASQSVD
51 YDGTSYMNWY QQKPGQPPKL LIYAASNLES EIPARFSGTG SGTDFTLNIH
101 PVEEEDITTY YCQQSNEDPF TFGGGTKLEI KRADAAPTVS IFPPSSEQLT
151 SGGASVVCFL NNFYPKDINV KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS
201 STLTLTKDEY ERHNSYTCEA THKTSTSPIV KSFNRNEC (SEQ ID NO:355)

包括訊號肽編碼序列之Ab-24 LC之核酸序列：

1 ATGGAGACAG ACACAATCCT GCTATGGGTG CTGCTGCTCT GGGTTCCAGG
51 CTCCACTGGT GACATTGTGT TGACCCAGTC TCCAGCTTCT TTGGCTGTGT
101 CTCTAGGGCA GAGGGCCACC ATCGCCTGCA AGGCCAGCCA AGTGTTGAT
151 TATGATGGTA CTAGTTATAT GAATTGGTAC CAACAGAAAC CAGGACAGCC
201 ACCCAAACTC CTCATCTATG CTGCATCCAA TCTAGAATCT GAGATCCCAG
251 CCAGGTTTAG TGGCACTGGG TCTGGGACAG ACTTCACCCT CAACATCCAT

301 CCTGTGGAGG AGGAGGATAT CACAACCTAT TACTGTCAGC AAAGTAATGA
351 GGATCCGTTC ACGTTCGGAG GGGGGACCAA GTTGGAAATA AAACGGGCTG
401 ATGCTGCACC AACTGTATCC ATCTTCCCAC CATCCAGTGA GCAGTTAACA
451 TCTGGAGGTG CCTCAGTCGT GTGCTTCTTG AACAACTTCT ACCCCAAAGA
501 CATCAATGTC AAGTGGAAGA TTGATGGCAG TGAACGACAA AATGGCGTCC
551 TGAACAGTTG GACTGATCAG GACAGCAAAG ACAGCACCTA CAGCATGAGC
601 AGCACCCTCA CGTTGACCAA GGACGAGTAT GAACGACATA ACAGCTATAC
651 CTGTGAGGCC ACTCACAAGA CATCAACTTC ACCCATTGTC AAGAGCTTCA
701 ACAGGAATGA GTGTTAG (SEQ ID NO:356)

Ab-24重鏈：

成熟形式(移除訊號肽)Ab-24 HC之胺基酸序列：

1 QVQLQQPGTE LVRPGTSVKL SCKASGYIFT TYWMNWVKQR PGQGLEWIGM
51 IHPSASEIRL DQKFKDKATL TLDKSSSTAY MHLSGPTSVD SAVYYCARSG
101 EWGSMDYWGQ GTSVTVSS***AK TTPPSVYPLA PGSAAQTNSM VTLGCLVKGY***
151 FPEPVTVTWN SGSLSSGVHT FPAVLQSDLY TLSSSVTVPS STWPSETVTC
201 NVAHPASSTK VDKKIVPRDC GCKPCICTVP EVSSVFIFPP KPKDVLTITL
251 TPKVTCVVVD ISKDDPEVQF SWFVDDVEVH TAQTQPREEQ FNSTFRSVSE
301 LPIMHQDWLN GKEFKCRVNS AAFPAPIEKT ISKTKGRPKA PQVYTIPPPK
351 EQMAKDKVSL TCMITDFFPE DITVEWQWNG QPAENYKNTQ PIMDTDGSYF
401 IYSKLNVQKS NWEAGNTFTC SVLHEGLHNH HTEKSLSHSP GK (SEQ ID NO:357)

編碼成熟形式(移除訊號肽)Ab-24 HC之核酸序列：

1 CAGGTCCAAC TACAGCAGCC TGGGACTGAG CTGGTGAGGC CTGGAACTTC
51 AGTGAAGTTG TCCTGTAAGG CTTCTGGCTA CATCTTCACC ACCTACTGGA
101 TGAACTGGGT GAAACAGAGG CCTGGACAAG GCCTTGAGTG GATTGGCATG
151 ATTCATCCTT CCGCAAGTGA AATTAGGTTG GATCAGAAAT TCAAGGACAA
201 GGCCACATTG ACTCTTGACA AATCCTCCAG CACAGCCTAT ATGCACCTCA
251 GCGGCCCGAC ATCTGTGGAT TCTGCGGTCT ATTACTGTGC AAGATCAGGG
301 GAATGGGGGT CTATGGACTA CTGGGGTCAA GGAACCTCAG TCACCGTCTC
351 CTCAGCCAAA ACGACACCCC CATCTGTCTA TCCACTGGCC CCTGGATCTG
401 CTGCCCAAAC TAACTCCATG GTGACCCTGG GATGCCTGGT CAAGGGCTAT
451 TTCCCTGAGC CAGTGACAGT GACCTGGAAC TCTGGATCCC TGTCCAGCGG
501 TGTGCACACC TTCCCAGCTG TCCTGCAGTC TGACCTCTAC ACTCTGAGCA
551 GCTCAGTGAC TGTCCCCTCC AGCACCTGGC CCAGCGAGAC CGTCACCTGC
601 AACGTTGCCC ACCCGGCCAG CAGCACCAAG GTGGACAAGA AAATTGTGCC
651 CAGGGATTGT GGTTGTAAGC CTTGCATATG TACAGTCCCA GAAGTATCAT
701 CTGTCTTCAT CTTCCCCCCA AAGCCCAAGG ATGTGCTCAC CATTACTCTG
751 ACTCCTAAGG TCACGTGTGT TGTGGTAGAC ATCAGCAAGG ATGATCCCGA
801 GGTCCAGTTC AGCTGGTTTG TAGATGATGT GGAGGTGCAC ACAGCTCAGA
851 CGCAACCCCG GGAGGAGCAG TTCAACAGCA CTTTCCGCTC AGTCAGTGAA

901 CTTCCCATCA TGCACCAGGA CTGGCTCAAT GGCAAGGAGT TCAAATGCAG
951 GGTCAACAGT GCAGCTTTCC CTGCCCCCAT CGAGAAAACC ATCTCCAAAA
1001 CCAAAGGCAG ACCGAAGGCT CCACAGGTGT ACACCATTCC ACCTCCCAAG
1051 GAGCAGATGG CCAAGGATAA AGTCAGTCTG ACCTGCATGA TAACAGACTT
1101 CTTCCCTGAA GACATTACTG TGGAGTGGCA GTGGAATGGG CAGCCAGCGG
1151 AGAACTACAA GAACACTCAG CCCATCATGG ACACAGATGG CTCTTACTTC
1201 ATCTACAGCA AGCTCAATGT GCAGAAGAGC AACTGGGAGG CAGGAAATAC
1251 TTTCACCTGC TCTGTGTTAC ATGAGGGCCT GCACAACCAC CATACTGAGA
1301 AGAGCCTCTC CCACTCTCCT GGTAAATGA (SEQ ID NO:361)

包括訊號肽之Ab-24 HC之胺基酸序列：

1 MGWSSIILFL VATATGVHSQ VQLQQPGTEL VRPGTSVKLS CKASGYIFTT
51 YWMNWVKQRP GQGLEWIGMI HPSASEIRLD QKFKDKATLT LDKSSSTAYM
101 HLSGPTSVDS AVYYCARSGE WGSMDYWGQG TSVTVSSAKT TPPSVYPLAP
151 GSAAQTNSMV TLGCLVKGYF PEPVTVTWNS GSLSSGVHTF PAVLQSDLYT
201 LSSSVTVPSS TWPSETVTCN VAHPASSTKV DKKIVPRDCG CKPCICTVPE
251 VSSVFIFPPK PKDVLTITLT PKVTCVVVDI SKDDPEVQFS WFVDDVEVHT
301 AQTQPREEQF NSTFRSVSEL PIMHQDWLNG KEFKCRVNSA AFPAPIEKTI
351 SKTKGRPKAP QVYTIPPPKE QMAKDKVSLT CMITDFFPED ITVEWQWNGQ
401 PAENYKNTQP IMDTDGSYFI YSKLNVQKSN WEAGNTFTCS VLHEGLHNHH
451 TEKSLSHSPG K (SEQ ID NO:362)

包括訊號肽編碼序列之Ab-24 HC之核酸序列：

1 ATGGGATGGA GCTCTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT
51 CCACTCCCAG GTCCAACTAC AGCAGCCTGG GACTGAGCTG GTGAGGCCTG
101 GAACTTCAGT GAAGTTGTCC TGTAAGGCTT CTGGCTACAT CTTCACCACC
151 TACTGGATGA ACTGGGTGAA ACAGAGGCCT GGACAAGGCC TTGAGTGGAT
201 TGGCATGATT CATCCTTCCG CAAGTGAAAT TAGGTTGGAT CAGAAATTCA
251 AGGACAAGGC CACATTGACT CTTGACAAAT CCTCCAGCAC AGCCTATATG
301 CACCTCAGCG GCCCGACATC TGTGGATTCT GCGGTCTATT ACTGTGCAAG
351 ATCAGGGGAA TGGGGGTCTA TGGACTACTG GGGTCAAGGA ACCTCAGTCA
401 CCGTCTCCTC AGCCAAAACG ACACCCCCAT CTGTCTATCC ACTGGCCCCT
451 GGATCTGCTG CCCAAACTAA CTCCATGGTG ACCCTGGGAT GCCTGGTCAA
501 GGGCTATTTC CCTGAGCCAG TGACAGTGAC CTGGAACTCT GGATCCCTGT
551 CCAGCGGTGT GCACACCTTC CCAGCTGTCC TGCAGTCTGA CCTCTACACT
601 CTGAGCAGCT CAGTGACTGT CCCCTCCAGC ACCTGGCCCA GCGAGACCGT
651 CACCTGCAAC GTTGCCCACC CGGCCAGCAG CACCAAGGTG GACAAGAAAA
701 TTGTGCCCAG GGATTGTGGT TGTAAGCCTT GCATATGTAC AGTCCCAGAA
751 GTATCATCTG TCTTCATCTT CCCCCCAAAG CCCAAGGATG TGCTCACCAT
801 TACTCTGACT CCTAAGGTCA CGTGTGTTGT GGTAGACATC AGCAAGGATG
851 ATCCCGAGGT CCAGTTCAGC TGGTTTGTAG ATGATGTGGA GGTGCACACA

901 GCTCAGACGC AACCCCGGGA GGAGCAGTTC AACAGCACTT TCCGCTCAGT
951 CAGTGAACTT CCCATCATGC ACCAGGACTG GCTCAATGGC AAGGAGTTCA
1001 AATGCAGGGT CAACAGTGCA GCTTTCCCTG CCCCCATCGA GAAAACCATC
1051 TCCAAAACCA AAGGCAGACC GAAGGCTCCA CAGGTGTACA CCATTCCACC
1101 TCCCAAGGAG CAGATGGCCA AGGATAAAGT CAGTCTGACC TGCATGATAA
1151 CAGACTTCTT CCCTGAAGAC ATTACTGTGG AGTGGCAGTG GAATGGGCAG
1201 CCAGCGGAGA ACTACAAGAA CACTCAGCCC ATCATGGACA CAGATGGCTC
1251 TTACTTCATC TACAGCAAGC TCAATGTGCA GAAGAGCAAC TGGGAGGCAG
1301 GAAATACTTT CACCTGCTCT GTGTTACATG AGGGCCTGCA CAACCACCAT
1351 ACTGAGAAGA GCCTCTCCCA CTCTCCTGGT AAATGA (SEQ ID NO:363)

Ab-24輕鏈可變區中之CDR序列如下：

CDR-L1: KASQSVDYDGTSYMN (SEQ ID NO:351)

CDR-L2: AASNLES (SEQ ID NO:352)

CDR-L3: QQSNEDPFT (SEQ ID NO:353)

Ab-24重鏈可變區中之CDR序列如下：

CDR-H1: TYWMN (SEQ ID NO:358)

CDR-H2: MIHPSASEIRLDQKFKD (SEQ ID NO:359)

CDR-H3: SGEWGSMDY (SEQ ID NO:360)

下文表1提供Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24之CDR的SEQ ID NO及胺基酸序列。根據Kabat編號系統(Kabat等人，1987於Sequences of Proteins of Immunological Interest中, U.S. Department of Health and Human Services, NIH, USA)，L1、L2及L3係指輕鏈CDR之1、2及3，且H1、H2及H3係指重鏈CDR之1、2及3。

表1		
SEQ ID NO	**描述**	**胺基酸序列**
54	Ab-A及Ab-1 CDR-L1	QSSQSVYDNNWLA
55	Ab-A及Ab-1 CDR-L2	DASDLAS
56	Ab-A及Ab-1 CDR-L3	QGAYNDVIYA
51	Ab-A及Ab-1 CDR-H1	SYWMN
52	Ab-A及Ab-1 CDR-H2	TIDSGGRTDYASWAKG
53	Ab-A及Ab-1 CDR-H3	NWNL
60	Ab-B CDR-L1	SASSSVSFVD
61	Ab-B CDR-L2	RTSNLGF
62	Ab-B CDR-L3	QQRSTYPPT
57	Ab-B CDR-H1	TSGMGVG
58	Ab-B CDR-H2	HIWWDDVKRYNPVLKS
59	Ab-B CDR-H3	EDFDYDEEYYAMDY
48	Ab-C CDR-L1	KASQSVDYDGDSYMN
49	Ab-C CDR-L2	AASNLES
50	Ab-C CDR-L3	QQSNEDPWT
45	Ab-C CDR-H1	DCYMN
46	Ab-C CDR-H2	DINPFNGGTTYNQKFKG
47	Ab-C CDR-H3	SHYYFDGRVPWDAMDY
42	Ab-D CDR-L1	QASQGTSINLN
43	Ab-D CDR-L2	GSSNLED
44	Ab-D CDR-L3	LQHSYLPYT
39	Ab-D CDR-H1	DHYMS
40	Ab-D CDR-H2	DINPYSGETTYNQKFKG
41	Ab-D CDR-H3	DDYDASPFAY
275	Ab-2 CDR-L1	RASSSVYYYMH
276	Ab-2 CDR-L2	ATSNLAS
277	Ab-2 CDR-L3	QQWSSDPLT
287	Ab-2 CDR-H1	DYFIH
288	Ab-2 CDR-H2	RLDPEDGESDYAPKFQD
289	Ab-2 CDR-H3	EDYDGTYTFFPY
278	Ab-3及Ab-15 CDR-L1	SVSSTISSNHLH
279	Ab-3及Ab-15 CDR-L2	GTSNLAS
280	Ab-3及Ab-15 CDR-L3	QQWSSYPLT
290	Ab-3及Ab-15 CDR-H1	DFYLH
291	Ab-3及Ab-15 CDR-H2	RIDPENGDTLYDPKFQD
292	Ab-3及Ab-15 CDR-H3	EADYFHDGTSYWYFDV
78	Ab-4及Ab-5 CDR-L1	RASQDISNYLN
79	Ab-4及Ab-5 CDR-L2	YTSRLLS

表1		
SEQ ID NO	**描述**	**胺基酸序列**
80	Ab-4及Ab-5 CDR-L3	QQGDTLPYT
245	Ab-4及Ab-5 CDR-H1	DYNMH
246	Ab-4及Ab-5 CDR-H2	EINPNSGGAGYNQKFKG
247	Ab-4及Ab-5 CDR-H3	LGYDDIYDDWYFDV
81	Ab-6 CDR-L1	RASQDISNYLN
99	Ab-6 CDR-L2	YTSRLHS
100	Ab-6 CDR-L3	QQGDTLPYT
248	Ab-6 CDR-H1	DYNMH
249	Ab-6 CDR-H2	EINPNSGGSGYNQKFKG
250	Ab-6 CDR-H3	LVYDGSYEDWYFDV
101	Ab-7 CDR-L1	RASQVITNYLY
102	Ab-7 CDR-L2	YTSRLHS
103	Ab-7 CDR-L3	QQGDTLPYT
251	Ab-7 CDR-H1	DYNMH
252	Ab-7 CDR-H2	EINPNSGGAGYNQQFKG
253	Ab-7 CDR-H3	LGYVGNYEDWYFDV
104	Ab-8 CDR-L1	RASQDISNYLN
105	Ab-8 CDR-L2	YTSRLLS
106	Ab-8 CDR-L3	QQGDTLPYT
254	Ab-8 CDR-H1	DYNMH
255	Ab-8 CDR-H2	EINPNSGGAGYNQKFKG
256	Ab-8 CDR-H3	LGYDDIYDDWYFDV
107	Ab-9 CDR-L1	RASQDISNYLN
108	Ab-9 CDR-L2	YTSRLFS
109	Ab-9 CDR-L3	QQGDTLPYT
257	Ab-9 CDR-H1	DYNMH
258	Ab-9 CDR-H2	EINPNSGGAGYNQKFKG
259	Ab-9 CDR-H3	LGYDDIYDDWYFDV
110	Ab-10 CDR-L1	RASQDISNYLN
111	Ab-10 CDR-L2	YTSRLLS
112	Ab-10 CDR-L3	QQGDTLPYT
260	Ab-10 CDR-H1	DYNMH
261	Ab-10 CDR-H2	EINPNSGGAGYNQKFKG
262	Ab-10 CDR-H3	LGYDDIYDDWYFDV
281	Ab-11及Ab-16 CDR-L1	RASSSISYIH
282	Ab-11及Ab-16 CDR-L2	ATSNLAS
283	Ab-11及Ab-16 CDR-L3	QQWSSDPLT
293	Ab-11及Ab-16 CDR-H1	DYYIH
294	Ab-11及Ab-16 CDR-H2	RVDPDNGETEFAPKFPG

表1		
SEQ ID NO	**描述**	**胺基酸序列**
295	Ab-11及Ab-16 CDR-H3	EDYDGTYTWFPY
113	Ab-12 CDR-L1	RASQDISNYLN
114	Ab-12 CDR-L2	YTSTLQS
115	Ab-12 CDR-L3	QQGDTLPYT
263	Ab-12 CDR-H1	DYNMH
264	Ab-12 CDR-H2	EINPNSGGSGYNQKFKG
265	Ab-12 CDR-H3	LGYYGNYEDWYFDV
284	Ab-13及Ab-14 CDR-L1	RASSSVTSSYLN
285	Ab-13及Ab-14 CDR-L2	STSNLAS
286	Ab-13及Ab-14 CDR-L3	QQYDFFPST
296	Ab-13及Ab-14 CDR-H1	DYYMN
297	Ab-13及Ab-14 CDR-H2	DINPYNDDTTYNHKFKG
298	Ab-13及Ab-14 CDR-H3	ETAVITTNAMD
116	Ab-17及Ab-18 CDR-L1	SVSSSISSSNLH
237	Ab-17及Ab-18 CDR-L2	GTSNLAS
238	Ab-17及Ab-18 CDR-L3	QQWTTTYT
266	Ab-17及Ab-18 CDR-H1	DYYIH
267	Ab-17及Ab-18 CDR-H2	RIDPDNGESTYVPKFQG
268	Ab-17及Ab-18 CDR-H3	EGLDYGDYYAVDY
239	Ab-19, Ab-20及Ab-23 CDR-L1	RASQDISSYLN
240	Ab-19, Ab-20及Ab-23 CDR-L2	STSRLNS
241	Ab-19, Ab-20及Ab-23 CDR-L3	QQDIKHPT
269	Ab-19, Ab-20及Ab-23 CDR-H1	DYIMH
270	Ab-19, Ab-20及Ab-23 CDR-H2	YINPYNDDTEYNEKFKG
271	Ab-19, Ab-20及Ab-23 CDR-H3	SIYYYDAPFAY
242	Ab-21及Ab-22 CDR-L1	KASQDVFTAVA
243	Ab-21及Ab-22 CDR-L2	WASTRHT
244	Ab-21及Ab-22 CDR-L3	QQYSSYPLT
272	Ab-21及Ab-22 CDR-H1	DYYMH
273	Ab-21及Ab-22 CDR-H2	RIDPENGDIIYDPKFQG
274	Ab-21及Ab-22 CDR-H3	DAGDPAWFTY
351	Ab-24 CDR-L1	KASQSVDYDGTSYMN
352	Ab-24 CDR-L2	AASNLES
353	Ab-24 CDR-L3	QQSNEDPFT
358	Ab-24 CDR-H1	TYWMN
359	Ab-24 CDR-H2	MIHPSASEIRLDQKFKD
360	Ab-24 CDR-H3	SGEWGSMDY

若寡肽或多肽具有與上文表1中至少一種CDR；及/或與交叉阻斷抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24之至少一種與殼硬蛋白之結合及/或由抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24之至少一種而交叉阻斷與殼硬蛋白之結合的殼硬蛋白結合劑之CDR；及/或與其中結合劑在以細胞為基礎之礦質化分析中可阻斷殼硬蛋白之抑制效應的殼硬蛋白結合劑(意即，殼硬蛋白中和結合劑)之CDR；及/或與結合至環2抗原決定基之殼硬蛋白結合劑之CDR；及/或與結合至T20.6抗原決定基之殼硬蛋白結合劑之CDR；及/或與結合至"T20.6衍生物(胱胺酸-結+4臂)"抗原決定基之殼硬蛋白結合劑之CDR至少75%、76%、77%、78%、79%、80%、81%、82%、83%、84%、85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%一致之胺基酸序列，則該寡肽或多肽在本發明之範疇內。

若殼硬蛋白結合劑多肽及抗體具有與抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24之至少一種之可變區至少85%、86%、87%、88%、89%、90%、91%、92%、

93%、94%、95%、96%、97%、98%或99%一致，且交叉阻斷抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24之至少一種與殼硬蛋白之結合，及/或由抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24之至少一種而交叉阻斷與殼硬蛋白之結合；及/或在以細胞為基礎之礦質化分析中可阻斷殼硬蛋白之抑制效應(意即，殼硬蛋白中和結合劑)；及/或結合至環2抗原決定基；及/或結合至T20.6抗原決定基；及/或結合至"T20.6衍生物(胱胺酸-結+ 4臂)"抗原決定基之胺基酸序列；則該等殼硬蛋白結合劑多肽及抗體在本發明之範疇內。

若編碼殼硬蛋白結合劑之聚核苷酸具有與編碼抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24之至少一種之可變區的聚核苷酸至少85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%一致之聚核苷酸序列，且其中經編碼殼硬蛋白結合劑交叉阻斷抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-

24之至少一種與殼硬蛋白之結合，及/或由抗體Ab-A、Ab-B、Ab-C、Ab-D、Ab-1、Ab-2、Ab-3、Ab-4、Ab-5、Ab-6、Ab-7、Ab-8、Ab-9、Ab-10、Ab-11、Ab-12、Ab-13、Ab-14、Ab-15、Ab-16、Ab-17、Ab-18、Ab-19、Ab-20、Ab-21、Ab-22、Ab-23及Ab-24之至少一種而交叉阻斷與殼硬蛋白之結合；及/或在以細胞為基礎之礦質化分析中可阻斷殼硬蛋白之抑制效應(意即，殼硬蛋白中和結合劑)；及/或結合至環2抗原決定基；及/或結合至T20.6抗原決定基；及/或結合至"T20.6衍生物(胱胺酸-結+ 4臂)"抗原決定基；則該等聚核苷酸在本發明之範疇內。

根據本發明抗體與人類殼硬蛋白具有小於或等於$1x10^{-7}$ M，小於或等於$1x10^{-8}$ M，小於或等於$1x10^{-9}$ M，小於或等於$1x10^{-10}$ M，小於或等於$1x10^{-11}$ M，或小於或等於$1x10^{-12}$ M之結合親合力。

結合劑(諸如抗體或結合搭配物)之親合力以及結合劑(諸如抗體)抑制結合之程度可藉由熟習此項技術者使用習知技術來測定，例如Scatchard等人(*Ann. N.Y. Acad. Sci.* 51:660-672 (1949))所述之技術，或藉由表面電漿共振(SPR; BIAcore, Biosensor, Piscataway, NJ)來測定。對於表面電漿共振而言，將標靶分子固定於固相上，且暴露於沿流動單元流動之移動相中之配位體。若發生配位體結合至固定標靶上，則局部折射率會改變，導致SPR角改變，此可藉由偵測反射光強度之改變即時監控。可分析SPR訊號之改變速率以得到結合反應之締合及解離階段的表觀速率常數。該等數值之比率定出表觀平衡常數(親合力)(參見，例如Wolff等人，*Cancer Res.* 53:2560-65 (1993))。

根據本發明抗體可屬於任何免疫球蛋白類，例如IgG、IgE、

IgM、IgD或IgA，其可獲自動物或源於動物，例如家禽(例如雞)及哺乳動物，該動物包括(但不限於)小鼠、大鼠、倉鼠、兔或其他齧齒動物、牛、馬、綿羊、山羊、駱駝、人類或其他靈長類動物。該抗體可為內化抗體。抗體之產生概括性地揭示於美國專利公開案第2004/0146888 A1號中。

表徵分析

在上述產生根據本發明抗體之方法中，包括操控特異性Ab-A、Ab-B、Ab-C、Ab-D及抗體1-24(Ab-1至Ab-24)CDR進入新穎框架及/或恆定區中，可利用適當分析來選擇所要抗體或結合劑(意即，用於判定與殼硬蛋白之結合親合力之分析；交叉阻斷分析；以Biacore為基礎之"人類殼硬蛋白肽抗原決定基競爭結合分析"；以MC3T3-E1細胞為基礎之分析；活體內分析)。

抗原決定基結合分析

成熟形式人類殼硬蛋白為具有胱胺酸結結構之190個胺基酸的糖蛋白(圖8及9)。除胱胺酸-結結構之外，蛋白之特徵在於其具有命名為環1、環2及環3之三個環。人類殼硬蛋白經受蛋白水解消化以產生片段。簡言之，使用不同之蛋白酶，包括胰蛋白酶、aspN及lysC，產生具有各種裂解位點及尺寸之片段。判定各種人類殼硬蛋白肽之序列及質量。評估抗體保護以判定對於蛋白水解可用性之影響，包括剪切位點遮蔽及肽移位。最後，進行基於BIAcore之"人類殼硬蛋白肽抗原決定基競爭分析"。

殼硬蛋白暴露於胰蛋白酶裂解導致如圖13中所概括之肽片段圖案。該等片段係指T19.2、T20、T20.6及T21-22。如圖19B中示意展

示，T20.6抗原決定基為由胱胺酸-結區域之三個二硫鍵所連接之四個獨立肽序列的複合物。該等肽之兩者由兩個二硫鍵連接。其他兩個肽由一個二硫鍵連接，該二硫鍵示意性平分前兩個多肽。

由胰蛋白酶消化所產生之T20.6抗原決定基保持原始多肽之胱胺酸-結結構且由抗體Ab-C及Ab-D來識別。抗原決定基T20.6之衍生物由胱胺酸-結區域及序列位置上關於SEQ ID NO：1之胺基酸58-64、73-81、112-117及138-141組成。該衍生抗原決定基展示於圖21中。包含胱胺酸-結區域之抗原決定基可具有存在於T20.6抗原決定基(圖19B)但不存在於T20.6衍生物抗原決定基(圖21)中之一或多個胺基酸。

含有抗原決定基之另一區域經鑒別位於人類殼硬蛋白之環2區域中(圖19A)且由抗體Ab-A及Ab-B來識別。環2抗原決定基包含SEQ ID NO：1之胺基酸86-111 (C4GPARLLPNAIGRGKWWRPSGPDFRC5，SEQ ID NO：6)。空間上，關於SEQ ID NO：1之全長殼硬蛋白，含有環2之結構在一端由位置86(C4)之半胱胺酸與位置144(C8)之半胱胺酸之間的二硫鍵來界定，且在另一端由位置111(C5)之半胱胺酸與位置57(C1)之半胱胺酸之間的二硫鍵來界定。

圖12展示由aspN裂解人類殼硬蛋白所產生之肽。在該圖中，該等肽命名為AspN14.6、AspN18.6及AspN22.7-23.5，且本文亦分別稱為N14.6、N18.6及N22.7-23.5。

如由基於Biacore之"人類殼硬蛋白肽抗原決定基競爭結合分析"所證明，一組抗體展示結合至某些抗原決定基之特異性圖案。簡言之，以將飽和抗體上之抗原決定基結合位點之濃度，以待測試之抗原決定基預培育抗體。隨後將抗體暴露於結合至晶片表面之殼硬蛋白。

在適當培育及洗滌程序之後，建立競爭性結合之圖案。如圖18所示，例示性抗體Ab-D結合至連接於晶片表面之殼硬蛋白分子。以殼硬蛋白預培育抗體Ab-D將該抗體與晶片上殼硬蛋白之結合降低至接近零。以由抗原決定基T19.2組成之肽預培育展示T19.2不與殼硬蛋白競爭抗體結合。然而，以命名為T20、T20.6、T21-22或N22.7-23.5之任一種抗原決定基預培育均消除了抗體與晶片上殼硬蛋白之大部分結合。相反，以命名為T19.2、N14.6或N18.6之任一種抗原決定基預培育抗體不消除該抗體結合至殼硬蛋白之能力。具有該結合概況(圖17)之第二種例示性抗體為Ab-C。

因此，如由阻斷抗體結合至殼硬蛋白之能力所量測，抗體Ab-D為結合至抗原決定基T20、T20.6、T21-22及N22.7-23.5，且與抗原決定基T19.2、N14.6及N18.6具有最小可偵測之結合的一組例示性及代表性抗體。具有此特徵性結合圖案之抗體在一或多個抗體分子區域中可共用或不共用胺基酸序列。抗體相似性功能上諸如藉由在以上述每一種抗原決定基預培育後結合至殼硬蛋白的能力來判定。展示與抗體Ab-D相似或一致之結合圖案的抗體包括於本發明內。例如，"相似"意謂抗體將展示結合至多肽T20、T20.6、T21-22及N22.7-23.5之每一者，藉此該結合將特異性競爭超出在不以殼硬蛋白或殼硬蛋白肽預培育之情況下所發生之抗體與殼硬蛋白結合的至少50%。該抗體亦將展示很少或無可偵測之與多肽T19.2、N14.6及N18.6之結合，導致在不以殼硬蛋白或殼硬蛋白肽預培育之情況下將發生之結合的30%或更少之降低。

例如，藉由特定機制而不結合，圖18之抗體結合圖案表明，抗

體Ab-D及具有Ab-D之抗原決定基結合圖案的其他抗體所結合之抗原決定基空間由包含殼硬蛋白之胱胺酸-結區域的多肽組成。

因此，如本文所揭示及參考圖19B，例示性T20.6抗原決定基包含經由三個獨立二硫鍵所連接之四個肽鏈。肽鏈SAKPVTELVC3SGQC4GPAR(SEQ ID NO：3)由C3至C7及C4至C8之二硫鍵連接至肽鏈LVASC7KC8KRLTR(SEQ ID NO：5)。肽鏈DVSEYSC1RELHFTR(SEQ ID NO：2)由C1至C5之二硫鍵連接至肽鏈WWRPSGPDFRC5IPDRYR(SEQ ID NO：4)。如圖19B所示，SEQ ID NO:3及5之多肽經由空間構造與SEQ ID NO:2及4之多肽保持締合，藉此C1-C5鍵穿過C4-C8及C3-C7鍵之平面且位於其間。

如本文所揭示及參考圖21，T20.6之例示性衍生抗原決定基包含經由三個獨立二硫鍵連接之四個肽鏈。肽鏈SAKPVTELVC3SGQC4(SEQ ID NO：70) 由C3至C7及C4至C8之二硫鍵連接至肽鏈LVASC7KC8(SEQ ID NO：71)。肽鏈C1RELHFTR(SEQ ID NO：72)由C1至C5之二硫鍵連接至肽鏈C5IPDRYR(SEQ ID NO：73)。如圖21所示，SEQ ID NO:70及71之多肽經由空間構造與SEQ ID NO:72及73之多肽保持締合，藉此C1-C5鍵穿過C4-C8及C3-C7鍵之平面且位於其間。

抗體Ab-A為具有與抗體Ab-C及Ab-D所獲得之不同的與人類殼硬蛋白肽之特徵性結合圖案的第二組例示性及代表性抗體。如由阻斷抗體結合至殼硬蛋白之能力所量測(圖15)，Ab-A及其代表之抗體組結合至N22.7-23.5抗原決定基且具有最小可偵測之與抗原決定基T19.2、T20、T20.6、T21-22、N14.6或N18.6之結合。具有此結合概況(圖16)

之第二種例示性抗體為Ab-B。具有此特徵性結合圖案之抗體在一或多個抗體分子區域中可共用或不共用胺基酸序列。抗體相似性功能上諸如藉由在以上述每一種抗原決定基預培育後結合至殼硬蛋白的能力來判定。展示與抗體Ab-A相似或一致之結合圖案的抗體包括於本發明內。例如，"相似"意謂抗體將展示結合至N22.7-23.5多肽，藉此該結合將特異性競爭超出在不以殼硬蛋白或殼硬蛋白肽預培育之情況下所發生之抗體與殼硬蛋白結合的至少50%。該抗體亦將展示很少或無可偵測之與多肽T19.2、T20、T20.6、T21-22、N14.6及N18.6之結合，導致在不以殼硬蛋白或殼硬蛋白肽預培育之情況下將發生之結合的30%或更少之降低。

例如，藉由特定機制而不結合，圖15之抗體結合圖案表明，抗體Ab-A及具有Ab-A之抗原決定基結合圖案的其他抗體所結合之抗原決定基空間由包含殼硬蛋白之環2區域的多肽組成。因此，如本文所揭示及參考圖19A，環2區域可描述為直鏈肽，但當其存在於原始殼硬蛋白或其中保留原始二硫鍵結構之殼硬蛋白之含有胱胺酸-結部分中時，其獲得三級結構。如實例中所討論，環2抗原決定基之直鏈或三級結構可影響抗體與其之結合。環2區域可包含以下胺基酸序列：C4GPARLLPNAIGRGKWWRPSGPDFRC5 SEQ ID NO：6)。"C4"係指位於關於SEQ ID NO：1之位置86之半胱胺酸殘基。"C5"係指位於關於SEQ ID NO：1之位置111之半胱胺酸殘基。在原始殼硬蛋白中，C4由二硫鍵連接至位置144(C8)之半胱胺酸，且C5由二硫鍵連接至位置57(C1)之半胱胺酸。源於環2區域之抗原決定基包括CGPARLLPNAIGRGKWWRPS (SEQ ID NO：63)、GPARLLPNAIGRG

KWWRPSG (SEQ ID NO：64)、PARLLPNAIGRGKWWRPSGP (SEQ ID NO：65)、ARLLPNAIGRGKWWRPSGPD (SEQ ID NO：66)、RLLPNAIGRGKWWRPSGPDF(SEQ ID NO：67)、LLPNAIGRGKWWRPSGPDFR(SEQ ID NO：68)及LPNAIGRGKWWRPSGPDFRC(SEQ ID NO：69)。

交叉阻斷分析

本文中術語"交叉阻斷"意謂抗體或其他結合劑干擾其他抗體或結合劑與殼硬蛋白結合之能力。

可使用競爭結合分析來判定抗體或其他結合劑可干擾另一者與殼硬蛋白結合之程度，及因此判定其是否可謂根據本發明之交叉阻斷。一種尤其合適之定量分析使用Biacore機械，其可使用表面電漿共振技術來量測交互作用之程度。另一種合適之定量交叉阻斷分析使用基於ELISA之方式來量測抗體或其他結合劑之間就其與殼硬蛋白之結合而言的競爭。

BIACORE交叉阻斷分析

下文大體描述一種用於判定抗體或其他結合劑是否根據本發明交叉阻斷或可交叉阻斷之合適Biacore分析。為便利起見，參考兩種抗體，但應瞭解，可對本文所述之任何殼硬蛋白結合劑使用該分析。根據產商之建議操作Biacore機械(例如Biacore 3000)。

因此，在一種交叉阻斷分析中，使用標準胺偶合化學將殼硬蛋白偶合至CM5 Biacore晶片上以產生經殼硬蛋白塗覆之表面。一般將200-800個共振單元之殼硬蛋白偶合至晶片(易於給出可量測結合水平，但易於由所用測試試劑濃度飽和之量)

將兩種待評估其相互交叉阻斷能力之抗體(稱為A*及B*)於合適緩衝劑中以結合位點之一對一莫耳比率混合以產生測試混合物。當基於結合位點計算濃度時，假設抗體之分子量為抗體之總分子量除以該抗體上殼硬蛋白結合位點之數目。

測試混合物中每一抗體之濃度應足夠高以便易於飽和在Biacore晶片上俘獲之殼硬蛋白分子上之抗體的結合位點。混合物中之抗體為相同之莫耳濃度(基於結合)且該濃度一般在1.00與1.5微莫耳之間(基於結合位點)。

亦製備僅含有抗體A*及僅含有抗體B*之獨立溶液。該等溶液中之抗體A*及抗體B*應處於與測試混合物相同之緩衝劑中且具有相同之濃度。

使測試混合物通過經殼硬蛋白塗覆之Biacore晶片且記錄結合總量。隨後以此方式處理晶片以移除結合抗體，而不破壞晶片結合之殼硬蛋白。一般藉由以30 mM HCl處理晶片歷時60秒鐘來進行此操作。

隨後使僅含抗體A*之溶液通過經殼硬蛋白塗覆之表面且記錄結合量。再次處理晶片以移除所有結合之抗體，而不破壞晶片結合之殼硬蛋白。

隨後使僅含抗體B*之溶液通過經殼硬蛋白塗覆之表面且記錄結合量。

接著計算抗體A*與抗體B*之混合物的最大理論結合，且為每一抗體單獨通過殼硬蛋白表面之結合的總和。若混合物之實際記錄結合小於此理論最大值，則該兩種抗體互相交叉阻斷。

因此，一般而言，根據本發明之交叉阻斷抗體或其他結合劑為

一種在以上Biacore交叉阻斷分析中結合至殼硬蛋白之抗體或結合劑，以使得在分析期間及在本發明之第二種抗體或其他結合劑存在下，所記錄之結合介於該兩種抗體或結合劑組合之最大理論結合的80%至0.1%之間(例如80%至4%)，特定言之介於最大理論結合之75%至0.1%之間(例如75%至4%)，且更特定言之介於最大理論結合(如上文所界定)之70%至0.1%之間(例如70%至4%)。

上述Biacore分析為用於判定抗體或其他結合劑是否根據本發明相互交叉阻斷之初步分析。在極少情況下，特定抗體或其他結合劑可不結合至經由胺化學偶合至CM5 Biacore晶片的殼硬蛋白(此通常發生於當殼硬蛋白上之相關結合位點由與晶片之偶合而遮蔽或破壞時)。在該等情況下，可使用經標記之殼硬蛋白變體來判定交叉阻斷，例如N-末端His-標記之殼硬蛋白(R & D Systems, Minneapolis, MN, USA; 2005目錄號1406-ST-025)。在此特定形式下，抗-His抗體偶合至Biacore晶片且隨後使經His-標記之殼硬蛋白通過晶片表面且由抗-His抗體俘獲。除在每一晶片再生循環之後，將新穎經His-標記之殼硬蛋白再次負載於抗-His抗體塗覆表面上以外，基本上如上文所述進行交叉阻斷分析。除使用N-末端經His-標記之殼硬蛋白給出之實例之外，可替代使用C-末端經His-標記之殼硬蛋白。此外，對於此交叉阻斷分析，可使用此項技術中已知之各種其他標記及標記結合蛋白之組合(例如，HA標記抗-HA抗體；FLAG標記抗-FLAG抗體；生物素標記抗生蛋白鏈菌素)。

基於ELISA之交叉阻斷分析

下文大體描述一種用於判定抗-殼硬蛋白抗體或其他殼硬蛋白結

合劑是否根據本發明交叉阻斷或可交叉阻斷之ELISA分析。為便利起見，參考兩種抗體(Ab-X及Ab-Y)，但應瞭解，可對本文所述之任何殼硬蛋白結合劑使用該分析。

該分析之通用原理為將抗-殼硬蛋白抗體塗覆於ELISA板之孔上。將過量之第二種可能交叉阻斷之抗-殼硬蛋白抗體添加至溶液中(意即，不結合至ELISA板)。隨後將有限量之殼硬蛋白添加至孔中。經塗覆之抗體與溶液中之抗體競爭與有限數量之殼硬蛋白分子結合。洗滌該板以移除未由所塗覆抗體結合之殼硬蛋白且亦移除第二種溶液相抗體以及在該第二種溶液相抗體與殼硬蛋白之間形成之任何複合物。隨後使用適當之殼硬蛋白偵測試劑量測所結合殼硬蛋白之量。溶液中可交叉阻斷經塗覆抗體之抗體將可導致經塗覆抗體可結合之殼硬蛋白分子數相對於在無第二種溶液相抗體存在下經塗覆抗體可結合之殼硬蛋白分子數下降。

下文對於Ab-X及Ab-Y更詳細描述此分析。在選擇Ab-X為固定抗體之情況下，將其塗覆於ELISA板之各孔上，之後將該等板以合適阻斷溶液阻斷以最小化隨後添加之試劑的非特異性結合。隨後向ELISA板中添加過量Ab-Y，以使得每一孔之Ab-Y殼硬蛋白結合位點之莫耳數高出在塗覆ELISA板期間每孔所用Ab-X殼硬蛋白結合位點之莫耳數至少10倍。隨後添加殼硬蛋白以使得每孔所添加之殼硬蛋白莫耳數低於用於塗覆各孔之Ab-X殼硬蛋白結合位點之莫耳數的至少25倍。在合適培育時期之後，洗滌該ELISA板且添加殼硬蛋白偵測試劑以量測由經塗覆抗-殼硬蛋白抗體(在此情況下為Ab-X)所特異性結合之殼硬蛋白的量。將用於分析之背景訊號界定為在含有經塗覆抗體(在此情

況下為Ab-X)、第二種溶液相抗體(在此情況下為Ab-Y)、僅含殼硬蛋白緩衝劑(意即，無殼硬蛋白)及殼硬蛋白偵測試劑之孔中所獲得之訊號。用於分析之陽性對照訊號界定為在含有經塗覆抗體(在此情況下為Ab-X)、僅含第二種溶液相抗體緩衝劑(意即，無第二種溶液相抗體)、殼硬蛋白及殼硬蛋白偵測試劑之孔中所獲得之訊號。ELISA分析需以此方式進行以使得陽性對照訊號至少為背景訊號之6倍。

為避免由選擇何種抗體用作塗覆抗體及何種抗體用作第二種(競爭)抗體所導致之任何人為因素(例如，Ab-X與Ab-Y之間對於殼硬蛋白顯著不同之親合力)，需要以以下兩種形式進行交叉阻斷分析：

1)形式1，其中Ab-X為塗覆於ELISA板上之抗體且Ab-Y為溶液中之競爭抗體；

及

2)形式2，其中Ab-Y為塗覆於ELISA板上之抗體且Ab-X為溶液中之競爭抗體。

若在形式1或形式2中，與在無溶液相抗-殼硬蛋白抗體(意即，陽性對照孔)存在下所獲得之殼硬蛋白偵測訊號相比，該溶液相抗-殼硬蛋白抗體可導致殼硬蛋白偵測訊號(意即，由經塗覆抗體所結合之殼硬蛋白之量)降低60%至100%，特定言之為70%至100%，且更特定言之為80%至100%，則將Ab-X及Ab-Y界定為交叉阻斷。

此基於ELISA之交叉阻斷分析之實例可見於實例7中("基於ELISA之交叉阻斷分析")。

基於細胞之中和分析

在培養物中由骨母細胞系細胞(原生細胞或細胞株)之礦質化用作

骨形成之活體外模型。礦質化歷經約一至六週而發生，以由一或多種分化劑誘發骨母細胞系細胞分化而開始。各事件之總順序包括細胞增殖、分化、細胞外基質產生、基質成熟及最終礦物質沉積，該沉積係指磷酸鈣之結晶及/或沉積。以細胞增殖及分化起始，且以礦物質沉積結束之此事件順序在本文中稱為礦質化。鈣(礦物質)之量測值為該分析之輸出量。

經由在分化劑存在下生長，MC3T3-E1細胞(Sudo H, Kodama H-A, Amagai Y, Yamamoto S, Kasai S. 1983. *In vitro differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvaria.* J. Cell Biol. 96:191-198)及原始細胞株之次純系可在培養物中形成礦物質。該等次純系包括MC3T3-E1-BF(Smith E, Redman R, Logg C, Coetzee G, Kasahara N, Frenkel B. 2000. *Glucocorticoids inhibit developmental stage-specific osteoblast cell cycle.* J. Biol. Chem. 275:19992-20001)。對於MC3T3-E1-BF次純系以及原始MC3T3-E1細胞兩者而言，殼硬蛋白均可抑制一或多種事件順序導致及包括礦物質沉積(意即，殼硬蛋白抑制礦質化)。可中和殼硬蛋白之抑制活性之抗-殼硬蛋白抗體允許在殼硬蛋白存在下培養物之礦質化，以使得與在僅含有殼硬蛋白(意即，無抗體)之處理組中所量測之鈣含量相比，其磷酸鈣(量測為鈣)沉積具有統計學上顯著之增加。圖22、23及24中所示之用於以細胞為基礎之礦質化分析實驗中之抗體具有約145 Kd之分子量且每一抗體分子具有2個殼硬蛋白結合位點。

當以判定特定抗-殼硬蛋白抗體或抗-殼硬蛋白結合劑是否可中和殼硬蛋白(意即，是否為殼硬蛋白中和抗體或其衍生物，或為殼硬蛋

白中和結合劑)為目的進行分析時，該分析中所使用殼硬蛋白之量需為與無殼硬蛋白組中所量測之鈣量相比，在僅含殼硬蛋白組中導致磷酸鈣(量測為鈣)沉積至少70%之統計學顯著減少的殼硬蛋白最小量。抗-殼硬蛋白中和抗體或抗-殼硬蛋白中和結合劑界定為與在僅含殼硬蛋白(意即，無抗體，無結合劑)之處理組中所量測之鈣量相比，導致磷酸鈣(量測為鈣)沉積統計學顯著增加者。為判定抗-殼硬蛋白抗體或抗-殼硬蛋白結合劑是否中和，分析中所使用抗-殼硬蛋白抗體或抗-殼硬蛋白結合劑之量需為此量，以使得與每孔之殼硬蛋白莫耳數相比，每孔具有過量之殼硬蛋白結合位點莫耳數。根據抗體之潛力，可需要之超過倍數可為24、18、12、6、3或1.5，且熟習此項技術者熟悉測試一種以上結合劑濃度之常規實踐。例如，與每孔殼硬蛋白之莫耳數相比，甚至當每孔之殼硬蛋白結合位點莫耳數過量小於6倍時，極為有效之抗-殼硬蛋白中和抗體或抗-殼硬蛋白中和結合劑仍可中和殼硬蛋白。僅在12、18或24倍過量時，有效性較差之抗-殼硬蛋白中和抗體或抗-殼硬蛋白中和結合劑可中和殼硬蛋白。在此整個有效性範圍內之殼硬蛋白結合劑均適合作為中和殼硬蛋白結合劑。實例8中詳細描述例示性以細胞為基礎之礦質化分析。

可中和人類殼硬蛋白之抗-殼硬蛋白抗體及其衍生物，及可中和人類殼硬蛋白之殼硬蛋白結合劑可用於治療由低骨形成、低骨礦物質密度、低骨礦質含量、低骨質、低骨品質及低骨強度之至少一者所導致、與其相關聯或導致其之人類病症/失調症。

活體內中和分析

與刺激新骨形成相關聯或由其導致之各個參數的增加可量測為

活體內測試殼硬蛋白結合劑之輸出量，以供鑒別可中和殼硬蛋白且因此可導致刺激新骨形成之彼等結合劑。該等參數包括各種血清合成代謝標記[例如，骨鈣蛋白、PINP(I型原膠原n-末端前肽)]、骨形成之組織形態標記(例如，骨母細胞表面/骨表面；骨形成速率/骨表面；小梁骨厚度)、骨礦質密度、骨礦質含量、骨質、骨品質及骨強度。殼硬蛋白中和結合劑界定為可導致與經媒劑處理之動物相比，與刺激新骨形成相關聯或由其導致之任何參數之統計學顯著增加者。該活體內測試可在任何合適之哺乳動物(例如小鼠、大鼠、猴)體內進行。該活體內測試之實例可見於實例5中("抗-殼硬蛋白單株抗體之活體內測試")。

儘管哺乳動物種類中殼硬蛋白之胺基酸序列並非100%一致(例如，小鼠殼硬蛋白與人類殼硬蛋白並非100%一致)，熟習此項技術者應瞭解，活體內可中和特定物種(例如，小鼠)之殼硬蛋白且亦可活體外結合人類殼硬蛋白之殼硬蛋白結合劑極可能可活體內中和人類殼硬蛋白。因此，該人類殼硬蛋白結合劑(例如，抗人類殼硬蛋白抗體)可用於治療由低骨形成、低骨礦質密度、低骨礦質含量、低骨質、低骨品質及低骨強度之至少一者所導致、與其相關聯或導致其之人類病症/失調症。其中已使用同源重組來刪除小鼠殼硬蛋白基因且在其位置上插入人類殼硬蛋白基因之小鼠(意即，人類殼硬蛋白基因敲進小鼠或人類SOST敲進小鼠)為額外活體內系統之實例。

本發明提供醫藥組合物，其包含上述結合劑之一種，諸如人類殼硬蛋白之抗體Ab-A、Ab-B、Ab-C、Ab-D及Ab-1至Ab-24之至少一種，以及醫藥學上或生理學上可接受之載劑、賦形劑或稀釋劑。2004年6月16日申請之同在申請中之申請案序號第10/868,497號中揭示用於

治療之醫藥組合物及方法，其主張序號第60/478,977號之優先權，二者均以引用的方式併入本文中。

此項技術中熟知在多種治療方案(包括例如皮下、經口、非經腸、靜脈內、鼻內及肌肉內投藥及調配物)中使用本文所述特定組合物之合適給藥及治療方案的進展，其中某些在下文中簡單討論以供說明之普遍目的。

在某些應用中，本文所揭示之醫藥組合物可經由經口投藥而傳遞至動物。同樣，該等組合物可與惰性稀釋劑或與可同化之可食用載劑一起調配，或其可封入硬或軟殼明膠膠囊中，或其可壓縮為錠劑，或其可直接併入飲食食物中。

在某些情況下，需要經皮下、非經腸、靜脈內、肌肉內或甚至腹膜內傳遞本文所揭示之醫藥組合物。熟習此項技術者熟知該等方法，其中某些進一步描述於例如美國專利第5,543,158號、美國專利第5,641,515號及美國專利第5,399,363號。在某些實施例中，可在水中與界面活性劑(諸如羥丙基纖維素)適當混合來製備作為游離鹼或藥理學上可接受之鹽之活性化合物溶液。亦可在甘油、液體聚乙二醇及其混合物中及在油中製備分散液。在普通儲存及使用條件下，該等製劑通常將含有防腐劑以防止微生物生長。

適合於可注射用途之說明性醫藥形式包括無菌水溶液或分散液及用於無菌可注射溶液或分散液之臨時製劑的無菌粉劑(例如，參見美國專利第5,466,468號)。在所有情況下，該形式須為無菌且須為流體至存在易於注射之程度。其在生產及儲存條件下須穩定且須防止微生物(諸如細菌及真菌)之污染作用。例如，載劑可為含有水、乙醇、

多元醇(例如甘油、丙二醇及液體聚乙二醇及其類似物)、其合適混合物及/或植物油之溶劑或分散培養基。例如，藉由使用塗佈劑(諸如卵磷脂)、藉由在分散液之情況下維持所要之粒徑及/或藉由使用界面活性劑來維持適當之流動性。可藉由各種抗菌劑及抗真菌劑，例如對氧苯甲酸酯、氯丁醇、苯酚、山梨酸、硫柳汞及其類似物來促進防止微生物之作用。在諸多情況下，較佳包括等張劑，例如糖或氯化鈉。可藉由在組合物中使用延遲吸收之藥劑，例如單硬脂酸鋁及明膠致使可注射組合物之延長吸收。

在一實施例中，對於水溶液中之非經腸投藥而言，若需要，溶液則應經適當緩衝且應首先以足夠生理食鹽水或葡萄糖使液體稀釋劑等張。該等特定水溶液尤其適合於靜脈內、肌肉內、皮下及腹膜內投藥。就此而言，根據本揭示案，熟習此項技術者將瞭解可採用之無菌水性培養基。例如，可將一個劑量溶解於1 ml等張NaCl溶液中且添加至1000 ml皮下灌注液體中或在建議灌輸位點注射(參見例如，*Remington's Pharmaceutical Sciences*，第15版，第1035-1038頁及第1570-1580頁)。必要時，根據受治療患者之病症對劑量進行某些改變。此外，對於人類投藥，製劑當然將較佳滿足如FDA機構之生物標準所要求之無菌、致熱性及一般安全性及純度標準。

在本發明之另一實施例中，本文揭示之組合物可調配為中性或鹽形式。說明性醫藥學上可接受之鹽包括酸加成鹽(以蛋白之游離胺基形成)及以無機酸(諸如鹽酸或磷酸)或有機酸(諸如乙酸、草酸、酒石酸、扁桃酸及其類似物)形成之鹽。以游離羧基形成之鹽亦可源於無機鹼(諸如氫氧化鈉、氫氧化鉀、氫氧化銨、氫氧化鈣或氫氧化鐵)

及有機鹼(諸如異丙胺、三甲胺、組胺酸、普魯卡因(procaine)及其類似物)。經調配，溶液將以與劑量調配物相容之方式及以治療有效之量來投藥。

載劑可進一步包含任何及所有溶劑、分散培養基、媒劑、塗佈劑、稀釋劑、抗菌劑及抗真菌劑、等張劑及吸收延遲劑、緩衝劑、載劑溶液、懸浮劑、膠體及其類似物。此項技術中已知使用該等培養基及藥劑用於醫藥活性物質。除任何習知培養基或藥劑均與活性成份不相容之程度以外，預期其在治療組合物中之使用。補充性活性成份亦可併入組合物中。短語"醫藥學上可接受"係指當投予至人類時不產生過敏性或類似不利反應之分子實體及組合物。

在某些實施例中，使用脂質體、奈米膠囊、微粒、脂質顆粒、微脂粒及其類似物來將本發明之組合物導入合適宿主細胞/生物體內。詳言之，本發明之組合物可囊封於脂質顆粒、脂質體、微脂粒、奈米球或奈米顆粒或其類似物中來調配以供傳遞。或者，本發明之組合物可共價或非共價結合至該等載劑媒劑之表面。

熟習此項技術者通常已知作為有效藥物載劑之脂質體及脂質體樣製劑的形成及使用(參見例如，Lasic, *Trends Biotechnol.* 16(7):307-21, 1998；Takakura, *Nippon Rinsho* 56(3):691-95, 1998；Chandran等人，*Indian J. Exp. Biol.* 35(8):801-09, 1997；Margalit, *Crit. Rev. Ther. Drug Carrier Syst.* 12(2-3):233-61, 1995；美國專利第5,567,434號；美國專利第5,552,157號；美國專利第5,565,213號；美國專利第5,738,868號及美國專利第5,795,587號，其各自特定以全文引用的方式併入本文中)。脂質體之使用在全身性傳遞之後似乎與自體免疫反

應或不可接受之毒性無關。在某些實施例中，脂質體自分散於水性培養基中之磷脂形成，且自發形成多層同心之雙層微脂粒(亦稱為多層微脂粒(MLV))。

或者，在其他實施例中，本發明提供本發明組合物之醫藥學上可接受之奈米膠囊調配物。奈米膠囊通常可以穩定且可再生之方式來誘獲化合物(參見，例如Quintanar-Guerrero等人，*Drug Dev. Ind. Pharm.* 24(12):1113-28, 1998)。為避免由於細胞內聚合過載之副作用，可使用活體內可降解之聚合物來設計該等超細顆粒(尺寸約0.1 μm)。例如，可如Couvreur等人，*Crit. Rev. Ther. Drug Carrier Syst.* 5(1):1-20, 1988；zur Muhlen等人，*Eur. J. Pharm. Biopharm.* 45(2):149-55, 1998；Zambaux等人，*J. Controlled Release* 50(1-3):31-40, 1998；及美國專利第5,145,684號所述來製造該等顆粒。

此外，本發明之醫藥組合物可連同提供關於使用該等醫藥組合物之說明的包裝材料一起放置於容器中。該等說明通常將包括描述試劑濃度之明確表現，以及在某些實施例中包括對於重構醫藥組合物而言必要之賦形劑成份或稀釋劑(例如，水、生理食鹽水或PBS)的相對量。

所投予之劑量範圍可為體重之0.01 mg/kg至100 mg/kg。如將對於熟習此項技術者顯而易見的，投藥量及頻率將當然取決於諸如經治療適應症之性質及嚴重性、所需反應、患者狀況等之因素。該等組合物一般可藉由如上所述之多種技術來投予。

骨礦物質含量及/或骨礦物質密度之增加可直接經由使用X-射線(例如，雙能X射線吸收法(Dual Energy X-ray Absorptometry)或

"DEXA")來判定，或經由量測：1)骨形成及/或骨母細胞活性之標記，諸如(但不限於)骨母細胞特異性鹼性磷酸酶、骨鈣蛋白、I型原膠原C'前肽(PICP)，總鹼性磷酸酶(參見Comier, *Curr. Opin. in Rheu.*7:243(1995))及血清I型原膠原N末端前肽(PINP)及/或2)骨吸收及/或破骨細胞活性之標記，包括(但不限於)吡啶啉、脫氧吡啶啉、N-端肽、尿羥基脯胺酸、血漿抗酒石酸鹽酸性磷酸酶及半乳糖基羥基離胺酸；(參見，Comier，*id*)、血清TRAP 5b(抗酒石酸鹽酸性磷酸酶同功異型物5b)及血清交聯C-端肽(sCTXI)來推斷。骨質之量亦可自體重來計算或藉由使用其他方法來計算(參見Guinness-Hey, *Metab. Bone Dis. Relat. Res.* 5:177-181, 1984)。此項技術中使用動物及特定動物模型來測試本發明之組合物及方法對於(例如)模擬諸如骨質疏鬆症及骨質減少之人類疾病病症的骨流失、骨再吸收、骨形成、骨強度或骨礦質化之參數的影響。該等模型之實例包括卵巢切除之大鼠模型(Kalu, D.N., *The ovariectomized rat model of postmenopausal bone loss. Bone and Mineral* 15:175-192 (1991)；Frost, H.M.及Jee, W.S.S. *On the rat model of human osteopenias and osteoporosis. Bone and Mineral* 18:227-236 (1992)；及Jee, W.S.S.及Yao, W., *Overview: animal models of osteopenia and osteoporosis. J. Musculoskel. Neuron. Interact.* 1:193-207 (2001))。

本發明之組合物可治療之特定病症包括發育不良，其中骨生長或發育異常且為骨質減少、骨質疏鬆症及骨流失之多種原因。該等病症之代表性實例包括軟骨發育不全、鎖骨顱骨發育不全、內生軟骨瘤病、骨纖維異常增殖症、高雪氏症(Gaucher's Disease)、低磷酸鹽性

佝僂症、馬凡氏症候群(Marfan's syndrome)、多發性遺傳性骨生疣、神經纖維瘤、成骨不全症、石骨症、骨斑點症、硬化病變、假性關節炎及化膿性骨髓炎、牙周病、抗癲癇藥誘發之骨流失、原發性及繼發性副甲狀腺功能亢進症、家族性副甲狀腺功能亢進症候群、體重下降誘發之骨流失、男性骨質疏鬆症、絕經後骨流失、骨性關節炎、腎性骨營養不良、浸潤性骨病、口腔骨流失、顎骨壞死、幼年性帕哲病(Paget's disease)、肢骨紋狀肥大、代謝性骨病、肥大細胞增生病、鐮刀形紅細胞貧血症/病、器官移植相關性骨流失、腎移植相關性骨流失、全身性紅斑性狼瘡症、強直性脊椎炎、癲癇症、幼年性關節炎性皮疹、地中海貧血、黏多醣貯積症、法布瑞氏症(fabry disease)、特納症候群(turner syndrome)、唐氏症候群(Down Syndrome)、克蘭費爾症候群(Klinefelter Syndrome)、痲瘋病、小兒股骨頭壞死症(Perthes' disease)、青少年特發性脊柱側凸、嬰幼兒發作性多系統發炎症、溫徹斯特症候群(Winchester Syndrome)、門克斯病(Menkes Disease)、威爾遜氏病(Wilson's Disease)、缺血性骨病(諸如兒童股骨頭缺血性壞死病(Legg-Calve-Perthes Disease)、侷限性移行性骨質疏鬆症)、貧血病症、類固醇導致之病症、糖皮質激素誘發之骨流失、肝素誘發之骨流失、骨髓病、壞血病、營養不良、鈣缺乏症、特發性骨質減少或骨質疏鬆症、先天性骨質減少或骨質疏鬆症、酒精中毒、慢性肝病、絕經後病況、慢性發炎性病症、類風濕性關節炎、發炎性大腸疾病、潰瘍性結腸炎、發炎性結腸炎、克羅恩氏病(Crohn's disease)、月經過少、閉經、妊娠、糖尿病、甲狀腺功能亢進症、甲狀腺症、副甲狀腺症、庫欣氏病(Cushing's disease)、肢端肥大症、性腺功能低下、長期不動

或失用症、反射性交感神經營養不良症候群、侷限性骨質疏鬆症、軟骨病、與關節置換相關聯之骨流失、與HIV相關聯之骨流失、與生長激素流失相關聯之骨流失、與囊性纖維變性相關聯之骨流失、骨纖維異常增殖症、與化療相關聯之骨流失、腫瘤誘發之骨流失、癌症相關骨流失、激素侵襲性骨流失、多發性骨髓瘤、藥物誘發之骨流失、神經性厭食症、與疾病相關聯之面部骨流失、與疾病相關聯之頭蓋骨骨流失、與疾病相關聯之顎骨骨流失、與疾病相關聯之顱骨骨流失及與太空飛行相關聯之骨流失。其他病症係關於與老化相關聯之骨流失，包括與老化相關聯之面部骨流失、與老化相關聯之頭蓋骨骨流失、與老化相關聯之顎骨骨流失及與老化相關聯之顱骨骨流失。

本發明之組合物亦可用於改良矯形外科程序、牙科程序、植入手術、關節置換、骨移植、骨整容手術及骨修復之結果，諸如骨折康復、骨不連合康復、延遲連合康復及面部重整。可在該程序、置換、移植、手術或修復之前、期間及/或之後投予一或多種組合物。

本發明亦提供一種包含根據本發明之至少一種抗-殼硬蛋白結合劑之診斷套組。該結合劑可為抗體。此外，該套組可視情況包含以下之一或多個：

(1)使用一或多種結合劑以供篩檢、診斷、預測、治療監控或任何該等應用之組合的說明書；

(2)抗-殼硬蛋白結合劑之經標記結合搭配物；

(3)抗-殼硬蛋白結合劑固定於其上之固相(諸如試劑帶)；及

(4)指示用於篩檢、診斷、預測或治療用途或其任何組合之調節核準的標籤或插入物。

若不提供結合劑之經標記結合搭配物，則結合劑本身可由一或多種可偵測標記(例如，化學發光、酶促、螢光或放射性部分)來標記。

提供以下實例以供說明，而非限制。

實例

實例1

殼硬蛋白之重組表現

重組人類殼硬蛋白/SOST可購自R&D系統(Minneapolis, MN, USA；2006目錄號1406-ST-025)。此外，重組小鼠殼硬蛋白/SOST可購自R&D系統(Minneapolis, MN, USA；2006目錄號1589-ST-025)。

或者，可在適應293T或293EBNA細胞之無血清懸浮液中瞬時表現不同種類之殼硬蛋白。可對500 mL或1 L之培養物進行轉染。以下試劑及材料購自Gibco BRL(目前之Invitrogen, Carlsbad, CA)。目錄號列於括號中：無血清DMEM(21068-028)、DMEM/F12(3:1)(21068/11765)、1X胰島素-運鐵蛋白-硒補充劑(51500-056)、1X Pen Strep Glut (10378-016)、2 mM l-麩胺醯胺(25030-081)、20 mM HEPES(15630-080)、0.01%泊洛尼克(Pluronic)F68(24040-032)。簡言之，在4℃下，將細胞接種物(5.0-10.0 X 10^5個細胞/mL X 培養物體積)以2,500 RPM離心10分鐘以移除經調整培養基。

在4℃下，將細胞再懸浮於無血清之DMEM中且以2,500 RPM再離心10分鐘。在抽出洗滌溶液之後，將細胞再懸浮於1 L或3 L旋轉燒瓶培養物中之生長培養基[DMEM/F12(3:1)+ 1X 胰島素-運鐵蛋白-硒補充劑+ 1X Pen Strep Glut+2 mM L-麩胺醯胺+ 20 mM HEPES+0.01%

泊洛尼克F68]中。將該旋轉燒瓶培養物以125 RPM保持於磁性攪拌板上，該板放置於保持在37℃及5% CO_2之增濕恆溫箱中。將含有殼硬蛋白之全部編碼區(及終止密碼子)與緊接起始位點ATG之5'位之Kozak一致序列(例如，CCACC)的哺乳動物表現質體DNA(例如，pcDNA3.1, pCEP4, Invitrogen Life Technologies, Carlsbad, CA)於50 mL錐形管中與轉染試劑複合。

可在無血清之DMEM或OPTI-MEM中製備最終培養物體積之5-10%的DNA-轉染試劑複合物。可用於此目的之轉染試劑包括X-tremeGene RO-1539(Roche Applied Science, Indianapolis, IN)、FuGene6(Roche Applied Science, Indianapolis, IN)、脂質體2000(Invitrogen, Carlsbad, CA)及293質體(Invitrogen, Carlsbad, CA)。首先將1-5 μg質體DNA/mL培養物添加至無血清之DMEM中，繼而添加1-5 μl轉染試劑/mL培養物。可將複合物於室溫下培育約10-30分鐘，且隨後添加至旋轉燒瓶中之細胞中。轉染/表現可進行4-7天，之後藉由於4℃下以4,000 RPM離心60分鐘來收穫經調整培養基(CM)。

實例2

重組殼硬蛋白之純化

如下自哺乳動物宿主細胞純化重組殼硬蛋白。所有純化製程均在室溫下進行。使用一種純化流程來純化各種殼硬蛋白，包括鼠類及人類殼硬蛋白。該純化流程使用親合性層析，繼而使用陽離子交換層析。

肝素層析

於4℃下，將哺乳動物宿主細胞經調整培養基(CM)於Beckman J6-

M1離心機中以4000 rpm離心1小時以移除細胞碎片。隨後將CM上清層經由無菌0.2 μm過濾器過濾。(此時該無菌經過濾CM可視情況冷凍儲存直至純化。)若CM經冷凍，則其在以下溫度或其組合下解凍：4℃、室溫或溫水。解凍之後，將CM經由無菌0.2 μm過濾器過濾且視情況藉由使用10 kD分子量截止膜之切向流超過濾(TFF)而濃縮。將CM濃縮物經由無菌0.2 μm過濾器過濾且隨後負載至於PBS中平衡之肝素高效(肝素HP)管柱(GE Healthcare，先前之Amersham Biosciences)上。或者，可將經過濾之CM上清層直接負載至於PBS中平衡之肝素HP管柱上。

負載之後，以PBS洗滌該肝素HP管柱直至流過物在280 nm下之吸收率返回至基線(意即，在負載CM上清層之前所量測之吸收率)。隨後使用PBS中150 mM至2 M氯化鈉之線性梯度自管柱中溶離殼硬蛋白。監控溶離液在280 nm下之吸收率且收集含有蛋白之溶離份。隨後藉由庫馬斯(Coomassie)染色之SDS-PAGE分析該等溶離份以識別含有以糖基化殼硬蛋白之尺寸遷移之多肽的溶離份。將來自管柱之適當溶離份組合以產生肝素HP池。

陽離子交換層析

將自肝素HP管柱溶離之殼硬蛋白藉由使用SP高效(SPHP)層析介質(GE Healthcare，先前為Amersham Biosciences)之陽離子交換層析進一步純化。將肝素HP池藉由使用10,000 MWCO膜(Pierce Slide-A-Lyzer)之透析緩衝交換於PBS中。隨後將經透析之肝素HP池負載至於PBS中平衡之SPHP管柱上。負載之後，以PBS洗滌管柱直至流過物在280 nm下之吸收率返回至基線。隨後使用PBS中150 mM至1 M氯化鈉

之線性梯度自SPHP管柱中溶離殼硬蛋白。監控溶離液在280 nm下之吸收率且逐份收集經溶離之殼硬蛋白。隨後藉由庫馬斯染色之SDS-PAGE分析該等溶離份以識別含有以糖基化殼硬蛋白之尺寸遷移之多肽的溶離份。將來自管柱之適當溶離份組合以產生SPHP池。

調配

純化之後，藉由使用10,000 MWCO膜(Pierce Slide-A-Lyzer)之透析於PBS中調配SPHP池。若需要濃縮殼硬蛋白，則使用具有10,000 MWCO膜之離心裝置(Amicon Centricon或Centriprep)。調配之後，將殼硬蛋白經由無菌0.2 μm過濾器過濾且於4℃儲存或冷凍。

實例3

肽結合ELISA

基於大鼠殼硬蛋白之已知胺基酸序列(SEQ ID NO：98)合成一系列重疊肽(各肽長度約為20-25個胺基酸)。設計該等肽以使其均含有經還原之半胱胺酸殘基；在其序列中尚未含有半胱胺酸之各肽的C-末端包括額外之半胱胺酸。此使得該等肽在含有1 mM EDTA之磷酸緩衝生理食鹽水(PBS：pH 6.5)中，在1 μg/ml之濃度下，使用市售之氫硫基結合板(Costar)，可藉由共價偶合而結合至分析板上。在室溫下培育1小時之後，將該等板以含有0.5%吐溫(Tween)20之PBS洗滌三次。將該等板藉由於室溫下以含有0.5%魚皮明膠(Sigma)之PBS溶液培育30分鐘而阻斷且隨後於含有0.5%吐溫20之PBS中洗滌三次。

將待測試之抗體於含有0.5%魚皮明膠之PBS中稀釋至1 μg/ml且與室溫下以經肽塗覆之板培育1小時。將過量抗體以PBS, 0.5%吐溫20洗滌三次而移除。隨後將該等板以共軛至辣根過氧化物酶(於含有0.5%

吐溫20之PBS中適當稀釋)且可結合至感興趣抗體之適當第二抗體培育。隨後將該等板洗滌三次：以含有0.5%吐溫20之PBS洗滌一次，且以PBS洗滌兩次。最後將該等板於室溫下以辣根過氧化物酶層析基質(TMB-穩定終止劑，RDI)培育5分鐘，以酸終止成色顯影，且量測450 nm下板之光學密度。

材料

Costar氫硫基結合板(VWR # 29442-278)

塗覆緩衝劑：1X PBS PH 6.5+1 mM EDTA

阻斷緩衝劑：1X PBS+0.5%魚皮明膠(CS之PBS；Sigma# G 7765之FSG)

洗滌緩衝劑：1X PBS+0.5%吐溫20

大鼠殼硬蛋白肽

抗體樣本：瞬時Ab、純化重組Ab、兔血清，等

適當第二Ab：山羊-抗-兔/小鼠-HRP(Jackson Immuno Research，115-036-072)

TMB-穩定終止劑(RDI# RDI-TMBSX-1L)

0.5M HCl

方法如下：

1. 100 µl/孔之於1X PBS PH 6.5+1 mM EDTA中稀釋為1 µg/ml之大鼠殼硬蛋白肽塗覆板。於室溫下培育板1小時。(應在開啟30分鐘內使用板)。
2. 以洗滌緩衝劑洗滌板3次。
3. 以每孔200 µl阻斷緩衝劑阻斷板。於室溫下培育板30分鐘。

4. 如(2)中所述重複洗滌。

5. 以50 μl/孔之於阻斷緩衝劑中稀釋之樣本培育板-血清滴定自1:100開始；瞬時重組Ab使用純液；經純化重組Ab使用1 μg/ml(所有樣本均重複兩次)。於室溫下培育板1 h。

6. 如(2)中所述洗滌板。

7. 以50 μl/孔之於阻斷緩衝劑中稀釋為1:1600之適當第二抗體(HRP標記)培育板。於室溫下培育板1小時。

8. 以洗滌緩衝劑洗滌板一次，以PBS洗滌兩次。

9. 於室溫下，以50 μl/孔之TMB培育板5分鐘。

10. 以50 μl/孔之0.5M HCl終止反應。

11. 在450 nm波長下讀板。

如上文所述篩檢以下肽序列：

QGWQAFKNDATEIIPGLREYPEPP(SEQ ID NO：82)

TEIIPGLREYPEPPQELENN(SEQ ID NO：83)

PEPPQELENNQTMNRAENGG(SEQ ID NO：84)

ENGGRPPHHPYDTKDVSEYS(SEQ ID NO：85)

CRELHYTRFVTDGP(SEQ ID NO：86)

CRELHYTRFVTDGPSRSAKPVTELV(SEQ ID NO：87)

CRSAKPVTELVSSGQSGPRARLL(SEQ ID NO：88)

CGPARLLPNAIGRVKWWRPNGPDFR(SEQ ID NO：89)

RAQRVQLLCPGGAAPRSRKV(SEQ ID NO：90)

PGGAAPRSRKVRLVAS(SEQ ID NO：91)

KRLTRFHNQSELKDFGPETARPQ(SEQ ID NO：92)

IPDRYAQRVQLLSPGG(SEQ ID NO：93)

SELKDFGPETARPQKGRKPRPRAR(SEQ ID NO：94)

KGRKPRPRARGAKANQAELENAY(SEQ ID NO：95)

PNAIGRVKWWRPNGPDFR(SEQ ID NO：96)

KWWRPNGPDFRCIPDRYRAQRV(SEQ ID NO：97)。

高親合力中和抗體(Ab-19)結合至以下兩種重疊肽序列：PNAIGRVKWWRPNGPDFR(SEQ ID NO：96)及KWWRPNGPDFRCIPDRYRAQRV (SEQ ID NO：97)。

此程序允許識別與表觀線性抗原決定基反應之抗體的抗原決定基。含有所有或部分抗體結合位點之肽將結合抗體且因此得以偵測。

實例4

人類殼硬蛋白抗原決定基之識別

殼硬蛋白結構

成熟形式(移除訊號肽)人類殼硬蛋白為190個胺基酸之蛋白(圖8)。圖9展示具有N-末端臂(自N-末端Q至半胱胺酸1)及C-末端臂(自半胱胺酸8至末端Y)之殼硬蛋白的大體結構示意圖。夾在該兩臂之間者為胱胺酸結結構及命名為環1、環2及環3的三個環。殼硬蛋白中之四個二硫鍵為序列位置57之Cys1與序列位置111之Cys5的連接(稱為C1-C5)，序列位置71之Cys2與序列位置125之Cys6的連接(稱為C2-C6)，序列位置82之Cys3與序列位置142之Cys7的連接(稱為C3-C7)，序列位置86之Cys4與序列位置144之Cys8的連接(稱為C4-C8)。經由C3-C7及C4-C8二硫鍵形成八員環結構。該環結構連同穿過該環之C1-C5二硫鍵一起形成典型之胱胺酸-結。C2-C6並非胱胺酸結之部分，其產生兩

個大環結構，即靠近之環1(殘基57至82)及環3(殘基111至142)。環2自C4(殘基86)至C5(殘基111)。

實驗

用於表徵抗-殼硬蛋白單株抗體所結合之抗原決定基的通用方法包括，以不同蛋白酶將人類殼硬蛋白分段為肽，判定各種人類殼硬蛋白肽之序列，分離該等肽且使用基於Biacore之"人類殼硬蛋白肽抗原決定基競爭結合分析"來測試其各自結合至特定單株抗體的能力。所得數據使得可確定結合抗原決定基之位置。

使肽消化物經受HPLC肽定位；收集個別峰，且藉由基質輔助雷射脫附質譜法(MALDI-MS)及電噴霧電離LC-MS(ESI-LC-MS)分析及/或藉由N-末端測序來識別及定位該等肽。使用逆相C8管柱(內徑2.1 mm x 長度15 cm)進行該等研究之所有HPLC分析。以0.05%三氟乙酸(固相A)至0.05%三氟乙酸中之90%乙腈的線性梯度進行HPLC肽定位。以0.2 ml/min之流速經50分鐘顯影管柱。

胰蛋白酶及AspN內蛋白酶消化

將成熟形式人類殼硬蛋白以胰蛋白酶(其在精胺酸及離胺酸之後裂解)或以AspN消化。在37℃下，將0.5-1.0 mg/ml之約200 μg殼硬蛋白於PBS(pH 7.2)中以8 μg胰蛋白酶或AspN培育20小時。

胰蛋白酶消化

胰蛋白酶消化物之HPLC層析產生若干個主峰(圖10A)。對胰蛋白酶消化之後自HPLC回收之肽峰進行序列分析。亦對肽消化物進行在線ESI LC-MS分析以確定由HPLC分離之肽的準確質量。因此確定肽峰中所存在之肽的身份(圖11)。圖13展示各種肽序列(T19.2, T20,

T20.6, T21-22)沿殼硬蛋白序列之比對。每一T後之數字(例如，T19.2)反映滯留時間。T19.2含有由C2-C6二硫鍵連接之兩個肽(一個來自環1且另一個來自環3)。T20含有由胱胺酸結結構保持在一起之兩個肽，完整之環1及3由C2-C6二硫鍵保持在一起且缺失大部分環2。T20.6含有由胱胺酸結結構保持在一起之四個序列，但缺失部分環1及3(T19.2部分)且缺失大部分環2。T21-22幾乎與T20一致，但在環2區域中具有3個額外之胺基酸。

AspN消化

AspN消化物之HPLC層析產生若干個主峰(圖10B)。對自HPLC回收之肽峰進行序列分析。亦對肽消化物進行在線ESI LC-MS分析以確定由HPLC分離之肽的準確質量。因此確定AspN消化之肽峰中所存在之肽的身份(圖12)。圖14展示各種肽序列(AspN14.6, AspN18.6, AspN22.7-23.5)沿殼硬蛋白序列之比對。每一AspN後之數字(例如，AspN18.6)反映滯留時間。AspN14.6含有來自殼硬蛋白之N-及C-末端臂的三個短肽，而AspN18.6為來自殼硬蛋白之N-末端臂的較大肽。AspN22.7-23.5含有104個胺基酸之單一肽片段，其包括所有八個半胱胺酸(四個二硫鍵)、胱胺酸結及所有環1、2及3。

表徵抗原決定基之策略為使用該等各種胰蛋白酶及AspN所產生之人類殼硬蛋白肽且判定何種肽仍可由各種抗體(Ab-A、Ab-B、Ab-C及Ab-D)來結合。特定而言，此係基於Biacore之"人類殼硬蛋白肽抗原決定基競爭結合分析"來測試，其中在各個不同分離之胰蛋白酶及AspN HPLC肽部片存在或不存在之情況下判定特定單株抗體與固定在Biacore晶片上之人類殼硬蛋白的結合。在無任何競爭肽存在下，特

定單株抗體可結合至晶片上之人類殼硬蛋白且產生共振單元(RU)反應。以溶液中之完整人類殼硬蛋白預培育特定單株抗體，繼而測試與晶片之結合，表明Mab與溶液中人類殼硬蛋白之結合阻止Mab與晶片上人類殼硬蛋白之結合，因此證實該競爭分析之通用原理。

對於各肽，個別重複該通用程序。強烈之RU反應可用以指示經測試之特定肽不可結合溶液中之Mab(因此Mab自由結合至已固定於晶片上之人類殼硬蛋白)。相反，無強烈之RU反應表明Mab可結合溶液中之殼硬蛋白肽。使用該等與已知身份之各種殼硬蛋白肽偶合之結合搭配物來判定由抗-殼硬蛋白抗體Ab-A、Ab-B、Ab-C及Ab-D所結合之殼硬蛋白的抗原決定基。

基於Biacore之人類殼硬蛋白肽抗原決定基競爭結合分析

人類殼硬蛋白表面之製備：

根據產商說明，進行將成熟形式人類殼硬蛋白固定於BIAcore感應器晶片(CM5)表面。簡言之，藉由注射60 μL含有0.2 M N-乙基-N'-(二甲胺基丙基)碳化二醯亞胺(EDC)及0.05 M N-羥基琥珀醯亞胺(NHS)之混合物來活化感應器晶片表面上之羧基。將人類殼硬蛋白於pH 4.0，濃度為20 μg/mL之10 mM乙酸鈉中稀釋，繼而沿活化CM5表面注射。藉由注射60 μL 1 M乙醇胺來失活表面上之過量反應性基團。對於人類殼硬蛋白表面而言，最終固定水平為約5000個共振單元(RU)。亦於感應器晶片上製備空白之假偶合參考表面。

結合特異性分析：

無氯化鈣或氯化鎂之1X磷酸鹽緩衝生理食鹽水購自Gibco/Invitrogen, Carlsbad, CA。牛血清白蛋白、V部分、游離IgG購

自Sigma-Aldrich, St. Louis, MO。將各Mab(2 nM)於樣本緩衝劑(1X PBS+0.005% P-20+0.1 mg/mL BSA)中以20 nM人類殼硬蛋白或特定人類殼硬蛋白肽(注意：AspN14.6中具有3個未連接之肽)單獨培育，之後沿固定之人類殼硬蛋白表面注射。樣本注射之流速為5 μL/min，繼而使用pH 2.0，30 μL/min之於8 mM甘胺酸中之1 M NaCl進行表面再生歷時30秒鐘。使用BIA評估3.2來分析數據，且呈現於圖15(Ab-A)、圖16(Ab-B)、圖17(Ab-C)及圖18(Ab-D)中。

環2及T20.6抗原決定基：

兩種代表性抗體(Ab-A及Ab-B)之殼硬蛋白肽結合圖案實際上一致(圖15及圖16)且展示該兩種抗體僅可結合AspN22.7-23.5肽。AspN22.7-23.5與所有其他殼硬蛋白肽之間之唯一區別在於AspN22.7-23.5含有完整環2。此展示Ab-A及Ab-B結合殼硬蛋白之環2區域，因此界定環2抗原決定基(圖19A)。Ab-C及Ab-D之殼硬蛋白肽結合圖案實際上彼此一致(圖17及圖18)，但與Ab-A及Ab-B所發現之結合圖案完全不同。在此實例所測試之肽中，Ab-C及Ab-D可結合之小型肽為T20.6肽。此結果界定T20.6抗原決定基(圖19B)。

蛋白酶保護分析：

該分析之通用原理為Mab與殼硬蛋白之結合可導致對於某些特異性蛋白酶裂解位點之保護且該資訊可用於確定Mab結合之殼硬蛋白區域。

"T20.6衍生物1(胱胺酸結+4個臂)"抗原決定基：

圖20展示人類殼硬蛋白Ab-D複合物之HPLC肽圖(圖20A：如上文所述在以胰蛋白酶消化之前，以與Ab-D 1:1之莫耳比率預培育人類殼

硬蛋白)及單獨人類殼硬蛋白之HPLC肽圖(圖20B：如上文所述以胰蛋白酶消化人類殼硬蛋白)。圖20A中T19.2及T20.6之肽峰展示與圖20B相比其各自峰高之明顯降低。此峰高之降低伴隨肽T20及T21-22之峰高的增加。該等數據表明，當Ab-D預結合至殼硬蛋白時，在Ab-D不存在之情況下由胰蛋白酶裂解以產生肽T19.2及T20.6之環1及環3中的鹼性胺基酸殘基可抵抗胰蛋白酶之裂解。T20、T20.6及T21-22之存在表明，當Ab-D預結合至殼硬蛋白時，環2仍可有效裂解。該等數據表明Ab-D結合至T20.6抗原決定基之環1及環3側，因此界定圖21中所示之較小"T20.6衍生物1(胱胺酸結+ 4個臂)"抗原決定基。

實例5

抗-殼硬蛋白單株抗體於小鼠中之活體內測試

自Charles River Laboratories(Raleigh, NC)獲得四週大之BDF1雄性小鼠且將其置於清潔籠中，每籠五隻動物。室溫保持在68至72°F之間，且相對濕度保持在34至73%之間。置放籠子之實驗室具有12-小時白天/黑夜循環且滿足所有AAALAC規格。每天一次對所有研究小鼠進行臨床觀察。

將純化抗-殼硬蛋白單株抗體(圖1之Ab-A、圖2之Ab-B、圖3之Ab-C、圖4之Ab-D)於無菌杜貝卡氏(Dulbecco)磷酸鹽緩衝食鹽水中稀釋。以每公克體重21 µl對小鼠經皮下注射抗-殼硬蛋白抗體或PBS媒劑，以25 mg/kg之量每週兩次(週一及週四)。將人雷PTH(1-34)於PTH緩衝劑(0.001 N HCl、0.15 M NaCl、2% BSA)中稀釋，且以100 µg/kg作為陽性對照，每週五次(週一、週二、週三、週四、週五)以每公克體重21 µl經皮下給藥(圖5及6)。，每組小鼠數在圖5及6中為N=5，且

在圖7中為N=6。

PIXImus活體內骨密度計

每週以GE/Lunar Medical Systems, Madison, WI之PIXImus2系統，藉由周邊雙能X-射線吸收法(pDEXA)來測定近端脛骨幹骺端及腰椎之骨礦物質密度(BMD)。放置25 mm^2之感興趣區域(ROI)以包括近端關節表面、骨骺及脛骨幹骺端之近端。放置感興趣區域(ROI)以包括腰椎(L1-L5)。分析近端脛骨及腰椎區域以確定總骨礦物質密度。報導組平均值之±標準偏差且與媒劑處理組比較以供統計分析。

統計分析

使用Dunnett及Tukey-Kramer(對於BMD數據使用MS Excel及JMP v. 5.0)進行統計分析。當P值小於0.05 ($P < 0.05$)時，認為各數據組之組平均值顯著不同。

抗體之殼硬蛋白中和活性

對於各Ab-A(圖5)、Ab-B(圖5)、Ab-C(圖6)及Ab-D(圖7)可見，與媒劑相比BMD之統計學上的顯著增加表明該四種抗體為殼硬蛋白中和抗體。此外，該數據展示，對於結合小鼠殼硬蛋白之抗-殼硬蛋白抗體而言，如上文所述對於小鼠之處理及分析可用於識別殼硬蛋白中和抗體。

實例6

阻斷抗體與人類殼硬蛋白結合之抗體的篩檢分析

使用標準胺偶合化學將人類殼硬蛋白偶合至CM5 Biacore晶片以產生經殼硬蛋白塗覆之表面。將殼硬蛋白之3 00個共振單元偶合至該表面。

將待測試之抗體於HBS-EP緩衝劑(為10 mM HEPES pH 7.4、150 mM NaCl、3 mM EDTA、0.005%(v/v)界面活性劑P20)中稀釋至200 μg/ml之濃度且隨後以一比一之莫耳比(基於結合位點)混合以產生測試混合物。因此該測試混合物含有濃度均為100 μg/ml(基於結合位點之1.3 μm)之每一抗體。亦製備僅含有測試混合物中之每種抗體的單獨溶液。該等溶液含有在HBS-EP緩衝劑中濃度為100 μg/ml(基於結合位點之1.3 μm)之個別抗體。

以10 μL/min之流速使20 μL測試混合物通過經殼硬蛋白塗覆之晶片且記錄結合量。隨後以兩次30 mM HCl之60秒鐘脈衝來處理晶片以移除所有結合抗體。隨後使僅含有測試混合物之抗體之一的溶液(基於結合位點，在與測試混合物相同之緩衝劑中為1.3 μM)以與測試混合物相同之方式通過晶片且記錄結合量。再次處理晶片以移除所有結合抗體且最後使僅含有測試混合物之另一種抗體的溶液(基於結合位點，在與測試混合物相同之緩衝劑中為1.3 μM)通過晶片且記錄結合量。

下表展示對一系列不同抗體交叉阻斷分析之結果。表中各方塊中之值代表當表之頂列所指示之抗體(基於結合位點，1.3 μM)或緩衝劑與表之第一行所指示之抗體(基於結合位點，1.3 μM)或緩衝劑混合時，所觀察之結合量(以RU計)。

	緩衝劑	Ab-4	Ab-13	Ab-A	Ab-3	Ab-19
緩衝劑	-0.5	693	428.5	707.3	316.1	649.9
Ab-4	687.7	795.1	1018.2	860.5	869.3	822.5
Ab-13	425.6	1011.3	442.7	1108.4	431.9	1042.4
Ab-A	692.4	833.1	1080.4	738.5	946.2	868.1
Ab-3	305.5	845.1	428.2	952.2	344.4	895.7
Ab-19	618.1	788.6	1022.5	863.3	891.5	658.7

使用對於上表中每一抗體組合之平均結合值(以RU計)(因為每一組合出現兩次)，可能計算每一抗體組合所展示之理論結合百分數。理論結合計算為每一測試混合物組份單獨分析時(意即，抗體及緩衝劑)之平均值的總和。

	緩衝劑	Ab-4	Ab-13	Ab-A	Ab-3	Ab-19
緩衝劑						
Ab-4			90.75	60.45	85.4	60.75
Ab-13				96.9	58.0	97.0
Ab-A					93.5	65.0
Ab-3						94.4
Ab-19						

由以上數據明顯可見，Ab-4、Ab-A與Ab-19互相交叉阻斷。類似地，Ab-13與Ab-3互相交叉阻斷。

實例7

基於ELISA之交叉阻斷分析

此實例中所用之液體體積為一般用於96孔板ELISA中之彼等體積(例如，50-200 μl/孔)。在該實例中，假設Ab-X及Ab-Y具有約145 Kd之分子量且每抗體分子具有2個殼硬蛋白結合位點。將抗-殼硬蛋白抗體(Ab-X)塗覆(例如，1 μg/ml之50 μl)至96孔ELISA板[例如，Corning 96孔EIA/RIA平底微定量盤(產品號3590)，Corning Inc., Acton, MA]上歷時至少一小時。在此塗覆步驟之後，移除抗體溶液，將板以洗滌溶液(例如，PBS及0.05%吐溫20)洗滌一次或兩次，且隨後使用適當阻斷溶液(例如，PBS、1% BSA、1%山羊血清及0.5%吐溫20)及此項技術中已知之製程阻斷。隨後將阻斷溶液自ELISA板移除，且將測試其交叉阻斷經塗覆抗體之能力的第二種抗-殼硬蛋白抗體(Ab-Y)於阻斷溶液中過量(例如10 μg/ml之50 μl)添加至ELISA板之適當孔中。此後，

隨後向適當孔中添加有限量(例如，10 ng/ml之50 μl)之阻斷溶液中之殼硬蛋白，且將該板於室溫下伴隨震盪培育至少一小時。然後將該板以洗滌溶液洗滌2-4次。向ELISA板中添加適當量之阻斷溶液中之殼硬蛋白偵測試劑[例如，已與適當量之抗生蛋白鏈菌素-辣根過氧化物酶(HRP)共軛物預複合之經結合生物素抗-殼硬蛋白多株抗體]，且於室溫下培育至少一小時。隨後將該板以洗滌溶液洗滌至少4次且以適當試劑[例如，HRP基質，諸如TMB(比色)或各種HRP發光基質]顯影。用於分析之背景訊號界定為在含有經塗覆抗體(在此情況下為Ab-X)、第二種溶液相抗體(在此情況下為Ab-Y)、僅含殼硬蛋白緩衝劑(意即，無殼硬蛋白)及殼硬蛋白偵測試劑之孔中所獲得之訊號。用於分析之陽性對照訊號界定為在含有經塗覆抗體(在此情況下為Ab-X)、僅含第二種溶液相抗體緩衝劑(意即，無第二種溶液相抗體)、殼硬蛋白及殼硬蛋白偵測試劑之孔中所獲得之訊號。ELISA分析需以此方式進行以使得陽性對照訊號至少為背景訊號之6倍。

為避免由選擇何種抗體用作塗覆抗體及何種抗體用作第二種(競爭)抗體所導致之任何人為因素(例如，Ab-X與Ab-Y之間對於殼硬蛋白顯著不同之親合力)，需要以以下兩種形式進行交叉阻斷分析：

1)形式1，其中Ab-X為塗覆於ELISA板上之抗體且Ab-Y為溶液中之競爭抗體；

及

2)形式2，其中Ab-Y為塗覆於ELISA板上之抗體且Ab-X為溶液中之競爭抗體。

若在形式1或形式2中，與在無溶液相抗-殼硬蛋白抗體(意即，陽

性對照孔)存在下所獲得之殼硬蛋白偵測訊號相比，該溶液相抗-殼硬蛋白抗體可導致殼硬蛋白偵測訊號(意即，由經塗覆抗體所結合之殼硬蛋白之量)降低60%至100%，特定言之為70%至100%，且更特定言之為80%至100%，則將Ab-X及Ab-Y界定為交叉阻斷。

在ELISA中使用經標記殼硬蛋白變體之情況下，諸如N-末端His-標記之殼硬蛋白(R&D Systems, Minneapolis, MN, USA；2005目錄號1406-ST-025)，則適當類型之殼硬蛋白偵測試劑將包括經HRP標記之抗-His抗體。除使用N-末端His-標記之殼硬蛋白以外，亦可使用C-末端His-標記之殼硬蛋白。此外，在此基於ELISA之交叉阻斷分析中，可使用此項技術中已知之各種其他標記及標記結合蛋白組合(例如，HA標記抗-HA抗體；FLAG標記抗-FLAG抗體；生物素標記抗生蛋白鏈菌素)。

實例8

用於識別可拮抗殼硬蛋白活性之藥劑在以細胞為基礎之礦質化分析

誘發

在培養物中由骨母細胞系細胞(原生細胞或細胞株)之礦質化用作骨形成之活體外模型。礦質化歷經約一至六週而發生，以由一或多種分化劑誘發骨母細胞系細胞分化而開始。各事件之總順序包括細胞增殖、分化、細胞外基質產生、基質成熟及最終礦物質沉積，該沉積係指磷酸鈣之結晶及/或沉積。以細胞增殖及分化起始，且以礦物質沉積結束之此事件順序在本文中稱為礦質化。鈣(礦物質)之量測值為該分析之輸出量。

礦物質之沉積具有強烈之生物物理特徵，因為礦物質 種子"一旦

開始形成，將沉積於整個培養物中之礦物質總量有時可相當快速沉積，諸如在此後之數天內。培養物中礦物質沉積之時序及程度部分受到所用特定骨母細胞系細胞/細胞株、生長條件、分化劑選擇及細胞培養基中所用特定血清批號之影響。對於骨母細胞系細胞/細胞株礦質化培養物而言，應測試來自一個以上供應商之至少八至十五個批次之血清以便鑒別出允許發生礦質化之特定血清批次。

經由在分化劑存在下生長後，MC3T3-E1細胞(Sudo H等人，*In vitro differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvaria.* J. Cell Biol. 96:191-198)及原始細胞株之次純系在培養物中可形成礦物質。該等次純系包括MC3T3-E1-BF(Smith E, Redman R, Logg C, Coetzee G, Kasahara N, Frenkel B. 2000. *Glucocorticoids inhibit developmental stage-specific osteoblast cell cycle.* J Biol Chem 275:19992-20001)。

殼硬蛋白中和抗體之鑒別

使用MC3T3-E1-BF細胞進行礦質化分析。使用抗壞血酸及B-甘油磷酸鹽以誘發MC3T3-E1-BF細胞分化，導致礦物質沉積。96-孔形式之特定篩檢實驗程序包括於週三塗覆細胞，繼而在12-天之時期內進行七次培養基改變(如下文進一步描述)，其中大多數礦物質沉積發生在最後約十八個小時內(例如，週日晚至週一)。對於任何給定之處理而言，使用3個孔(N=3)。礦物質沉積之特定時序及程度可部分視所用之特定血清批號而變化。如細胞培養實驗之技術中通常所熟知，對照實驗將說明該等變數。

在該分析系統中，殼硬蛋白抑制導致且包括礦物質沉積之一或

多種事件順序(意即，殼硬蛋白抑制礦質化)。可中和殼硬蛋白抑制活性之抗-殼硬蛋白抗體允許培養物在殼硬蛋白存在下之礦質化，以使得與僅含殼硬蛋白(意即，無抗體)之處理組中所量測之鈣量相比，其磷酸鈣(量測為鈣)之沉積具有統計學上顯著之增加。對於統計分析(使用MS Excel及JMP)而言，使用單因子變異數分析(1-way-ANOVA)，繼而使用唐那氏(Dunnett)比較來判定各組之間的差異。當P值小於0.05($P<0.05$)時，認為各數據組之組平均值顯著不同。進行該分析之代表性結果展示於圖22中。在無重組小鼠殼硬蛋白存在下，導致且包括礦物質沉積之事件順序正常進行。各處理組之鈣含量展示為平均值±平均值之標準差(SEM)。在此例示性實驗中，鈣分析之鈣含量為約31 μg/ml。然而，添加重組小鼠殼硬蛋白導致對於礦質化之抑制，且鈣降低了約85%。與僅含殼硬蛋白組相比，連同重組殼硬蛋白一起添加抗-殼硬蛋白單株抗體Ab-19或Ab-4導致礦物質沉積之統計學上顯著之增加，因為殼硬蛋白之抑制活性由任一種抗體而中和。此實驗之結果表明Ab-19及Ab-4為殼硬蛋白中和單株抗體(Mab)。

圖23展示使用重組人類殼硬蛋白及兩種人化抗-殼硬蛋白Mab之極為類似之結果。圖24亦展示如所指示之使用重組人類殼硬蛋白及小鼠及人化抗-殼硬蛋白Mab之極為類似之結果。

圖22、23及24中所示之用於該等實驗之抗體具有約145 Kd之分子量且每一抗體分子具有2個殼硬蛋白結合位點。

下文詳細描述MC3T3-E1-BF細胞培養實驗程序。

試劑及培養基

試劑	公司	目錄號
α-MEM	Gibco-Invitrogen	12571-048
抗壞血酸	Sigma	A4544
β-甘油磷酸鹽	Sigma	G6376
100X PenStrep麩胺醯胺	Gibco-Invitrogen	10378-016
二甲基亞碸(DMSO)	Sigma	D5879或D2650
胎牛血清(FBS)	Cansera	CS-C08-500(批號SF50310)
或胎牛血清(FBS)	TerraCell Int.	CS-C08-1000A(批號SF-20308)

α-MEM通常生產為具有1年之截止日期。對於細胞培養而言，使用不超過生產日期後6個月之α-MEM。

膨脹培養基(α-MEM/10% FBS/PenStrepGlu)如下製備：

將500 ml瓶之FBS解凍且經由0.22微米過濾器無菌過濾。

將100 ml該FBS添加至1公升α-MEM中，繼而添加10 ml之100x PenStrep麩胺醯胺。將未使用之FBS等分且再冷凍以供後續使用。

分化培養基(α-MEM/10% FBS/PenStrepGlu+50 μg/ml抗壞血酸+10 mM β-甘油磷酸鹽)如下製備：

藉由補充100 ml如下之含有抗壞血酸及β-甘油磷酸鹽之膨脹培養基來製備100 ml分化培養基：

	儲備濃度(見下文)	體積	最終濃度
抗壞血酸	10 mg/ml	0.5 ml	100 μg/ml(50 μg/ml+50 μg/ml)
β-甘油磷酸鹽	1 M	1.0 ml	10 mM

僅在分化培養基預備用於細胞培養當天藉由補充膨脹培養基來製備分化培養基。分化培養基中抗壞血酸之最終濃度為100 μg/ml，

因為α-MEM已含有50 μg/ml之抗壞血酸。製備抗壞血酸儲備溶液(10 mg/ml)且等分以供在-80℃下冷凍。每一等分試樣僅使用一次(意即，不再冷凍)。製備β-甘油磷酸鹽儲備溶液(1 M)且等分以供在-20℃下冷凍。將各等分試樣冷凍且解凍最多5次，之後丟棄。

用於MC3T3-E1-BF細胞膨脹之細胞培養物

在37℃及5% CO_2下進行細胞培養。為篩檢殼硬蛋白中和抗體之目的生產細胞庫。如下建立細胞庫：

將一瓶冷凍MC3T3-E1-BF細胞於37℃水浴中藉由攪拌而解凍。將經解凍細胞放入50 ml管中之10 ml膨脹培養基(α-MEM/10% FBS/PenStrepGlu)中且溫和旋轉5分鐘。隨後將該等細胞再懸浮於4 ml之α-MEM/10% FBS/PenStrepGlu中。在使用錐蟲藍及血球計測定細胞數目之後，在一T175燒瓶中將$1x10^6$個細胞塗覆於50 ml之α-MEM/10% FBS/ PenStrepGlu培養基中。

當該繼代長滿時(約7天)，將該等細胞以胰蛋白酶/EDTA(0.05%胰蛋白酶、0.53 mM EDTA)胰蛋白酶化，溫和旋轉5分鐘且隨後再懸浮於5 ml之α-MEM/10% FBS/PenStrepGlu中。在使用錐蟲藍及血球計測定細胞數目之後，在每一T175燒瓶中將細胞以$1x10^6$個細胞塗覆於50 ml之α-MEM/10% FBS/PenStrepGlu培養基中。此時用於塗覆之T175燒瓶數目取決於可提供之細胞總數及用於下一繼代所需之燒瓶數目。將多餘細胞以$1-2x10^6$個活細胞/ml冷凍於90% FBS/10% DMSO中。

當該繼代長滿時(約3-4天)，將該等細胞以胰蛋白酶/EDTA(0.05%胰蛋白酶、0.53 mM EDTA)胰蛋白酶化，溫和旋轉5分鐘且隨後再懸浮於5 ml之α-MEM/10% FBS/PenStrepGlu中。在使用錐蟲藍及血球計

測定細胞數目之後，在每一T175燒瓶中將細胞以1x10^{6}個細胞塗覆於50 ml之α-MEM/10% FBS/PenStrepGlu培養基中。此時用於塗覆之T175燒瓶數目取決於可提供之細胞總數及用於下一繼代所需之燒瓶數目。將多餘細胞以1-2 x 10^{6}個活細胞/ml冷凍於90% FBS/10% DMSO中。

當該繼代長滿時(約3-4天)，將該等細胞以胰蛋白酶/EDTA(0.05%胰蛋白酶、0.53 mM EDTA)胰蛋白酶化，溫和旋轉5分鐘且隨後再懸浮於5 ml之α-MEM/10% FBS/PenStrepGlu中。在使用錐蟲藍及血球計測定細胞數目之後，在每一T175燒瓶中將細胞以1x10^{6}個細胞塗覆於50 ml之α-MEM/10% FBS/PenStrepGlu培養基中。此時用於塗覆之T175燒瓶數目取決於可提供之細胞總數及用於下一繼代所需之燒瓶數目。將多餘細胞以1-2 x 10^{6}個活細胞/ml冷凍於90% FBS/10% DMSO中。

當該繼代長滿時(約3-4天)，將該等細胞以胰蛋白酶/EDTA(0.05%胰蛋白酶、0.53 mM EDTA)胰蛋白酶化，溫和旋轉5分鐘且隨後再懸浮於5 ml之α-MEM/10% FBS/ PenStrepGlu中。在使用錐蟲藍及血球計測定細胞數目之後，將細胞以1-2 x 10^{6}個活細胞/ml冷凍於90% FBS/10% DMSO中。該冷凍細胞之"最終繼代"為用於篩檢分析之繼代。

用於礦質化MC3T3-E1-BF細胞之細胞培養物

在37℃及5% CO_2下進行細胞培養。在礦質化細胞培養物程序期間需要使溫度及% CO_2波動最小化。此可藉由最小化在飼養期間板在恆溫箱外所消耗之時間，亦及藉由最小化在礦質化細胞培養物程序期

間恆溫箱門開啟及關閉的次數來達成。就此而言，具有專門用於指示礦質化細胞培養物之組織培養物恆溫箱(且因此無需超過必要之開啟及關閉)可為有益的。

將如上文所述製備之適當數目之"最終繼代"小瓶於37℃水浴中藉由攪拌而解凍。將經解凍細胞放入50 ml管中之10 ml膨脹培養基(α-MEM/10% FBS/PenStrepGlu)中且溫和旋轉5分鐘。隨後將該等細胞再懸浮於4 ml之α-MEM/10% FBS/PenStrepGlu中。在使用錐蟲藍及血球計測定細胞數目之後，在經膠原蛋白I塗覆之96-孔板(Becton Dickinson Labware，目錄號354407)上，將2500個細胞塗覆於每孔之200微升膨脹培養基中。

為避免礦質化板緣效應，細胞不塗覆於所有圍繞板之最外列/行中。相反，將200微升PBS添加至該等孔中。

例示性細胞培養程序

在以下程序中，將塗覆細胞之起始日指定為週三。若使用不同之工作日作為塗覆細胞之起始日，則此日將引發如下文所示之在整個製程期間移除及添加培養基之日程表。例如，若在週二塗覆細胞，則在第一個週五及週六，及第二個週五及週六均不應移除及添加培養基。以週二起始，則將在最後之週日製備用於鈣分析之板。

週三將細胞以2500個細胞塗覆於200 μl之膨脹培養基中。

週四移除所有膨脹培養基且添加200 μl分化培養基。

週五移除100 μl培養基且添加100 μl新鮮分化培養基。

週一移除100 μl培養基且添加100 μl新鮮分化培養基。

週二移除100 μl培養基且添加100 μl新鮮分化培養基。

週三移除100 μl培養基且添加100 μl新鮮分化培養基。

週四移除100 μl培養基且添加100 μl新鮮分化培養基。

週五移除100 μl培養基且添加100 μl新鮮分化培養基。

在下一週一，如下製備用於鈣分析之板：

將板以10 mM Tris、HCl pH 7-8洗滌各次。

在通風櫥中操作，每孔添加200 μl之0.5 N HCl。隨後將板於-80℃下冷凍。

剛好在量測鈣之前，使板冷凍-解凍兩次，且隨後使用多道移液管研磨以分散板中之內容物。隨後使板之內容物於4℃下沉降30分鐘，此時移除適當量之上清層以便使用市售鈣套組來量測鈣。例示性及非限制性套組為Calcium(CPC)Liquicolor，目錄號0150-250，Stanbio Laboratory, Boerne, TX。

在此基於細胞之分析中，殼硬蛋白抑制導致且包括礦物質沉積之一或多個事件順序(意即，殼硬蛋白抑制礦質化)。因此，在其中特定細胞培養實驗中包括殼硬蛋白之實驗中，在開始第一個週四及其後每隔一個飼養日向培養基中添加重組殼硬蛋白。在其中測試抗-殼硬蛋白單株抗體(Mab)中和殼硬蛋白之能力的情況下，意即使得藉由中和殼硬蛋白抑制礦質化之能力而礦質化，在開始第一個週四及其後每隔一個飼養日向培養基中添加Mab。根據實驗程序，如下完成此操作：在37℃下，將Mab以重組殼硬蛋白於分化培養基中預培育45-60分鐘且隨後將該培養基用於飼養細胞。

上述為MC3T3-E1-BF細胞之12-天礦質化實驗程序。使用相同之試劑及飼養實驗程序，自RIKEN細胞庫(RCB 1126, RIKEN

BioResource Center 3-1-1 Koyadai, Tsukuba-shi, Ibaraki 305-0074 Japan)獲得之原始MC3T3-E1細胞(Sudo H, Kodama H-A, Amagai Y, Yamamoto S, Kasai S. 1983. *In vitro differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvaria.* J Cell Biol 96:191-198)之礦質化比MC3T3-E1-BF細胞消耗較長之時間(礦質化共20天)。重組殼硬蛋白抑制了原始MC3T3-E1細胞之礦質化，且使用殼硬蛋白中和抗體阻斷了此抑制。

實例9

抗-殼硬蛋白抗體保護免於在SCID小鼠結腸炎之CD4 CD45RB^{HI}遷移模型中發炎誘發之骨流失

模型概述

將CD4+ T細胞之CD45RB^{高}子集注射入C.B-17 *scid*小鼠中導致慢性腸炎，其特徵與人類發炎性大腸疾病(IBD)之特徵類似。在伴隨上皮細胞增生及肉芽腫形成而以白血球嚴重浸潤至結腸中發生細胞遷移後3-5週時，注意到腹瀉及消耗病。接收表現CD45RB^{低}之CD4+細胞之倒數子集的C.B-17 *scid*小鼠不展現結腸炎且具有與未注射*scid*小鼠無法區別之重量增益。除結腸炎症狀以外，結腸炎之CD4+ CD45RB^{高}T細胞遷移模型伴隨骨礦質密度(BMD)之降低，認為其主要係經由發炎機制而非飲食吸收不良(Byrne, F. R.等人，*Gut* 54:78-86, 2005)。

結腸炎之誘發及發炎誘發之骨流失

自雌性balb/c小鼠取得脾臟且經由70 μm細胞濾器而破壞。隨後藉由使用對抗B220、MAC-1、CD8及I-A^{d}之抗體以Dynabead消極選擇而使CD4+群富集。隨後將該富集群以FITC共軛之抗-CD4及PE共軛之

抗-CD45RB染色，且藉由Moflo(Dakocytomation)上之兩色分類而分為CD4+CD45RB^{高}及CD4+CD45RB^{低}群。CD45RB^{高}及CD45RB^{低}群分別界定為最亮染色40%及最暗染色20%之CD4+細胞。隨後在0天時將5 x 10^5個細胞經腹膜內注射入C.B-17 *scid*小鼠，且經由軟糞便之外觀或腹瀉及重量減輕來監控結腸炎之發展。在研究終止時(第88天)進行骨礦質密度之量測。

抗-殼硬蛋白治療對於結腸炎症狀及BMD之影響

在CD4+CD45RB^{高}細胞轉移前一天以10 mg/kg經皮下給藥Ab-A IgG，且與接收亦以10 mg/kg經皮下給藥之陰性對照抗體101.4的小鼠相比較。此後每週給藥抗體。將接收非病源性CD4+CD45RB^{低}細胞且以10 mg/kg之101.4給藥之小鼠組作為對照進行研究。在研究終止時(第88天)，量測骨礦質密度且取部分結腸以供分析細胞浸潤及評估組織損傷。

a)對結腸炎症狀無影響

以Ab-A治療不影響典型結腸炎症狀，諸如重量減輕及發炎性細胞浸潤至結腸中。類似地，在以Ab-A治療後對結腸之組織損害無改良。

b)對於發炎誘發之骨礦質密度流失之抑制

將細胞轉移至C.B-17 *scid*小鼠中後第88天時，量測骨礦質密度(總BMD、椎骨BMD及股骨BMD)。如圖25中所示，與接收CD4+CD45RB^{低}非病源性細胞之對照小鼠相比，接收CD4+CD45RB^{高}T細胞及陰性對照抗體101.4之小鼠具有降低之骨礦質密度。相反，在以Ab-A治療後未注意到BMD降低。總之，在接收CD4+CD45RB^{高}T細

胞且以Ab-A治療之小鼠中，BMD之椎骨及股骨量測值均顯著高於接收CD4+ CD45RB^{高}T細胞且以101.4治療之小鼠(P<0.001，藉由Bonferroni多重比較測試)。

實例10

基於KINEXA測定抗-殼硬蛋白抗體與人類殼硬蛋白之親合力(K_D)

使用KinExA® 3000(Sapidyne Instruments Inc., Boise, ID)，藉由溶液平衡結合分析來評估若干種抗-殼硬蛋白抗體與人類殼硬蛋白之親合力。對於該等量測，在4℃下，以pH為9.6之50 mM Na_2CO_3中之40 μg/ml人類殼硬蛋白隔夜預塗覆Reacti-Gel 6x珠粒(Pierce, Rockford, IL)。將該等珠粒隨後在4℃下以pH為7.5之1 M Tris-HCl中之1 mg/ml BSA阻斷歷時兩小時。將10 pM、30 pM或100 pM之抗體與各種濃度之人類殼硬蛋白混合，其濃度介於0.1 pM至1 nM之間，且於室溫下於含有0.1 mg/ml BSA及0.005% P20之PBS中平衡歷時超過8小時。隨後使該等混合物通過經人類殼硬蛋白塗覆之珠粒。對於小鼠或人類抗體樣本而言，分別使用螢光Cy5-標記之山羊抗小鼠IgG或螢光Cy5-標記之山羊抗人類IgG抗體(Jackson Immuno Research, West Grove, PA)來定量珠粒結合之抗-殼硬蛋白抗體之量。所量測之螢光訊號之量與平衡時每一反應混合物中之游離抗-殼硬蛋白抗體的濃度成比例。使用KinExA Pro軟體所提供之n-曲線一點均勻結合模型，自競爭曲線之非線性回歸獲得解離平衡常數(K_D)。所選抗體之KinExA分析結果概述於下表中。

抗體	抗原	K_D(pM)	95%信賴區間
Ab-13	人類殼硬蛋白	0.6	0.4 ~ 0.8 pM
Ab-4	人類殼硬蛋白	3	1.8 ~ 4 pM
Ab-19	人類殼硬蛋白	3	1.7 ~ 4 pM
Ab-14	人類殼硬蛋白	1	0.5 ~ 2 pM
Ab-5	人類殼硬蛋白	6	4.3 ~ 8 pM
Ab-23	人類殼硬蛋白	4	2.1 ~ 8 pM

實例11

用於測定人化抗-殼硬蛋白抗體與人類殼硬蛋白之親合力的BIACORE方法

BIAcore技術即時監控生物分子間之結合且無對於標記之要求。將相互作用物之一(稱為配位體)直接固定於固定表面上或於固定表面上俘獲，而另一者(稱為分析物)於溶液中流經俘獲表面。當分析物結合至配位體以於表面上形成複合物時，感應器偵測該感應器表面上質量之改變。此對應於締合過程。當由緩衝劑代替分析物時，監控解離過程。在親合力BIAcore分析中，配位體為抗-殼硬蛋白抗體且分析物為殼硬蛋白。

器具

Biacore® 3000, Biacore AB, Uppsala, Sweden

感應器晶片

CM5(研究級)目錄號：BR-1001-14, Biacore AB, Uppsala, Sweden。將晶片儲存於4℃下。

BIA標準化溶液

70%(w/w)甘油。部分BIA維持套組目錄號：BR-1002-51, Biacore AB, Uppsala, Sweden。將BIA維持套組儲存於4℃下。

胺偶合套組

目錄號：BR-1000-50, Biacore AB, Uppsala, Sweden。

乙基-3-(3-二甲胺基丙基)碳化二醯亞胺鹽酸鹽(EDC)。於蒸餾水中製備為75 mg/mL且以200 μL等分試樣儲存於-70℃下。

N-羥基琥珀醯亞胺(NHS)。於蒸餾水中製備為11.5 mg/mL且以200 μL等分試樣儲存於-70℃下。

1 M乙醇胺鹽酸鹽-NaOH pH 8.5。以200 μL等分試樣儲存於-70℃下。

緩衝劑

用於固定俘獲抗體之流動緩衝劑：HBS-EP(為0.01 M HEPES pH 7.4、0.15 M NaCl、3 mM EDTA、0.005%界面活性劑P20)。目錄號：BR-1001-88, Biacore AB, Uppsala, Sweden。緩衝劑儲存於4℃下。

固定緩衝劑：乙酸鹽5.0(為10 mM乙酸鈉，pH 5.0)。目錄號：BR-1003-51, Biacore AB, Uppsala, Sweden。緩衝劑儲存於4℃下。

用於結合分析之流動緩衝劑：HBS-EP(為0.01 M HEPES pH 7.4、0.15 M NaCl、3 mM EDTA、0.005%界面活性劑P20，目錄號：BR-1001-88, Biacore AB, Uppsala, Sweden)，含有以1 mg/mL添加之CM-葡聚糖(目錄號27560, Fluka BioChemika, Buchs, Switzerland)。緩衝劑儲存於4℃下。

配位體俘獲物

山羊抗人類IgG親和純$F(ab')_2$片段，特異性Fc片段。Jackson ImmunoResearch Inc (Pennsylvania, USA)目錄號：109-006-098。試劑儲存於4℃下。

配位體

人化抗-人類殼硬蛋白抗體Ab5、Ab14及Ab20。

分析物

重組人類殼硬蛋白。等分試樣儲存於-70℃下且對於每一分析解凍一次。

再生溶液

藉由以蒸餾水自11.6 M儲備溶液(BDH, Poole, England。目錄號：101254H)稀釋來製備40 mM HCl。

藉由以蒸餾水自50 mM儲備溶液稀釋來製備5 mM NaOH。目錄號：BR-1003-58, Biacore AB, Uppsala, Sweden。

分析方法

分析形式為藉由固定化抗人類IgG-Fc俘獲抗-殼硬蛋白抗體，隨後經俘獲表面滴定殼硬蛋白。

下文給出該程序之實例：

使用BIAcore 3000(BIAcore AB)進行BIA(Bia分子交互作用分析)。經由胺偶合化學將山羊抗人類IgG親合純$F(ab')_2$片段、特異性Fc片段(Jackson ImmunoResearch)固定於CM5感應器晶片上，其俘獲水平≈4000個共振單元(RU)。將含有1 mg/mL CM-葡聚糖之HBS-EP緩衝劑(10 mM HEPES pH 7.4、0.15 M NaCl、3 mM EDTA、0.005%界面活性劑P20、BIAcore AB)用作流動緩衝劑，其流速為10 μl/min。以約5 μg/mL注射10 μl抗-殼硬蛋白抗體用於藉由固定化抗人類IgG-Fc來俘獲。抗體俘獲水平一般為100-200個RU。以30 μL/min之流速，以各種濃度經俘獲抗-殼硬蛋白抗體滴定殼硬蛋白。藉由以10 μL/min之流速注射兩次10 μL之40 mM HCl，繼而注射5 μL之5 mM NaOH使表面再

生。

根據標準程序，使用BIA評估軟體(3.2版)來分析背景減結合曲線。由擬合算法測定動力學參數。

表2中給出動力學數據及所計算之解離常數。

表2：抗-殼硬蛋白抗體與殼硬蛋白之親合力

抗體	ka(1/Ms)	kd(1/s)	Kd(pM)
Ab-5	1.78E+06	1.74E-04	97.8
Ab-14	3.30E+06	4.87E-06	1.48
Ab-20	2.62E+06	4.16E-05	15.8

實例12

CYNOMOLGOUS猴體內抗-殼硬蛋白單株抗體之活體內測試

在此2個月之研究中使用33個約3-5歲之雌性cynomolgus猴(長尾猴(*Macaca fascicularis*))。該研究含有11個組：

組1：媒劑(N=4)

組2：Ab-23(N=2，以3 mg/kg給藥)

組3：Ab-23(N=3，以10 mg/kg給藥)

組4：Ab-23(N=3，以30 mg/kg給藥)

組5：Ab-5(N=3，以3 mg/kg給藥)

組6：Ab-5(N=3，以10 mg/kg給藥)

組7：Ab-5(N=3，以30 mg/kg給藥)

組8：Ab-14(N=3，以3 mg/kg給藥)

組9：Ab-14(N=3，以10 mg/kg給藥)

組10：Ab-14(N=3，以30 mg/kg給藥)

組11：副甲狀腺激素(1-34) [PTH(1-34)](N=3，以10 μg/kg給藥)

所有給藥均經皮下。PTH(1-34)為每天給藥，單株抗體(Mab)為給藥兩次(第一次給藥在研究開始時，且第二次給藥在一個月之時間點時)。對於評估骨參數(例如，骨礦質密度)而言，在研究開始之前(以獲得基線值)及一個月之後(第二次給藥Mab之前)及最後在研究結束時(2個月之時間點)進行pQCT(周邊定量電腦斷層攝影術)及DXA(雙能X-射線吸收法)掃描，在最後之時間點對猴子進行驗屍以供進一步分析(例如，組織形態分析)。對動物進行螢光染料標記(第14、24、47及第57天)以進行動態組織形態分析。在研究期間之不同時間點收集血清[第1天預給藥(第一次給藥Mab之日)，第1天給藥十二個小時後，第2天，第3天，第5天，第7天，第14天，第21天，第28天，第29天給藥十二個小時後(第29天為第二次及最後一次給藥Mab之日)，第30天，第31天，第33天，第35天，第42天，第49天及第56天]。

使用市售套組來量測三種骨相關之血清生物標記：

骨鈣蛋白(OC)(DSL骨鈣蛋白放射免疫分析套組；Diagnostic Systems Laboratories, Inc.,Webster, TX, USA)

I型原膠原N-末端前肽(PINP)(PINP放射免疫分析套組；Orion Diagnostica, Espoo, Finland)

I型膠原蛋白a1鏈C-端肽片段(sCTXI)(Serum CrossLaps® ELISA；Nordic Bioscience Diagnostics A/S, Herlev, Denmark)。

pQCT及DXA掃描產生多個骨骼位點處(包括脛骨幹骺端及骨幹、徑向幹骺端及骨幹、股骨頸、腰椎)關於各種骨參數的數據(包括骨礦質密度(BMD)及骨礦質含量)。對於該骨數據(各動物自基線之百分數改變)及合成代謝(OC、PINP)血清生物標記數據(各動物自基線之百分

數改變)之分析揭示，對比媒劑組，在各Mab之某些時間點及給藥時之某些參數具有統計學上顯著之增加。該骨參數數據，血清生物標記數據，以及組織形態數據表明3種Mab(Ab-23、Ab-5及Ab-14)之每一者均可中和cynomolgous猴體內之殼硬蛋白。對於Ab-23及Ab-5而言，此活性最強，尤其在最高劑量(30 mg/kg)時，骨形成(合成代謝效應)以及骨淨增益(例如BMD)明顯增加。對於陽性對照組(PTH(1-34))而言，亦發現骨參數及合成代謝組織形態參數具有統計學上顯著之增加。

在各個時間點及劑量時，血清骨形成標記(PINP，骨鈣蛋白)增加(相對媒劑(VEH)而言$p<0.05$)，但尤其對於Ab-23及Ab-5之30 mg/kg組。在Ab-23及Ab-5較高劑量時，組織形態分析表明在腰椎及近端脛骨之網狀骨中(高達5倍增加)，以及股骨中段之皮層內表面(高達10倍增加)處之骨形成速率明顯增加(相對VEH而言$p<0.05$)。以高劑量之Ab-23及Ab-5，腰椎中之小梁骨厚度增加(>60%，相對VEH而言$p<0.05$)。研究結束時(2個月)，在股骨頸、遠端橈骨(Ab-23，30 mg/kg)及腰椎(Ab-5，30 mg/kg)處作為自基線之百分數改變的區域BMD增加(相對VEH而言$p<0.05$)。腰椎區域BMD之增加伴隨椎骨強度之增加(對於Ab-23而言椎骨最大負載增加97%，30 mg/kg，相對VEH而言$p<0.05$)；給藥Mab之前腰椎區域BMD之基線值在所有組之間統計類似。概括而言，在cynomolgous猴體內短期投予殼硬蛋白-中和Mab部分導致骨形成、BMD及椎骨強度之增加。

由以上所述，儘管本文已為說明之目的描述本發明之特定實施例，但可在不偏離本發明之精神及範疇下進行各種修改。因此，本發

明僅受所附申請專利範圍之限制。本文所揭示之所有公開案、公開之專利申請案及專利文獻均以引用的形式併入本文中。

【序列表】

<110> 1.比利時商UCB有限公司(UCB PHARMA S.A.)
2.美商安美基公司(AMGEN INC.)

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<151> 2006-04-25

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Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro His His Pro Phe Glu
        35                  40                  45
Thr Lys Asp Val Ser Glu Tyr Ser Cys Arg Glu Leu His Phe Thr Arg
    50                  55                  60
Tyr Val Thr Asp Gly Pro Cys Arg Ser Ala Lys Pro Val Thr Glu Leu
65                  70                  75                  80
Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu Leu Pro Asn Ala Ile
                85                  90                  95
Gly Arg Gly Lys Trp Trp Arg Pro Ser Gly Pro Asp Phe Arg Cys Ile
            100                 105                 110
Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu Leu Cys Pro Gly Gly
        115                 120                 125
Glu Ala Pro Arg Ala Arg Lys Val Arg Leu Val Ala Ser Cys Lys Cys
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130 135 140

Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu Leu Lys Asp Phe Gly
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Thr Glu Ala Ala Arg Pro Gln Lys Gly Arg Lys Pro Arg Pro Arg Ala
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            20   25   30
Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Gly Ser Ser Asn Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Asp
65   70   75   80
Glu Asp Leu Ala Thr Tyr Phe Cys Leu Gln His Ser Tyr Leu Pro Tyr
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100   105   110
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115   120   125
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130   135   140
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145   150   155   160
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165   170   175
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180   185   190
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
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Leu Ser Ala Ser Leu Gly Asp Ile Val Thr Met Thr Cys Gln Ala Ser
        35   40   45
Gln Gly Thr Ser Ile Asn Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys
    50   55   60
Ala Pro Lys Leu Leu Ile Tyr Gly Ser Ser Asn Leu Glu Asp Gly Val
65   70   75   80
Pro Ser Arg Phe Ser Gly Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr
                85   90   95
Ile Ser Ser Leu Glu Asp Glu Asp Leu Ala Thr Tyr Phe Cys Leu Gln
            100   105   110
His Ser Tyr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115   120   125
Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser
    130   135   140
Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn
145   150   155   160
Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu
                165   170   175
Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp
            180   185   190
Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr
        195   200   205
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Tyr Met Ser Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45
Gly Asp Ile Asn Pro Tyr Ser Gly Glu Thr Thr Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Thr Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Ile Ala Tyr
65                  70                  75                  80
Met Glu Ile Arg Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Asp Tyr Asp Ala Ser Pro Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr
        115                 120                 125
Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu
    130                 135                 140
Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp
145                 150                 155                 160
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                165                 170                 175
Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser
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Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205
Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys
    210                 215                 220
Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro
225                 230                 235                 240
Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr
                245                 250                 255
Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser
            260                 265                 270
Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg
        275                 280                 285
Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile
    290                 295                 300
Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn
305                 310                 315                 320
Ser Pro Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
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Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu
            340                 345                 350
Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe
        355                 360                 365
Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala
    370                 375                 380
Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr
385                 390                 395                 400
Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly
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Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35   40   45
Thr Asp His Tyr Met Ser Trp Val Lys Gln Ser His Gly Lys Ser Leu
    50   55   60
Glu Trp Ile Gly Asp Ile Asn Pro Tyr Ser Gly Glu Thr Thr Tyr Asn
65   70   75   80
Gln Lys Phe Lys Gly Thr Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85   90   95
Ile Ala Tyr Met Glu Ile Arg Gly Leu Thr Ser Glu Asp Ser Ala Val
            100   105   110
Tyr Tyr Cys Ala Arg Asp Asp Tyr Asp Ala Ser Pro Phe Ala Tyr Trp
        115   120   125
Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro
    130   135   140
Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met
145   150   155   160
Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
                165   170   175
Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
            180   185   190
Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
        195   200   205

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Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys
225                 230                 235                 240
Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe
                245                 250                 255
Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro
            260                 265                 270
Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val
        275                 280                 285
Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr
    290                 295                 300
Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu
305                 310                 315                 320
Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys
                325                 330                 335
Arg Val Asn Ser Pro Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350
Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro
        355                 360                 365
Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile
    370                 375                 380
Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly
385                 390                 395                 400
Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp
                405                 410                 415
Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp
            420                 425                 430
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gacgcctctc cgtttgctta ctggggccaa gggactctgg tcactgtctc tgcagccaaa 420
acgacacccc catctgtcta tccactggcc cctggatctg ctgcccaaac taactccatg 480
gtgaccctgg gatgcctggt caagggctat ttccctgagc cagtgacagt gacctggaac 540
tctggatccc tgtccagcgg tgtgcacacc ttcccagctg tcctgcagtc tgacctctac 600
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actctgagca gctcagtgac tgtcccctcc agcacctggc ccagcgagac cgtcacctgc 660
aacgttgccc acccggccag cagcaccaag gtggacaaga aaattgtgcc cagggattgt 720
ggttgtaagc cttgcatatg tacagtccca gaagtatcat ctgtcttcat cttccccca 780
aagcccaagg atgtgctcac cattactctg actcctaagg tcacgtgtgt tgtggtagac 840
atcagcaagg atgatcccga ggtccagttc agctggtttg tagatgatgt ggaggtgcac 900
acagctcaga cgcaaccccg ggaggagcag ttcaacagca ctttccgctc agtcagtgaa 960
cttcccatca tgcaccagga ctggctcaat ggcaaggagt tcaaatgcag ggtcaacagt 1020
ccagctttcc ctgcccccat cgagaaaacc atctccaaaa ccaaaggcag accgaaggct 1080
ccacaggtgt acaccattcc acctcccaag gagcagatgg ccaaggataa agtcagtctg 1140
acctgcatga taacagactt cttccctgaa gacattactg tggagtggca gtggaatggg 1200
cagccagcgg agaactacaa gaacactcag cccatcatgg acacagatgg ctcttacttc 1260
atctacagca agctcaatgt gcagaagagc aactgggagg caggaaatac tttcacctgc 1320
tctgtgttac atgagggcct gcacaaccac catactgaga agagcctctc ccactctcct 1380
ggtaaatga 1389

<210> 15
<211> 218
<212> PRT
<213> 小家鼠

<400> 15
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Thr Val Ser Leu Gly
 1   5   10   15
Leu Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20   25   30
Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45
Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
    50   55   60
Arg Phe Ser Gly Asn Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65   70   75   80
Pro Val Glu Glu Glu Asp Ala Val Thr Tyr Tyr Cys Gln Gln Ser Asn
                85   90   95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100   105   110
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
        115   120   125
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
    130   135   140
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145   150   155   160
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
                165   170   175
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
            180   185   190
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
        195   200   205
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
    210   215

<210> 16
<211> 657
<212> DNA
<213> 小家鼠

<400> 16
gacattgtgc tgacccaatc tccagcttct ttgactgtgt ctctaggcct gagggccacc 60
atctcctgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtac 120
cagcagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct 180
gggatcccag ccaggtttag tggcaatggg tctgggacag acttcaccct caacatccat 240
cctgtggagg aggaggatgc tgtaacctat tactgtcaac aaagtaatga ggatccgtgg 300
acgttcggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc 360
atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 420
aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 480
aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 540
agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 600
actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag 657

<210> 17
<211> 238
<212> PRT
<213> 小家鼠

<400> 17
Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
 1   5   10   15
Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Thr
            20   25   30
Val Ser Leu Gly Leu Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser
        35   40   45
Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
    50   55   60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
65   70   75   80
Gly Ile Pro Ala Arg Phe Ser Gly Asn Gly Ser Gly Thr Asp Phe Thr
                85   90   95
Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Val Thr Tyr Tyr Cys
            100   105   110
Gln Gln Ser Asn Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
        115   120   125
Glu Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro
    130   135   140
Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu
145   150   155   160
Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly
                165   170   175
Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser
            180   185   190
Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp

195 200 205
Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr
210 215 220
Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230 235

<210> 18
<211> 717
<212> DNA
<213> 小家鼠

<400> 18
atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60
gacattgtgc tgacccaatc tccagcttct ttgactgtgt ctctaggcct gagggccacc 120
atctcctgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtac 180
cagcagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct 240
gggatcccag ccaggtttag tggcaatggg tctgggacag acttcaccct caacatccat 300
cctgtggagg aggaggatgc tgtaacctat tactgtcaac aaagtaatga ggatccgtgg 360
acgttcggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc 420
atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 480
aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 540
aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 600
agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 660
actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag 717

<210> 19
<211> 449
<212> PRT
<213> 小家鼠

<400> 19
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Thr
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Cys
20 25 30
Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Asp Ile Asn Pro Phe Asn Gly Gly Thr Thr Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Asn Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser His Tyr Tyr Phe Asp Gly Arg Val Pro Trp Asp Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr
115 120 125
Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
130 135 140

Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
180 185 190
Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
195 200 205
Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
210 215 220
Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
225 230 235 240
Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
245 250 255
Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
260 265 270
Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
275 280 285
Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
290 295 300
Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
325 330 335
Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
340 345 350
Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
355 360 365
Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
370 375 380
Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
385 390 395 400
Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys
405 410 415
Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
420 425 430
Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
435 440 445
Lys

<210> 20
<211> 1350
<212> DNA
<213> 小家鼠

<400> 20
gaggtccagc tgcaacaatc tggacctgag ctggtgaagc ctgggacttc agtgaagatg 60
tcctgtaagg cttctggata cacattcact gactgctaca tgaactgggt gaagcagagc 120

catgggaaga gccttgaatg gattggagat attaatcctt tcaacggtgg tactacctac 180
aaccagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240
atgcagctca acagcctgac atctgacgac tctgcagtct attactgtgc aagatcccat 300
tattacttcg atggtagagt cccttgggat gctatggact actggggtca aggaacctca 360
gtcaccgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct 420
gctgcccaaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttccctgag 480
ccagtgacag tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct 540
gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccctc cagcacctgg 600
cccagcgaga ccgtcacctg caacgttgcc cacccggcca gcagcaccaa ggtggacaag 660
aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca 720
tctgtcttca tcttcccccc aaagcccaag gatgtgctca ccattactct gactcctaag 780
gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctggttt 840
gtagatgatg tggaggtgca cacagctcag acgcaacccc gggaggagca gttcaacagc 900
actttccgct cagtcagtga acttcccatc atgcaccagg actggctcaa tggcaaggag 960
ttcaaatgca gggtcaacag tgcagctttc cctgccccca tcgagaaaac catctccaaa 1020
accaaaggca gaccgaaggc tccacaggtg tacaccattc cacctcccaa ggagcagatg 1080
gccaaggata aagtcagtct gacctgcatg ataacagact tcttccctga agacattact 1140
gtggagtggc agtggaatgg gcagccagcg gagaactaca agaacactca gcccatcatg 1200
gacacagatg gctcttactt catctacagc aagctcaatg tgcagaagag caactgggag 1260
gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag 1320
aagagcctct cccactctcc tggtaaatga 1350

<210> 21
<211> 468
<212> PRT
<213> 小家鼠

<400> 21
Met Gly Trp Asn Trp Ile Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
 1   5   10   15
Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys
            20   25   30
Pro Gly Thr Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35   40   45
Thr Asp Cys Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu
    50   55   60
Glu Trp Ile Gly Asp Ile Asn Pro Phe Asn Gly Gly Thr Thr Tyr Asn
65   70   75   80
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85   90   95
Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr Ser Asp Asp Ser Ala Val
            100   105   110
Tyr Tyr Cys Ala Arg Ser His Tyr Tyr Phe Asp Gly Arg Val Pro Trp
        115   120   125
Asp Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
    130   135   140
Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
145   150   155   160
Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
                165   170   175

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
180 185 190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
195 200 205
Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
210 215 220
Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
225 230 235 240
Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
245 250 255
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
260 265 270
Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
275 280 285
Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
290 295 300
Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
305 310 315 320
Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
325 330 335
Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
340 345 350
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
355 360 365
Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
370 375 380
Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
385 390 395 400
Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
405 410 415
Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn
420 425 430
Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
435 440 445
Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
450 455 460
Ser Pro Gly Lys
465

<210> 22
<211> 1407
<212> DNA
<213> 小家鼠

<400> 22
atgggatgga actggatctt tctcttcctc ttgtcaggaa ctgcaggtgt ctactctgag 60
gtccagctgc aacaatctgg acctgagctg gtgaagcctg ggacttcagt gaagatgtcc 120
tgtaaggctt ctggatacac attcactgac tgctacatga actgggtgaa gcagagccat 180
gggaagagcc ttgaatggat tggagatatt aatcctttca acggtggtac tacctacaac 240

cagaagttca agggcaaggc cacattgact gtagacaaat cctccagcac agcctacatg 300
cagctcaaca gcctgacatc tgacgactct gcagtctatt actgtgcaag atcccattat 360
tacttcgatg gtagagtccc ttgggatgct atggactact ggggtcaagg aacctcagtc 420
accgtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc tggatctgct 480
gcccaaacta actccatggt gaccctggga tgcctggtca agggctattt ccctgagcca 540
gtgacagtga cctggaactc tggatccctg tccagcggtg tgcacacctt cccagctgtc 600
ctgcagtctg acctctacac tctgagcagc tcagtgactg tcccctccag cacctggccc 660
agcgagaccg tcacctgcaa cgttgcccac ccggccagca gcaccaaggt ggacaagaaa 720
attgtgccca gggattgtgg ttgtaagcct tgcatatgta cagtcccaga agtatcatct 780
gtcttcatct tccccccaaa gcccaaggat gtgctcacca ttactctgac tcctaaggtc 840
acgtgtgttg tggtagacat cagcaaggat gatcccgagg tccagttcag ctggtttgta 900
gatgatgtgg aggtgcacac agctcagacg caaccccggg aggagcagtt caacagcact 960
ttccgctcag tcagtgaact tcccatcatg caccaggact ggctcaatgg caaggagttc 1020
aaatgcaggg tcaacagtgc agctttccct gcccccatcg agaaaaccat ctccaaaacc 1080
aaaggcagac cgaaggctcc acaggtgtac accattccac ctcccaagga gcagatggcc 1140
aaggataaag tcagtctgac ctgcatgata acagacttct tccctgaaga cattactgtg 1200
gagtggcagt ggaatgggca gccagcggag aactacaaga acactcagcc catcatggac 1260
acagatggct cttacttcat ctacagcaag ctcaatgtgc agaagagcaa ctgggaggca 1320
ggaaatactt tcacctgctc tgtgttacat gaggggcctgc acaaccacca tactgagaag 1380
agcctctccc actctcctgg taaatga 1407

<210> 23
<211> 217
<212> PRT
<213> 兔-小鼠嵌合體

<400> 23
Ala Gln Val Leu Thr Gln Thr Pro Ala Ser Val Ser Ala Ala Val Gly
 1   5   10   15
Gly Thr Val Thr Ile Asn Cys Gln Ser Ser Gln Ser Val Tyr Asp Asn
            20   25   30
Asn Trp Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
        35   40   45
Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser Gly Val Pro Ser Arg Phe
    50   55   60
Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Gly Val
65   70   75   80
Gln Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gly Ala Tyr Asn Asp
                85   90   95
Val Ile Tyr Ala Phe Gly Gly Gly Thr Glu Val Val Val Lys Arg Thr
            100   105   110
Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu
        115   120   125
Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro
    130   135   140
Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn
145   150   155   160
Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr
                165   170   175
Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His

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            180                 185                 190
Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile
        195                 200                 205
Val Lys Ser Phe Asn Arg Asn Glu Cys
    210                 215
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<210> 24
<211> 654
<212> DNA
<213> 兔-小鼠嵌合體

<400> 24
gcgcaagtgc tgacccagac tccagcctcc gtgtctgcag ctgtgggagg cacagtcacc 60
atcaattgcc agtccagtca gagtgtttat gataacaact ggttagcctg gtttcagcag 120
aaaccagggc agcctcccaa gctcctgatt tatgatgcat ccgatctggc atctggggtc 180
ccatcgcggt tcagtggcag tggatctggg acacagttca ctctcaccat cagcggcgtg 240
cagtgtgccg atgctgccac ttactactgt caaggcgctt ataatgatgt tatttatgct 300
ttcggcggag gaccgaggt ggtggtcaaa cgtacggatg ctgcaccaac tgtatccatc 360
ttcccaccat ccagtgagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac 420
aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat 480
ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc 540
accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact 600
cacaagacat caacttcacc cattgtcaag agcttcaaca ggaatgagtg ttag 654

<210> 25
<211> 239
<212> PRT
<213> 兔-小鼠嵌合體

<400> 25
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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1               5                  10                  15
Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ala Ser
            20                  25                  30
Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser Ser
        35                  40                  45
Gln Ser Val Tyr Asp Asn Asn Trp Leu Ala Trp Phe Gln Gln Lys Pro
    50                  55                  60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser
65                  70                  75                  80
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr
                85                  90                  95
Leu Thr Ile Ser Gly Val Gln Cys Ala Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110
Gln Gly Ala Tyr Asn Asp Val Ile Tyr Ala Phe Gly Gly Gly Thr Glu
        115                 120                 125
Val Val Val Lys Arg Thr Asp Ala Ala Pro Thr Val Ser Ile Phe Pro
    130                 135                 140
Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe
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145 150 155 160
Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp
165 170 175
Gly Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp
180 185 190
Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys
195 200 205
Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys
210 215 220
Thr Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230 235

<210> 26
<211> 720
<212> DNA
<213> 兔-小鼠嵌合體

<400> 26
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60
acatttgcgc aagtgctgac ccagactcca gcctccgtgt ctgcagctgt gggaggcaca 120
gtcaccatca attgccagtc cagtcagagt gtttatgata acaactggtt agcctggttt 180
cagcagaaac cagggcagcc tcccaagctc ctgatttatg atgcatccga tctggcatct 240
ggggtcccat cgcggttcag tggcagtgga tctgggacac agttcactct caccatcagc 300
ggcgtgcagt gtgccgatgc tgccacttac tactgtcaag gcgcttataa tgatgttatt 360
tatgctttcg gcggagggac cgaggtggtg gtcaaacgta cggatgctgc accaactgta 420
tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 480
ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga 540
caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 600
agcagcaccc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 660
gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgttag 720

<210> 27
<211> 433
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體

<400> 27
Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15
Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser Ser Tyr Trp
20 25 30
Met Asn Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Ile Gly
35 40 45
Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser Trp Ala Lys Gly
50 55 60

Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Met Asp Leu Lys Met Thr
65 70 75 80
Ser Leu Thr Thr Gly Asp Thr Ala Arg Tyr Phe Cys Ala Arg Asn Trp
85 90 95
Asn Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
100 105 110
Lys Gly Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
115 120 125
Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
130 135 140
Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
145 150 155 160
Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
165 170 175
Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
180 185 190
Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
195 200 205
Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
210 215 220
Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
225 230 235 240
Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
245 250 255
Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
260 265 270
Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
275 280 285
Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
290 295 300
Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
305 310 315 320
Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
325 330 335
Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
340 345 350
Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
355 360 365
Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
370 375 380
Asn Thr Asn Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys
385 390 395 400
Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
405 410 415
Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
420 425 430
Lys

<210> 28
<211> 1302
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體

<400> 28
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60
tgcacagcct ctggattctc cctcagtagt tattggatga actgggtccg ccaggctcca 120
ggggaggggc tggaatggat cggaaccatt gattctggtg gtaggacgga ctacgcgagc 180
tgggcaaaag gccgattcac catctccaga acctcgacta cgatggatct gaaaatgacc 240
agtctgacga ccgggggacac ggcccgttat ttctgtgcca gaaattggaa cttgtggggc 300
caaggcaccc tcgtcaccgt ctcgagcgct tctacaaagg gcccatctgt ctatccactg 360
gcccctggat ctgctgccca aactaactcc atggtgaccc tgggatgcct ggtcaagggc 420
tatttccctg agccagtgac agtgacctgg aactctggat ccctgtccag cggtgtgcac 480
accttcccag ctgtcctgca gtctgacctc tacactctga gcagctcagt gactgtcccc 540
tccagcacct ggcccagcga gaccgtcacc tgcaacgttg cccacccggc cagcagcacc 600
aaggtggaca agaaaattgt gcccagggat tgtggttgta agccttgcat atgtacagtc 660
ccagaagtat catctgtctt catcttcccc ccaaagccca aggatgtgct caccattact 720
ctgactccta aggtcacgtg tgttgtggta gacatcagca aggatgatcc cgaggtccag 780
ttcagctggt ttgtagatga tgtggaggtg cacacagctc agacgcaacc ccgggaggag 840
cagttcaaca gcactttccg ctcagtcagt gaacttccca tcatgcacca ggactggctc 900
aatggcaagg agttcaaatg cagggtcaac agtgcagctt tccctgcccc catcgagaaa 960
accatctcca aaaccaaagg cagaccgaag gctccacagg tgtacaccat tccacctccc 1020
aaggagcaga tggccaagga taaagtcagt ctgacctgca tgataacaga cttcttccct 1080
gaagacatta ctgtggagtg gcagtggaat gggcagccag cggagaacta caagaacact 1140
cagcccatca tggacacaga tggctcttac ttcgtctaca gcaagctcaa tgtgcagaag 1200
agcaactggg aggcaggaaa tactttcacc tgctctgtgt tacatgaggg cctgcacaac 1260
caccatactg agaagagcct ctcccactct cctggtaaat ga 1302

<210> 29
<211> 452
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體

<400> 29
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
 1   5   10   15
Val His Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20   25   30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
        35   40   45
Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
    50   55   60
Trp Ile Gly Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser Trp

65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Met Asp Leu
85 90 95
Lys Met Thr Ser Leu Thr Thr Gly Asp Thr Ala Arg Tyr Phe Cys Ala
100 105 110
Arg Asn Trp Asn Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125
Ala Ser Thr Lys Gly Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
130 135 140
Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
145 150 155 160
Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
165 170 175
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
180 185 190
Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
195 200 205
Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
210 215 220
Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
225 230 235 240
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
245 250 255
Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
260 265 270
Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
275 280 285
Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
290 295 300
Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
305 310 315 320
Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
325 330 335
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
340 345 350
Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
355 360 365
Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
370 375 380
Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
385 390 395 400
Pro Ile Met Asn Thr Asn Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
405 410 415
Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
420 425 430
Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
435 440 445
Ser Pro Gly Lys
450

<210> 30
<211> 1359
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體

<400> 30
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccactgtcag 60
tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120
acagcctctg gattctccct cagtagttat tggatgaact gggtccgcca ggctccaggg 180
gaggggctgg aatggatcgg aaccattgat tctggtggta ggacggacta cgcgagctgg 240
gcaaaaggcc gattcaccat ctccagaacc tcgactacga tggatctgaa aatgaccagt 300
ctgacgaccg gggacacggc ccgttatttc tgtgccagaa attggaactt gtggggccaa 360
ggcaccctcg tcaccgtctc gagcgcttct acaaagggcc catctgtcta tccactggcc 420
cctggatctg ctgcccaaac taactccatg gtgaccctgg gatgcctggt caagggctat 480
ttccctgagc cagtgacagt gacctggaac tctggatccc tgtccagcgg tgtgcacacc 540
ttcccagctg tcctgcagtc tgacctctac actctgagca gctcagtgac tgtccctcc 600
agcacctggc ccagcgagac cgtcacctgc aacgttgccc acccggccag cagcaccaag 660
gtggacaaga aaattgtgcc cagggattgt ggttgtaagc cttgcatatg tacagtccca 720
gaagtatcat ctgtcttcat cttccccca aagcccaagg atgtgctcac cattactctg 780
actcctaagg tcacgtgtgt tgtggtagac atcagcaagg atgatcccga ggtccagttc 840
agctggtttg tagatgatgt ggaggtgcac acagctcaga cgcaaccccg ggaggagcag 900
ttcaacagca ctttccgctc agtcagtgaa cttcccatca tgcaccagga ctggctcaat 960
ggcaaggagt tcaaatgcag ggtcaacagt gcagctttcc ctgccccat cgagaaaacc 1020
atctccaaaa ccaaaggcag accgaaggct ccacaggtgt acaccattcc acctcccaag 1080
gagcagatgg ccaaggataa agtcagtctg acctgcatga taacagactt cttccctgaa 1140
gacattactg tggagtggca gtggaatggg cagccagcgg agaactacaa gaacactcag 1200
cccatcatgg acacagatgg ctcttacttc gtctacagca agctcaatgt gcagaagagc 1260
aactgggagg caggaaatac tttcacctgc tctgtgttac atgagggcct gcacaaccac 1320
catactgaga agagcctctc ccactctcct ggtaaatga 1359

<210> 31
<211> 213
<212> PRT
<213> 小家鼠

<400> 31
Gln Ile Val Leu Thr Gln Ser Pro Thr Ile Val Ser Ala Ser Pro Gly
 1   5   10   15
Glu Lys Val Thr Leu Ile Cys Ser Ala Ser Ser Ser Val Ser Phe Val
            20   25   30
Asp Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Arg Trp Ile Tyr
        35   40   45
Arg Thr Ser Asn Leu Gly Phe Gly Val Pro Ala Arg Phe Ser Gly Gly
    50   55   60
Gly Ser Gly Thr Ser His Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65   70   75   80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Thr Tyr Pro Pro Thr
85 90 95
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
100 105 110
Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
115 120 125
Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
130 135 140
Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
145 150 155 160
Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
165 170 175
Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
180 185 190
Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
195 200 205
Asn Arg Asn Glu Cys
210

<210> 32
<211> 642
<212> DNA
<213> 小家鼠

<400> 32
caaattgttc tcacccagtc tccaacaatc gtgtctgcat ctccagggga gaaggtcacc 60
ctaatctgca gtgccagttc aagtgtaagt ttcgtggact ggttccagca gaagccaggc 120
acttctccca aacgctggat ttacagaaca tccaacctgg gttttggagt ccctgctcgc 180
ttcagtggcg gtggatctgg gacctctcac tctctcacaa tcagccgaat ggaggctgaa 240
gatgctgcca cttattactg ccagcaaagg agtacttacc cacccacgtt cggtgctggg 300
accaagctgg aactgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc 360
agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420
aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480
agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg 540
accaaggacg agtatgaacg acataacagc tatacctgtg aggccactca caagacatca 600
acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag 642

<210> 33
<211> 235
<212> PRT
<213> 小家鼠

<400> 33
Met His Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15
Val Ile Val Ser Arg Gly Gln Ile Val Leu Thr Gln Ser Pro Thr Ile
20 25 30
Val Ser Ala Ser Pro Gly Glu Lys Val Thr Leu Ile Cys Ser Ala Ser
35 40 45

Ser Ser Val Ser Phe Val Asp Trp Phe Gln Gln Lys Pro Gly Thr Ser
50 55 60
Pro Lys Arg Trp Ile Tyr Arg Thr Ser Asn Leu Gly Phe Gly Val Pro
65 70 75 80
Ala Arg Phe Ser Gly Gly Gly Ser Gly Thr Ser His Ser Leu Thr Ile
85 90 95
Ser Arg Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg
100 105 110
Ser Thr Tyr Pro Pro Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
115 120 125
Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
130 135 140
Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
145 150 155 160
Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
165 170 175
Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
180 185 190
Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
195 200 205
Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
210 215 220
Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230 235

<210> 34
<211> 708
<212> DNA
<213> 小家鼠

<400> 34
atgcattttc aagtgcagat tttcagcttc ctgctaatca gtgcctcagt catagtgtcc 60
agagggcaaa ttgttctcac ccagtctcca acaatcgtgt ctgcatctcc aggggagaag 120
gtcaccctaa tctgcagtgc cagttcaagt gtaagtttcg tggactggtt ccagcagaag 180
ccaggcactt ctcccaaacg ctggatttac agaacatcca acctgggttt tggagtccct 240
gctcgcttca gtggcggtgg atctgggacc tctcactctc tcacaatcag ccgaatggag 300
gctgaagatg ctgccactta ttactgccag caaaggagta cttacccacc cacgttcggt 360
gctgggacca agctggaact gaaacgggct gatgctgcac caactgtatc catcttccca 420
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 480
taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc 540
ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 600
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660
acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag 708

<210> 35
<211> 449
<212> PRT
<213> 小家鼠

<400> 35

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30
Gly Met Gly Val Gly Trp Ile Arg His Pro Ser Gly Lys Asn Leu Glu
35 40 45
Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Val
50 55 60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Asn Ser Gln Val
65 70 75 80
Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95
Cys Ala Arg Ile Glu Asp Phe Asp Tyr Asp Glu Glu Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Ser Val Ile Val Ser Ser Ala Lys Thr
115 120 125
Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
130 135 140
Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
180 185 190
Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
195 200 205
Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
210 215 220
Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
225 230 235 240
Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
245 250 255
Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
260 265 270
Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
275 280 285
Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
290 295 300
Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
325 330 335
Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
340 345 350
Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
355 360 365
Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
370 375 380
Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met

385 390 395 400
Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys
405 410 415
Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
420 425 430
Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
435 440 445
Lys

<210> 36
<211> 1350
<212> DNA
<213> 小家鼠

<400> 36
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60
acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120
cacccatcag ggaagaatct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180
tataacccag tcctgaagag ccgactgact atctccaagg atacctccaa cagccaggta 240
ttcctcaaga tcgccaatgt ggacactgca gatactgcca catactactg tgctcgaata 300
gaggactttg attacgacga ggagtattat gctatggact actggggtca aggaacctca 360
gtcatcgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct 420
gctgcccaaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttcctgag 480
ccagtgacag tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct 540
gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtcccctc cagcacctgg 600
cccagcgaga ccgtcacctg caacgttgcc cacccggcca gcagcaccaa ggtggacaag 660
aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca 720
tctgtcttca tcttcccccc aaagcccaag gatgtgctca ccattactct gactcctaag 780
gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctggttt 840
gtagatgatg tggaggtgca cacagctcag acgcaacccc gggaggagca gttcaacagc 900
actttccgct cagtcagtga acttcccatc atgcaccagg actggctcaa tggcaaggag 960
ttcaaatgca gggtcaacag tgcagctttc cctgccccca tcgagaaaac catctccaaa 1020
accaaaggca gaccgaaggc tccacaggtg tacaccattc cacctcccaa ggagcagatg 1080
gccaaggata aagtcagtct gacctgcatg ataacagact tcttccctga agacattact 1140
gtggagtggc agtggaatgg gcagccagcg gagaactaca agaacactca gcccatcatg 1200
gacacagatg gctcttactt cgtctacagc aagctcaatg tgcagaagag caactgggag 1260
gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag 1320
aagagcctct cccactctcc tggtaaatga 1350

<210> 37
<211> 468
<212> PRT
<213> 小家鼠

<400> 37
Met Gly Arg Leu Thr Ser Ser Phe Leu Leu Leu Ile Val Pro Ala Tyr
1 5 10 15
Val Leu Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln

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            20                  25                  30
Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
        35                  40                  45
Ser Thr Ser Gly Met Gly Val Gly Trp Ile Arg His Pro Ser Gly Lys
    50                  55                  60
Asn Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr
65                  70                  75                  80
Asn Pro Val Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Asn
                85                  90                  95
Ser Gln Val Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Thr Ala
            100                 105                 110
Thr Tyr Tyr Cys Ala Arg Ile Glu Asp Phe Asp Tyr Asp Glu Glu Tyr
        115                 120                 125
Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Ile Val Ser Ser
    130                 135                 140
Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
145                 150                 155                 160
Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
                165                 170                 175
Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
            180                 185                 190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
        195                 200                 205
Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
    210                 215                 220
Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
225                 230                 235                 240
Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
                245                 250                 255
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
            260                 265                 270
Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
        275                 280                 285
Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
    290                 295                 300
Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
305                 310                 315                 320
Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
                325                 330                 335
Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
            340                 345                 350
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
        355                 360                 365
Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
    370                 375                 380
Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
385                 390                 395                 400
Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
                405                 410                 415
Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
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420 425 430
Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
435 440 445
Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
450 455 460
Ser Pro Gly Lys
465

<210> 38
<211> 1407
<212> DNA
<213> 小家鼠

<400> 38
atgggcaggc ttacttcttc attcctgcta ctgattgtcc ctgcatatgt cctgtcccag 60
gttactctga aagagtctgg ccctgggata ttgcagccct cccagaccct cagtctgact 120
tgttctttct ctgggttttc actgagcact tctggtatgg gtgtaggctg gattcgtcac 180
ccatcaggga agaatctgga gtggctggca cacatttggt gggatgatgt caagcgctat 240
aacccagtcc tgaagagccg actgactatc tccaaggata cctccaacag ccaggtattc 300
ctcaagatcg ccaatgtgga cactgcagat actgccacat actactgtgc tcgaatagag 360
gactttgatt acgacgagga gtattatgct atggactact ggggtcaagg aacctcagtc 420
atcgtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc tggatctgct 480
gcccaaacta actccatggt gaccctggga tgcctggtca agggctattt ccctgagcca 540
gtgacagtga cctggaactc tggatccctg tccagcggtg tgcacacctt cccagctgtc 600
ctgcagtctg acctctacac tctgagcagc tcagtgactg tcccctccag cacctggccc 660
agcgagaccg tcacctgcaa cgttgcccac ccggccagca gcaccaaggt ggacaagaaa 720
attgtgccca gggattgtgg ttgtaagcct tgcatatgta cagtcccaga agtatcatct 780
gtcttcatct tcccccccaaa gcccaaggat gtgctcacca ttactctgac tcctaaggtc 840
acgtgtgttg tggtagacat cagcaaggat gatcccgagg tccagttcag ctggtttgta 900
gatgatgtgg aggtgcacac agctcagacg caaccccggg aggagcagtt caacagcact 960
ttccgctcag tcagtgaact tcccatcatg caccaggact ggctcaatgg caaggagttc 1020
aaatgcaggg tcaacagtgc agctttccct gcccccatcg agaaaaccat ctccaaaacc 1080
aaaggcagac cgaaggctcc acaggtgtac accattccac ctcccaagga gcagatggcc 1140
aaggataaag tcagtctgac ctgcatgata acagacttct tccctgaaga cattactgtg 1200
gagtggcagt ggaatgggca gccagcggag aactacaaga acactcagcc catcatggac 1260
acagatggct cttacttcgt ctacagcaag ctcaatgtgc agaagagcaa ctgggaggca 1320
ggaaatactt tcacctgctc tgtgttacat gaggggcctgc acaaccacca tactgagaag 1380
agcctctccc actctcctgg taaatga 1407

<210> 39
<211> 5
<212> PRT
<213> 小家鼠

<400> 39
Asp His Tyr Met Ser
1 5

<210> 40
<211> 17
<212> PRT
<213> 小家鼠

<400> 40
Asp Ile Asn Pro Tyr Ser Gly Glu Thr Thr Tyr Asn Gln Lys Phe Lys
 1   5   10   15
Gly

<210> 41
<211> 10
<212> PRT
<213> 小家鼠

<400> 41
Asp Asp Tyr Asp Ala Ser Pro Phe Ala Tyr
 1   5   10

<210> 42
<211> 11
<212> PRT
<213> 小家鼠

<400> 42
Gln Ala Ser Gln Gly Thr Ser Ile Asn Leu Asn
 1   5   10

<210> 43
<211> 7
<212> PRT
<213> 小家鼠

<400> 43
Gly Ser Ser Asn Leu Glu Asp
 1   5

<210> 44
<211> 9
<212> PRT
<213> 小家鼠

<400> 44
Leu Gln His Ser Tyr Leu Pro Tyr Thr
 1   5

<210> 45
<211> 5
<212> PRT
<213> 小家鼠

<400> 45
Asp Cys Tyr Met Asn
 1   5

<210> 46
<211> 17
<212> PRT
<213> 小家鼠

<400> 46
Asp Ile Asn Pro Phe Asn Gly Gly Thr Thr Tyr Asn Gln Lys Phe Lys
 1   5   10   15
Gly

<210> 47
<211> 16
<212> PRT
<213> 小家鼠

<400> 47
Ser His Tyr Tyr Phe Asp Gly Arg Val Pro Trp Asp Ala Met Asp Tyr
 1   5   10   15

<210> 48
<211> 15
<212> PRT
<213> 小家鼠

<400> 48
Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn
 1   5   10   15

<210> 49
<211> 7
<212> PRT
<213> 小家鼠

<400> 49

Ala Ala Ser Asn Leu Glu Ser
1 5

<210> 50
<211> 9
<212> PRT
<213> 小家鼠

<400> 50
Gln Gln Ser Asn Glu Asp Pro Trp Thr
1 5

<210> 51
<211> 5
<212> PRT
<213> 兔-小鼠嵌合體

<400> 51
Ser Tyr Trp Met Asn
1 5

<210> 52
<211> 16
<212> PRT
<213> 兔-小鼠嵌合體

<400> 52
Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 53
<211> 4
<212> PRT
<213> 兔-小鼠嵌合體

<400> 53
Asn Trp Asn Leu
1

<210> 54
<211> 13
<212> PRT
<213> 兔-小鼠嵌合體

<400> 54

Gln Ser Ser Gln Ser Val Tyr Asp Asn Asn Trp Leu Ala
1 5 10

<210> 55
<211> 7
<212> PRT
<213> 兔-小鼠嵌合體

<400> 55
Asp Ala Ser Asp Leu Ala Ser
1 5

<210> 56
<211> 10
<212> PRT
<213> 兔-小鼠嵌合體

<400> 56
Gln Gly Ala Tyr Asn Asp Val Ile Tyr Ala
1 5 10

<210> 57
<211> 7
<212> PRT
<213> 小家鼠

<400> 57
Thr Ser Gly Met Gly Val Gly
1 5

<210> 58
<211> 16
<212> PRT
<213> 小家鼠

<400> 58
His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Val Leu Lys Ser
1 5 10 15

<210> 59
<211> 14
<212> PRT
<213> 小家鼠

<400> 59

Glu Asp Phe Asp Tyr Asp Glu Glu Tyr Tyr Ala Met Asp Tyr
1 5 10

<210> 60
<211> 10
<212> PRT
<213> 小家鼠

<400> 60
Ser Ala Ser Ser Ser Val Ser Phe Val Asp
1 5 10

<210> 61
<211> 7
<212> PRT
<213> 小家鼠

<400> 61
Arg Thr Ser Asn Leu Gly Phe
1 5

<210> 62
<211> 9
<212> PRT
<213> 小家鼠

<400> 62
Gln Gln Arg Ser Thr Tyr Pro Pro Thr
1 5

<210> 63
<211> 20
<212> PRT
<213> 人類

<400> 63
Cys Gly Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp
1 5 10 15
Trp Arg Pro Ser
20

<210> 64
<211> 20
<212> PRT
<213> 人類

<400> 64
Gly Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp
 1   5   10   15
Arg Pro Ser Gly
            20

<210> 65
<211> 20
<212> PRT
<213> 人類

<400> 65
Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg
 1   5   10   15
Pro Ser Gly Pro
            20

<210> 66
<211> 20
<212> PRT
<213> 人類

<400> 66
Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro
 1   5   10   15
Ser Gly Pro Asp
            20

<210> 67
<211> 20
<212> PRT
<213> 人類

<400> 67
Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser
 1   5   10   15
Gly Pro Asp Phe
            20

<210> 68
<211> 20
<212> PRT
<213> 人類

<400> 68

Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser Gly
1 5 10 15
Pro Asp Phe Arg
20

<210> 69
<211> 20
<212> PRT
<213> 人類

<400> 69
Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser Gly Pro
1 5 10 15
Asp Phe Arg Cys
20

<210> 70
<211> 14
<212> PRT
<213> 人類

<400> 70
Ser Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys
1 5 10

<210> 71
<211> 7
<212> PRT
<213> 人類

<400> 71
Leu Val Ala Ser Cys Lys Cys
1 5

<210> 72
<211> 8
<212> PRT
<213> 人類

<400> 72
Cys Arg Glu Leu His Phe Thr Arg
1 5

<210> 73
<211> 7

<212> PRT
<213> 人類

<400> 73
Cys Ile Pro Asp Arg Tyr Arg
 1   5

<210> 74
<211> 399
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 74
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acatttgctc aagttctgac ccagagtcca agcagtctct ccgccagcgt aggcgatcgt 120
gtgactatta cctgtcaatc tagtcagagc gtgtatgata acaattggct ggcgtggtac 180
cagcaaaaac cgggcaaagc cccgaagctg ctcatctatg acgcgtccga tctggctagc 240
ggtgtgccaa gccgtttcag tggcagtggc agcggtactg actttaccct cacaatttcg 300
tctctccagc cggaagattt cgccacttac tattgtcaag gtgcttacaa cgatgtgatt 360
tatgccttcg gtcagggcac taaagtagaa atcaaacgt   399

<210> 75
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 75
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1   5   10   15
Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Ser Pro Ser Ser
            20   25   30
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ser Ser
        35   40   45
Gln Ser Val Tyr Asp Asn Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro
    50   55   60
Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser
65   70   75   80
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
                85   90   95
Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
            100   105   110
Gln Gly Ala Tyr Asn Asp Val Ile Tyr Ala Phe Gly Gln Gly Thr Lys
        115   120   125

Val Glu Ile Lys Arg
130

<210> 76
<211> 393
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 76
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gtgcagctgt tggagtctgg aggcgggctt gtccagcctg gagggagcct gcgtctctct 120
tgtgcagcaa gcggcttcag cttatcctct tactggatga attgggtgcg gcaggcacct 180
gggaagggcc tggagtgggt gggcaccatt gattccggag gccgtacaga ctacgcgtct 240
tgggcaaagg gccgtttcac catttcccgc gacaactcca aaaataccat gtacctccag 300
atgaactctc tccgcgcaga ggacacagca cgttattact gtgcacgcaa ctggaatctg 360
tggggtcaag gtactcttgt aacagtctcg agc 393

<210> 77
<211> 131
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 77
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val His Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
20 25 30
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu
35 40 45
Ser Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60
Glu Trp Val Gly Thr Ile Asp Ser Gly Gly Arg Thr Asp Tyr Ala Ser
65 70 75 80
Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
85 90 95
Met Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Arg Tyr
100 105 110
Tyr Cys Ala Arg Asn Trp Asn Leu Trp Gly Gln Gly Thr Leu Val Thr
115 120 125
Val Ser Ser
130

<210> 78
<211> 11
<212> PRT
<213> 小家鼠

<400> 78
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
 1   5   10

<210> 79
<211> 7
<212> PRT
<213> 小家鼠

<400> 79
Tyr Thr Ser Arg Leu Leu Ser
 1   5

<210> 80
<211> 9
<212> PRT
<213> 小家鼠

<400> 80
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
 1   5

<210> 81
<211> 11
<212> PRT
<213> 小家鼠

<400> 81
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
 1   5   10

<210> 82
<211> 24
<212> PRT
<213> 褐家鼠

<400> 82
Gln Gly Trp Gln Ala Phe Lys Asn Asp Ala Thr Glu Ile Ile Pro Gly
 1   5   10   15
Leu Arg Glu Tyr Pro Glu Pro Pro
            20

<210> 83
<211> 20
<212> PRT
<213> 褐家鼠

<400> 83
Thr Glu Ile Ile Pro Gly Leu Arg Glu Tyr Pro Glu Pro Pro Gln Glu
 1   5   10   15
Leu Glu Asn Asn
            20

<210> 84
<211> 20
<212> PRT
<213> 褐家鼠

<400> 84
Pro Glu Pro Pro Gln Glu Leu Glu Asn Asn Gln Thr Met Asn Arg Ala
 1   5   10   15
Glu Asn Gly Gly
            20

<210> 85
<211> 20
<212> PRT
<213> 褐家鼠

<400> 85
Glu Asn Gly Gly Arg Pro Pro His His Pro Tyr Asp Thr Lys Asp Val
 1   5   10   15
Ser Glu Tyr Ser
            20

<210> 86
<211> 14
<212> PRT
<213> 褐家鼠

<400> 86
Cys Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro
 1   5   10

<210> 87
<211> 25

<212> PRT
<213> 褐家鼠

<400> 87
Cys Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro Ser Arg
 1   5   10   15
Ser Ala Lys Pro Val Thr Glu Leu Val
            20   25

<210> 88
<211> 23
<212> PRT
<213> 褐家鼠

<400> 88
Cys Arg Ser Ala Lys Pro Val Thr Glu Leu Val Ser Ser Gly Gln Ser
 1   5   10   15
Gly Pro Arg Ala Arg Leu Leu
            20

<210> 89
<211> 25
<212> PRT
<213> 褐家鼠

<400> 89
Cys Gly Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Val Lys Trp
 1   5   10   15
Trp Arg Pro Asn Gly Pro Asp Phe Arg
            20   25

<210> 90
<211> 20
<212> PRT
<213> 褐家鼠

<400> 90
Arg Ala Gln Arg Val Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg
 1   5   10   15
Ser Arg Lys Val
            20

<210> 91
<211> 16
<212> PRT
<213> 褐家鼠

<400> 91
Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val Ala Ser
 1   5   10   15

<210> 92
<211> 23
<212> PRT
<213> 褐家鼠

<400> 92
Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu Leu Lys Asp Phe Gly
 1   5   10   15
Pro Glu Thr Ala Arg Pro Gln
            20

<210> 93
<211> 16
<212> PRT
<213> 褐家鼠

<400> 93
Ile Pro Asp Arg Tyr Ala Gln Arg Val Gln Leu Leu Ser Pro Gly Gly
 1   5   10   15

<210> 94
<211> 24
<212> PRT
<213> 褐家鼠

<400> 94
Ser Glu Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly
 1   5   10   15
Arg Lys Pro Arg Pro Arg Ala Arg
            20

<210> 95
<211> 23
<212> PRT
<213> 褐家鼠

<400> 95
Lys Gly Arg Lys Pro Arg Pro Arg Ala Arg Gly Ala Lys Ala Asn Gln
 1   5   10   15
Ala Glu Leu Glu Asn Ala Tyr
            20

<210> 96
<211> 18
<212> PRT
<213> 褐家鼠

<400> 96
Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro Asp
 1   5   10   15
Phe Arg

<210> 97
<211> 22
<212> PRT
<213> 褐家鼠

<400> 97
Lys Trp Trp Arg Pro Asn Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg
 1   5   10   15
Tyr Arg Ala Gln Arg Val
            20

<210> 98
<211> 213
<212> PRT
<213> 褐家鼠

<400> 98
Met Gln Leu Ser Leu Ala Pro Cys Leu Ala Cys Leu Leu Val His Ala
 1   5   10   15
Ala Phe Val Ala Val Glu Ser Gln Gly Trp Gln Ala Phe Lys Asn Asp
            20   25   30
Ala Thr Glu Ile Ile Pro Gly Leu Arg Glu Tyr Pro Glu Pro Pro Gln
        35   40   45
Glu Leu Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
    50   55   60
Pro Pro His His Pro Tyr Asp Thr Lys Asp Val Ser Glu Tyr Ser Cys
65   70   75   80
Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro Cys Arg Ser
                85   90   95
Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala
            100   105   110
Arg Leu Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn
        115   120   125
Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
    130   135   140

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Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg
145                 150                 155                 160
Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln
                165                 170                 175
Ser Glu Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly
            180                 185                 190
Arg Lys Pro Arg Pro Arg Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu
        195                 200                 205
Leu Glu Asn Ala Tyr
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<210> 99
<211> 7
<212> PRT
<213> 小家鼠

<400> 99
Tyr Thr Ser Arg Leu His Ser
1 5

<210> 100
<211> 9
<212> PRT
<213> 小家鼠

<400> 100
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 101
<211> 11
<212> PRT
<213> 小家鼠

<400> 101
Arg Ala Ser Gln Val Ile Thr Asn Tyr Leu Tyr
1 5 10

<210> 102
<211> 7
<212> PRT
<213> 小家鼠

<400> 102
Tyr Thr Ser Arg Leu His Ser
1 5

<210> 103
<211> 9
<212> PRT
<213> 小家鼠

<400> 103
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
 1   5

<210> 104
<211> 11
<212> PRT
<213> 小家鼠

<400> 104
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
 1   5   10

<210> 105
<211> 7
<212> PRT
<213> 小家鼠

<400> 105
Tyr Thr Ser Arg Leu Leu Ser
 1   5

<210> 106
<211> 9
<212> PRT
<213> 小家鼠

<400> 106
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
 1   5

<210> 107
<211> 11
<212> PRT
<213> 小家鼠

<400> 107
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
 1   5   10

<210> 108
<211> 7
<212> PRT
<213> 小家鼠

<400> 108
Tyr Thr Ser Arg Leu Phe Ser
 1   5

<210> 109
<211> 9
<212> PRT
<213> 小家鼠

<400> 109
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
 1   5

<210> 110
<211> 11
<212> PRT
<213> 小家鼠

<400> 110
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
 1   5   10

<210> 111
<211> 7
<212> PRT
<213> 小家鼠

<400> 111
Tyr Thr Ser Arg Leu Leu Ser
 1   5

<210> 112
<211> 9
<212> PRT
<213> 小家鼠

<400> 112
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
 1   5

<210> 113
<211> 11
<212> PRT
<213> 小家鼠

<400> 113
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
 1   5   10

<210> 114
<211> 7
<212> PRT
<213> 小家鼠

<400> 114
Tyr Thr Ser Thr Leu Gln Ser
 1   5

<210> 115
<211> 9
<212> PRT
<213> 小家鼠

<400> 115
Gln Gln Gly Asp Thr Leu Pro Tyr Thr
 1   5

<210> 116
<211> 12
<212> PRT
<213> 小家鼠

<400> 116
Ser Val Ser Ser Ser Ile Ser Ser Ser Asn Leu His
 1   5   10

<210> 117
<211> 213
<212> PRT
<213> 小家鼠

<400> 117
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Thr Ser Pro Gly
 1   5   10   15

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Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Tyr Tyr Met
            20                  25                  30
His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45
Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Thr Arg Val Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asp Pro Leu Thr
                85                  90                  95
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
            100                 105                 110
Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
        115                 120                 125
Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
    130                 135                 140
Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
145                 150                 155                 160
Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
                165                 170                 175
Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
            180                 185                 190
Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
        195                 200                 205
Asn Arg Asn Glu Cys
    210
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<210> 118
<211> 642
<212> DNA
<213> 小家鼠

<400> 118
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atgacttgca gggccagctc aagtgtatat tacatgcact ggtaccagca gaagccagga 120
tcctccccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgttcgc 180
ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcaccagagt ggaggctgaa 240
gatgctgcca cttattactg ccagcagtgg agtagtgacc cactcacgtt cggtgctggg 300
accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc 360
agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420
aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480
agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg 540
accaaggacg agtatgaacg acataacagc tatacctgtg aggccactca caagacatca 600
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<210> 119
<211> 235
<212> PRT
<213> 小家鼠

<400> 119

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Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
 1               5                  10                  15
Val Ile Met Ser Arg Gly Gln Ile Val Leu Ser Gln Ser Pro Ala Ile
            20                  25                  30
Leu Ser Thr Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
        35                  40                  45
Ser Ser Val Tyr Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Ser Ser
    50                  55                  60
Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro
65                  70                  75                  80
Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile
                85                  90                  95
Thr Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
            100                 105                 110
Ser Ser Asp Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
        115                 120                 125
Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
    130                 135                 140
Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
145                 150                 155                 160
Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
                165                 170                 175
Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
            180                 185                 190
Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
        195                 200                 205
Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
    210                 215                 220
Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230                 235
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<210> 120
<211> 708
<212> DNA
<213> 小家鼠

<400> 120

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gtcacaatga cttgcagggc cagctcaagt gtatattaca tgcactggta ccagcagaag 180
ccaggatcct cccccaaacc ctggatttat gccacatcca acctggcttc tggagtccct 240
gttcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcac cagagtggag 300
gctgaagatg ctgccactta ttactgccag cagtggagta gtgacccact cacgttcggt 360
gctgggacca agctggagct gaaacgggct gatgctgcac caactgtatc catcttccca 420
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 480
taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc 540
ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 600
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acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660
acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag 708

<210> 121
<211> 445
<212> PRT
<213> 小家鼠

<400> 121
Glu Val Gln Val Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Tyr
20 25 30
Phe Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala Pro Lys Phe
50 55 60
Gln Asp Lys Ala Ile Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80
Leu Gln Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95
Glu Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Phe Phe Pro Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser
115 120 125
Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
130 135 140
Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
180 185 190
Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro
195 200 205
Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
210 215 220
Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
225 230 235 240
Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
245 250 255
Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
260 265 270
Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln
275 280 285
Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
290 295 300
Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
305 310 315 320
Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys

```
                325                 330                 335
Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
            340                 345                 350
Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr
        355                 360                 365
Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln
    370                 375                 380
Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
385                 390                 395                 400
Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu
                405                 410                 415
Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
            420                 425                 430
His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445
```

<210> 122
<211> 1338
<212> DNA
<213> 小家鼠

<400> 122

```
gaggttcagg tgcagcagtc tgggccagaa cttgtgaagc caggggcctc agtcaagttg 60
tcctgcacag cttctggctt caacattaaa gactacttta tacactgggt gaagcagagg 120
cctgaacagg gcctggagtg gattggaagg cttgatcctg aggatggtga aagtgattat 180
gccccgaagt tccaggacaa ggccattatg acagcagaca catcatccaa cacagcctat 240
cttcagctca gaagcctgac atctgaggac actgccatct attattgtga gagagaggac 300
tacgatggta cctacacctt ttttccttac tggggccaag ggactctggt cactgtctct 360
gcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact 420
aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg 480
acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct 540
gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc 600
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc 720
ttcccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt 780
gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg 840
gaggtgcaca cagctcagac gcaacccccgg gaggagcagt tcaacagcac tttccgctca 900
gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 960
gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga 1020
ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1080
gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag 1140
tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc 1200
tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact 1260
ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320
cactctcctg gtaaatga                                              1338
```

<210> 123
<211> 464
<212> PRT

<213> 小家鼠

<400> 123

```
Met Lys Cys Ser Trp Val Ile Phe Phe Leu Met Ala Val Val Thr Gly
 1               5                  10                  15
Val Asn Ser Glu Val Gln Val Gln Gln Ser Gly Pro Glu Leu Val Lys
            20                  25                  30
Pro Gly Ala Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
        35                  40                  45
Lys Asp Tyr Phe Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
    50                  55                  60
Glu Trp Ile Gly Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala
65                  70                  75                  80
Pro Lys Phe Gln Asp Lys Ala Ile Met Thr Ala Asp Thr Ser Ser Asn
                85                  90                  95
Thr Ala Tyr Leu Gln Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Ile
            100                 105                 110
Tyr Tyr Cys Glu Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Phe Phe Pro
        115                 120                 125
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr
    130                 135                 140
Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
145                 150                 155                 160
Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
                165                 170                 175
Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
            180                 185                 190
Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
        195                 200                 205
Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
    210                 215                 220
Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
225                 230                 235                 240
Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
                245                 250                 255
Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
            260                 265                 270
Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
        275                 280                 285
Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
    290                 295                 300
Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
305                 310                 315                 320
Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
                325                 330                 335
Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
            340                 345                 350
Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
        355                 360                 365
Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
```

```
    370                 375                 380
Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
385                 390                 395                 400
Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
                405                 410                 415
Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
            420                 425                 430
Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
        435                 440                 445
Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
    450                 455                 460
```

<210> 124
<211> 1395
<212> DNA
<213> 小家鼠

<400> 124

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atgaaatgca gctgggtcat cttcttcctg atggcagtgg ttacaggggt caattcagag 60
gttcaggtgc agcagtctgg gccagaactt gtgaagccag gggcctcagt caagttgtcc 120
tgcacagctt ctggcttcaa cattaaagac tactttatac actgggtgaa gcagaggcct 180
gaacagggcc tggagtggat tggaaggctt gatcctgagg atggtgaaag tgattatgcc 240
ccgaagttcc aggacaaggc cattatgaca gcagacacat catccaacac agcctatctt 300
cagctcagaa gcctgacatc tgaggacact gccatctatt attgtgagag agaggactac 360
gatggtacct acacctttt tccttactgg ggccaaggga ctctggtcac tgtctctgca 420
gccaaaacga caccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac 480
tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc 540
tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac 600
ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc 660
acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg 720
gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 780
cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg 840
gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag 900
gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 960
agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 1020
aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg 1080
aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 1140
agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg 1200
aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 1260
tacttcatct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 1320
acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380
tctcctggta aatga                                                  1395
```

<210> 125
<211> 215
<212> PRT
<213> 小家鼠

<400> 125

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ala Ala Ser Pro Gly
 1               5                  10                  15
Glu Lys Val Thr Ile Thr Cys Ser Val Ser Ser Thr Ile Ser Ser Asn
            20                  25                  30
His Leu His Trp Phe Gln Gln Lys Ser Asp Thr Ser Pro Lys Pro Trp
        35                  40                  45
Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser
    50                  55                  60
Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65                  70                  75                  80
Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
                85                  90                  95
Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg Arg Ala Asp Ala
            100                 105                 110
Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser
        115                 120                 125
Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp
    130                 135                 140
Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val
145                 150                 155                 160
Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met
                165                 170                 175
Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser
            180                 185                 190
Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys
        195                 200                 205
Ser Phe Asn Arg Asn Glu Cys
    210                 215
```

<210> 126
<211> 648
<212> DNA
<213> 小家鼠

<400> 126
gaaattgtgc tcacccagtc tccagcactc atggctgcat ctccgggggga gaaggtcacc 60
atcacctgca gtgtcagttc aactataagt tccaaccact tgcactggtt ccagcagaag 120
tcagacacct cccccaaacc ctggatttat ggcacatcca acctggcttc tggagtccct 180
gttcgcttca gtggcagtgg atctgggacc tcttattctc tcacaatcag cagcatggag 240
gctgaggatg ctgccactta ttactgtcaa cagtggagta gttacccact cacgttcggc 300
gctgggacca agctggagct gagacgggct gatgctgcac caactgtatc catcttccca 360
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 420
taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc 480
ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 540
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 600
acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag 648

<210> 127
<211> 237

<212> PRT
<213> 小家鼠

<400> 127

```
Met Asp Phe His Val Gln Ile Phe Ser Phe Met Leu Ile Ser Val Thr
 1               5                  10                  15
Val Ile Leu Ser Ser Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Leu
            20                  25                  30
Met Ala Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Val Ser
        35                  40                  45
Ser Thr Ile Ser Ser Asn His Leu His Trp Phe Gln Gln Lys Ser Asp
    50                  55                  60
Thr Ser Pro Lys Pro Trp Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly
65                  70                  75                  80
Val Pro Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
                85                  90                  95
Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
            100                 105                 110
Gln Trp Ser Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu
        115                 120                 125
Leu Arg Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser
    130                 135                 140
Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn
145                 150                 155                 160
Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser
                165                 170                 175
Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys
            180                 185                 190
Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu
        195                 200                 205
Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser
    210                 215                 220
Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230                 235
```

<210> 128
<211> 714
<212> DNA
<213> 小家鼠

<400> 128

```
atggattttc atgtgcagat tttcagcttc atgctaatca gtgtcacagt cattttgtcc 60
agtggagaaa ttgtgctcac ccagtctcca gcactcatgg ctgcatctcc gggggagaag 120
gtcaccatca cctgcagtgt cagttcaact ataagttcca accacttgca ctggttccag 180
cagaagtcag acacctcccc caaaccctgg atttatggca catccaacct ggcttctgga 240
gtccctgttc gcttcagtgg cagtggatct gggacctctt attctctcac aatcagcagc 300
atggaggctg aggatgctgc cacttattac tgtcaacagt ggagtagtta cccactcacg 360
ttcggcgctg ggaccaagct ggagctgaga cgggctgatg ctgcaccaac tgtatccatc 420
ttcccaccat ccagtgagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac 480
```

aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat 540
ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc 600
accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact 660
cacaagacat caacttcacc cattgtcaag agcttcaaca ggaatgagtg ttag 714

<210> 129
<211> 449
<212> PRT
<213> 小家鼠

<400> 129
Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15
Leu Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Phe
20 25 30
Tyr Leu His Trp Met Arg Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45
Gly Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe
50 55 60
Gln Asp Lys Ala Thr Leu Thr Thr Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80
Leu Gln Leu Ser Gly Leu Thr Ser Glu Thr Thr Ala Val Tyr Tyr Cys
85 90 95
Ser Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr Trp Tyr Phe
100 105 110
Asp Val Trp Gly Ala Gly Thr Thr Ile Thr Val Ser Ser Ala Lys Thr
115 120 125
Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
130 135 140
Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
180 185 190
Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
195 200 205
Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
210 215 220
Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
225 230 235 240
Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
245 250 255
Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
260 265 270
Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
275 280 285
Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser
290 295 300
Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu

305 310 315 320
Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
325 330 335
Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
340 345 350
Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
355 360 365
Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
370 375 380
Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
385 390 395 400
Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys
405 410 415
Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
420 425 430
Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
435 440 445
Lys

<210> 130
<211> 1350
<212> DNA
<213> 小家鼠

<400> 130
gaggttcagc tgcagcagtc tggggctgaa cttgtgaggc cagggggcctt agtcaagttg 60
tcctgcacag cttctgactt caacattaaa gacttctatc tacactggat gaggcagcgg 120
cctgaacagg gcctggactg gattggaagg attgatcctg agaatggtga tactttatat 180
gacccgaagt tccaggacaa ggccactctt acaacagaca catcctccaa cacagcctac 240
ctgcagctca gcggcctgac atctgagacc actgccgtct attactgttc tagagaggcg 300
gattatttcc acgatggtac ctcctactgg tacttcgatg tctggggcgc agggaccaca 360
atcaccgtct cctcagccaa aacgacaccc ccatctgtct atccactggc ccctggatct 420
gctgcccaaa ctaactccat ggtgaccctg ggatgcctgg tcaagggcta tttccctgag 480
ccagtgacag tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct 540
gtcctgcagt ctgacctcta cactctgagc agctcagtga ctgtccctc cagcacctgg 600
cccagcgaga ccgtcacctg caacgttgcc cacccggcca gcagcaccaa ggtggacaag 660
aaaattgtgc ccagggattg tggttgtaag ccttgcatat gtacagtccc agaagtatca 720
tctgtcttca tcttcccccc aaagcccaag gatgtgctca ccattactct gactcctaag 780
gtcacgtgtg ttgtggtaga catcagcaag gatgatcccg aggtccagtt cagctggttt 840
gtagatgatg tggaggtgca cacagctcag acgcaacccc gggaggagca gttcaacagc 900
actttccgct cagtcagtga acttcccatc atgcaccagg actggctcaa tggcaaggag 960
ttcaaatgca gggtcaacag tgcagctttc cctgccccca tcgagaaaac catctccaaa 1020
accaaaggca gaccgaaggc tccacaggtg tacaccattc cacctcccaa ggagcagatg 1080
gccaaggata aagtcagtct gacctgcatg ataacagact tcttccctga agacattact 1140
gtggagtggc agtggaatgg gcagccagcg gagaactaca agaacactca gcccatcatg 1200
gacacagatg gctcttactt catctacagc aagctcaatg tgcagaagag caactgggag 1260
gcaggaaata ctttcacctg ctctgtgtta catgagggcc tgcacaacca ccatactgag 1320
aagagcctct cccactctcc tggtaaatga 1350

<210> 131
<211> 468
<212> PRT
<213> 小家鼠

<400> 131

```
Met Lys Cys Ser Trp Val Ile Phe Phe Leu Met Ala Val Val Thr Gly
 1               5                  10                  15
Val Asn Ser Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg
            20                  25                  30
Pro Gly Ala Leu Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile
        35                  40                  45
Lys Asp Phe Tyr Leu His Trp Met Arg Gln Arg Pro Glu Gln Gly Leu
    50                  55                  60
Asp Trp Ile Gly Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp
65                  70                  75                  80
Pro Lys Phe Gln Asp Lys Ala Thr Leu Thr Thr Asp Thr Ser Ser Asn
                85                  90                  95
Thr Ala Tyr Leu Gln Leu Ser Gly Leu Thr Ser Glu Thr Thr Ala Val
            100                 105                 110
Tyr Tyr Cys Ser Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr
        115                 120                 125
Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Ile Thr Val Ser Ser
    130                 135                 140
Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
145                 150                 155                 160
Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
                165                 170                 175
Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
            180                 185                 190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
        195                 200                 205
Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
    210                 215                 220
Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
225                 230                 235                 240
Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
                245                 250                 255
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
            260                 265                 270
Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
        275                 280                 285
Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
    290                 295                 300
Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
305                 310                 315                 320
Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
                325                 330                 335
Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
```

```
            340                 345                 350
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
        355                 360                 365
Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
    370                 375                 380
Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
385                 390                 395                 400
Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
                405                 410                 415
Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn
            420                 425                 430
Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
        435                 440                 445
Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
    450                 455                 460
Ser Pro Gly Lys
465
```

<210> 132
<211> 1407
<212> DNA
<213> 小家鼠

<400> 132

```
atgaaatgca gctgggtcat cttcttcctg atggcagtgg ttacaggggt caattcagag 60
gttcagctgc agcagtctgg ggctgaactt gtgaggccag gggccttagt caagttgtcc 120
tgcacagctt ctgacttcaa cattaaagac ttctatctac actggatgag gcagcggcct 180
gaacagggcc tggactggat tggaaggatt gatcctgaga atggtgatac tttatatgac 240
ccgaagttcc aggacaaggc cactcttaca acagacacat cctccaacac agcctacctg 300
cagctcagcg gcctgacatc tgagaccact gccgtctatt actgttctag agaggcggat 360
tatttccacg atggtacctc ctactggtac ttcgatgtct ggggcgcagg gaccacaatc 420
accgtctcct cagccaaaac gacaccccca tctgtctatc cactggcccc tggatctgct 480
gcccaaacta actccatggt gaccctggga tgcctggtca agggctattt ccctgagcca 540
gtgacagtga cctggaactc tggatccctg tccagcggtg tgcacacctt cccagctgtc 600
ctgcagtctg acctctacac tctgagcagc tcagtgactg tcccctccag cacctggccc 660
agcgagaccg tcacctgcaa cgttgcccac ccggccagca gcaccaaggt ggacaagaaa 720
attgtgccca gggattgtgg ttgtaagcct tgcatatgta cagtcccaga agtatcatct 780
gtcttcatct tcccccaaa gcccaaggat gtgctcacca ttactctgac tcctaaggtc 840
acgtgtgttg tggtagacat cagcaaggat gatcccgagg tccagttcag ctggtttgta 900
gatgatgtgg aggtgcacac agctcagacg caaccccggg aggagcagtt caacagcact 960
ttccgctcag tcagtgaact tcccatcatg caccaggact ggctcaatgg caaggagttc 1020
aaatgcaggg tcaacagtgc agctttccct gcccccatcg agaaaaccat ctccaaaacc 1080
aaaggcagac cgaaggctcc acaggtgtac accattccac ctcccaagga gcagatggcc 1140
aaggataaag tcagtctgac ctgcatgata acagacttct tccctgaaga cattactgtg 1200
gagtggcagt ggaatgggca gccagcggag aactacaaga acactcagcc catcatggac 1260
acagatggct cttacttcat ctacagcaag ctcaatgtgc agaagagcaa ctgggaggca 1320
ggaaatactt tcacctgctc tgtgttacat gaggggcctgc acaaccacca tactgagaag 1380
agcctctccc actctcctgg taaatga                                     1407
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<210> 133
<211> 214
<212> PRT
<213> 小家鼠

<400> 133
Asp Ile Gln Met Thr Gln Ile Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1   5   10   15
Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe Lys Leu Leu Ile
        35   40   45
Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
65   70   75   80
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100   105   110
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115   120   125
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130   135   140
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145   150   155   160
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165   170   175
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180   185   190
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195   200   205
Phe Asn Arg Asn Glu Cys
    210

<210> 134
<211> 645
<212> DNA
<213> 小家鼠

<400> 134
gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag cacctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 135
<211> 234
<212> PRT
<213> 小家鼠

<400> 135
Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
1 5 10 15
Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Ile Thr Ser Ser Leu Ser
20 25 30
Ala Ser Leu Gly Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp
35 40 45
Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe
50 55 60
Lys Leu Leu Ile Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr
85 90 95
Asn Leu Glu Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp
100 105 110
Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
115 120 125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
130 135 140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145 150 155 160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
165 170 175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
180 185 190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
195 200 205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
210 215 220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230

<210> 136
<211> 705
<212> DNA
<213> 小家鼠

<400> 136
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 120

atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 180
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 360
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 705

<210> 137
<211> 447
<212> PRT
<213> 小家鼠

<400> 137
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30
Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu Glu Trp Ile
        35   40   45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Ala Tyr
65   70   75   80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
            100   105   110
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr Pro
        115   120   125
Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser
    130   135   140
Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
145   150   155   160
Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe
                165   170   175
Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
            180   185   190
Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala
        195   200   205
His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
    210   215   220
Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val
225   230   235   240
Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
                245   250   255
Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu

```
            260                 265                 270
Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln
        275                 280                 285
Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
    290                 295                 300
Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
305                 310                 315                 320
Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335
Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro
            340                 345                 350
Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
        355                 360                 365
Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
    370                 375                 380
Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
385                 390                 395                 400
Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
                405                 410                 415
Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
            420                 425                 430
His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445
```

<210> 138
<211> 1344
<212> DNA
<213> 小家鼠

<400> 138

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gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagaac 120
caaggaaaga ccctagagtg gataggagaa attaatccta acagtggtgg tgctggctac 180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggccccctgg atctgctgcc 420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
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tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctcccact ctcctggtaa atga 1344

<210> 139
<211> 466
<212> PRT
<213> 小家鼠

<400> 139
Met Gly Trp Ser Trp Thr Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
 1 5 10 15
Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20 25 30
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35 40 45
Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu
    50 55 60
Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65 70 75 80
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
                85 90 95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
            100 105 110
Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
        115 120 125
Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130 135 140
Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145 150 155 160
Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165 170 175
Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180 185 190
His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195 200 205
Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210 215 220
Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225 230 235 240
Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245 250 255
Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
            260 265 270
Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
        275 280 285
Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
    290 295 300
Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg

305 310 315 320
Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
325 330 335
Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
340 345 350
Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
355 360 365
Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
370 375 380
Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385 390 395 400
Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
405 410 415
Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
420 425 430
Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
435 440 445
Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
450 455 460
Gly Lys
465

<210> 140
<211> 1401
<212> DNA
<213> 小家鼠

<400> 140
atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccaactgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaaccaa 180
ggaaagaccc tagagtggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
gatgatatct acgacgactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420
tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480
actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
tctgacctct acactctgag cagctcagtg actgtccctc ccagcacctg gcccagcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080
agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260

ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaatg a 1401

<210> 141
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 141
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Thr Leu Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 142
<211> 642
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 142
gacatccaga tgacccagtc tccatcctcc ctctccgcat ccgtaggcga ccgcgtaacc 60
ataacatgta gagcatctca agatatttcc aactatttga attggtacca acaaaaaccc 120
ggcaaagcac ctaaactcct catttactat acatcaagac tcctctccgg cgttccatca 180
cgattctcag gctccggctc cggcacagat ttcacactca ctatttcctc cctccaacca 240
gaagattttg caacctatta ctgtcaacaa ggcgatacac tcccatacac attcggcggc 300
ggcacaaaag ttgaaattaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 143
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 143
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1   5   10   15
Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20   25   30
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35   40   45
Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50   55   60
Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Arg Leu Leu Ser Gly Val
65   70   75   80
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85   90   95
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100   105   110
Gly Asp Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115   120   125
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130   135   140
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145   150   155   160
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165   170   175
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180   185   190
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195   200   205
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser

```
    210                 215                 220
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 144
<211> 708
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 144

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atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc 60
agatgtgaca tccagatgac ccagtctcca tcctccctct ccgcatccgt aggcgaccgc 120
gtaaccataa catgtagagc atctcaagat atttccaact atttgaattg gtaccaacaa 180
aaacccggca aagcacctaa actcctcatt tactatacat caagactcct ctccggcgtt 240
ccatcacgat tctcaggctc cggctccggc acagatttca cactcactat ttcctccctc 300
caaccagaag attttgcaac ctattactgt caacaaggcg atacactccc atacacattc 360
ggcggcggca caaaagttga aattaaacgt acggtggctg caccatctgt cttcatcttc 420
ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480
ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540
tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600
ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660
cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgt              708
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<210> 145
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 145

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Glu 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 Asp Tyr
            20                  25                  30
Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
            100                 105                 110
```

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125
Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190
Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
195 200 205
Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
210 215 220
Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
225 230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270
Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
290 295 300
Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
325 330 335
Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
385 390 395 400
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445
Lys

<210> 146
<211> 1347
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 146
gaggtgcagc tggtgcagag cggcgccgag gtaaaaaaac caggagcaag cgttaaagtt 60
tcttgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg 120
ccaggacaag gattggaatg gatgggcgaa attaacccta atagtggagg agcaggctac 180
aatcaaaaat tcaaagggag agttacaatg acaacagaca caagcacttc aacagcatat 240
atggaactgc gatcacttag aagcgacgat acagctgtat actattgcgc acgacttggg 300
tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc 360
gtctctagtg cctccaccaa gggcccatcg gtcttccccc tggcgccctg ctccaggagc 420
acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 480
acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta 540
cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag caacttcggc 600
acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 660
gttgagcgca aatgttgtgt cgagtgccca ccgtgcccag caccacctgt ggcaggaccg 720
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 780
gtcacgtgcg tggtggtgga cgtgagccac gaagaccccg aggtccagtt caactggtac 840
gtggacggcg tggaggtgca taatgccaag acaaagccac gggaggagca gttcaacagc 900
acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 960
tacaagtgca aggtctccaa caaaggcctc ccagccccca tcgagaaaac catctccaaa 1020
accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1080
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1140
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg 1200
gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1260
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1320
aagagcctct ccctgtctcc gggtaaa 1347

<210> 147
<211> 468
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 147
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
 1   5   10   15
Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20   25   30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35   40   45
Thr Asp Tyr Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50   55   60
Glu Trp Met Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65   70   75   80
Gln Lys Phe Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85   90   95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
100 105 110
Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
115 120 125
Phe Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
130 135 140
Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
145 150 155 160
Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
165 170 175
Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
180 185 190
His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
195 200 205
Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
210 215 220
Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
225 230 235 240
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
245 250 255
Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
260 265 270
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
275 280 285
His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
290 295 300
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
305 310 315 320
Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
325 330 335
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
340 345 350
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
355 360 365
Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
370 375 380
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385 390 395 400
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
405 410 415
Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
420 425 430
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
435 440 445
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
450 455 460
Ser Pro Gly Lys
465

<210> 148
<211> 1404
<212> DNA
<213> 小家鼠

<400> 148
atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60
gtgcagctgg tgcagagcgg cgccgaggta aaaaaaccag gagcaagcgt taaagtttct 120
tgtaaagcaa gcggatatac atttacagat tacaacatgc attgggtaag acaagcgcca 180
ggacaaggat tggaatggat gggcgaaatt aaccctaata gtggaggagc aggctacaat 240
caaaaattca aagggagagt tacaatgaca acagacacaa gcacttcaac agcatatatg 300
gaactgcgat cacttagaag cgacgataca gctgtatact attgcgcacg acttgggtat 360
gatgatatat atgatgactg gtatttcgat gtttggggcc agggaacaac agttaccgtc 420
tctagtgcct ccaccaaggg cccatcggtc ttcccctgg cgccctgctc caggagcacc 480
tccgagagca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 540
gtgtcgtgga actcaggcgc tctgaccagc ggcgtgcaca ccttcccagc tgtcctacag 600
tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcaa cttcggcacc 660
cagacctaca cctgcaacgt agatcacaag cccagcaaca ccaaggtgga caagacagtt 720
gagcgcaaat gttgtgtcga gtgcccaccg tgcccagcac cacctgtggc aggaccgtca 780
gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc 840
acgtgcgtgg tggtggacgt gagccacgaa gaccccgagg tccagttcaa ctggtacgtg 900
gacggcgtgg aggtgcataa tgccaagaca aagccacggg aggagcagtt caacagcacg 960
ttccgtgtgg tcagcgtcct caccgttgtg caccaggact ggctgaacgg caaggagtac 1020
aagtgcaagg tctccaacaa aggcctccca gccccatcg agaaaaccat ctccaaaacc 1080
aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc 1140
aagaaccagg tcagcctgac ctgcctggtc aaaggcttct accccagcga catcgccgtg 1200
gagtgggaga gcaatgggca gccggagaac aactacaaga ccacacctcc catgctggac 1260
tccgacggct ccttcttcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag 1320
gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag 1380
agcctctccc tgtctccggg taaa 1404

<210> 149
<211> 214
<212> PRT
<213> 小家鼠

<400> 149
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1   5   10   15
Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20   25   30
Leu Asn Trp Phe Gln Gln Lys Pro Asp Gly Thr Leu Lys Leu Leu Ile
        35   40   45
Phe Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65   70   75   80
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Arg Arg Ala Asp Ala Ala

```
            100                 105                 110
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205
Phe Asn Arg Asn Glu Cys
    210
```

<210> 150
<211> 645
<212> DNA
<213> 小家鼠

<400> 150

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gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 60
atcagttgca gggcaagtca ggacattagc aattatttaa actggtttca gcagaaacca 120
gatggaactc ttaaactcct gatcttctac acatcaagat tacactcagg agttccatca 180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 240
gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcgggggg 300
gggaccaagc tggaaataag acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                 645
```

<210> 151
<211> 234
<212> PRT
<213> 小家鼠

<400> 151

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Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
 1               5                  10                  15
Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
            20                  25                  30
Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp
        35                  40                  45
Ile Ser Asn Tyr Leu Asn Trp Phe Gln Gln Lys Pro Asp Gly Thr Leu
    50                  55                  60
Lys Leu Leu Ile Phe Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser
```

65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser
85 90 95
Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asp
100 105 110
Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Arg Arg
115 120 125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
130 135 140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145 150 155 160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
165 170 175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
180 185 190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
195 200 205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
210 215 220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230

<210> 152
<211> 705
<212> DNA
<213> 小家鼠

<400> 152
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 120
atcagttgca gggcaagtca ggacattagc aattatttaa actggtttca gcagaaacca 180
gatggaactc ttaaactcct gatcttctac acatcaagat tacactcagg agttccatca 240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 300
gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcgggggg 360
gggaccaagc tggaaataag acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 705

<210> 153
<211> 447
<212> PRT
<213> 小家鼠

<400> 153
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Leu Val Tyr Asp Gly Ser Tyr Glu Asp Trp Tyr Phe Asp Val
100 105 110
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr Pro
115 120 125
Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser
130 135 140
Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
145 150 155 160
Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe
165 170 175
Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
180 185 190
Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala
195 200 205
His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
210 215 220
Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val
225 230 235 240
Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
245 250 255
Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
260 265 270
Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln
275 280 285
Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
290 295 300
Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
305 310 315 320
Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro
340 345 350
Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
355 360 365
Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
370 375 380
Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
385 390 395 400
Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
405 410 415

```
Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
            420                 425                 430
His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445
```

<210> 154
<211> 1344
<212> DNA
<213> 小家鼠

<400> 154

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gaggtccagc tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cacattcact gactacaaca tgcactgggt gaaacagaac 120
caaggaaaga gcctagagtg gataggagaa attaatccta acagtggtgg tagtggctac 180
aaccaaaagt tcaaaggcaa ggccacattg actgtagaca agtcttccag cacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattggtc 300
tacgatggca gctacgagga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctcccact ctcctggtaa atga                                       1344
```

<210> 155
<211> 466
<212> PRT
<213> 小家鼠

<400> 155

```
Met Gly Trp Ser Trp Thr Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
 1               5                  10                  15
Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45
Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Ser Leu
    50                  55                  60
```

Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn
65 70 75 80
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
85 90 95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
100 105 110
Tyr Tyr Cys Ala Arg Leu Val Tyr Asp Gly Ser Tyr Glu Asp Trp Tyr
115 120 125
Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
130 135 140
Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145 150 155 160
Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
165 170 175
Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
180 185 190
His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
195 200 205
Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
210 215 220
Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225 230 235 240
Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
245 250 255
Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
260 265 270
Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
275 280 285
Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
290 295 300
Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305 310 315 320
Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
325 330 335
Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
340 345 350
Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
355 360 365
Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
370 375 380
Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385 390 395 400
Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
405 410 415
Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
420 425 430
Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
435 440 445
Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
450 455 460

Gly Lys
465

<210> 156
<211> 1401
<212> DNA
<213> 小家鼠

<400> 156
atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccagctgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatacac attcactgac tacaacatgc actgggtgaa acagaaccaa 180
ggaaagagcc tagagtggat aggagaaatt aatcctaaca gtggtggtag tggctacaac 240
caaaagttca aaggcaaggc cacattgact gtagacaagt cttccagcac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attggtctac 360
gatggcagct acgaggactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420
tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480
actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
tctgacctct acactctgag cagctcagtg actgtccctc ccagcacctg gcccagcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080
agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaatg a 1401

<210> 157
<211> 214
<212> PRT
<213> 小家鼠

<400> 157
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1   5   10   15
Asp Arg Val Thr Ile Cys Cys Arg Ala Ser Gln Val Ile Thr Asn Tyr
            20   25   30
Leu Tyr Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe Lys Leu Leu Ile
        35   40   45
Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln

65 70 75 80
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
100 105 110
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
115 120 125
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
130 135 140
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145 150 155 160
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
165 170 175
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
180 185 190
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
195 200 205
Phe Asn Arg Asn Glu Cys
210

<210> 158
<211> 642
<212> DNA
<213> 小家鼠

<400> 158
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 60
atctgttgca gggcaagtca ggtcattacc aattatttat actggtatca gcagaaacca 120
gatggaactt ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggaacag 240
gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg 300
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 159
<211> 234
<212> PRT
<213> 小家鼠

<400> 159
Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
1 5 10 15
Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
20 25 30
Ala Ser Leu Gly Asp Arg Val Thr Ile Cys Cys Arg Ala Ser Gln Val

```
        35                  40                  45
Ile Thr Asn Tyr Leu Tyr Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe
    50                  55                  60
Lys Leu Leu Ile Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser
65                  70                  75                  80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser
                85                  90                  95
Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asp
            100                 105                 110
Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
        115                 120                 125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130                 135                 140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210                 215                 220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 160
<211> 702
<212> DNA
<213> 小家鼠

<400> 160

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 120
atctgttgca gggcaagtca ggtcattacc aattatttat actggtatca gcagaaacca 180
gatggaactt ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca 240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggaacag 300
gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg 360
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt                    702
```

<210> 161
<211> 447
<212> PRT
<213> 小家鼠

<400> 161

```
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
Asn Met His Trp Met Lys Gln Asn Gln Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Gln Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Gly Tyr Val Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
            100                 105                 110
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr Pro
        115                 120                 125
Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser
    130                 135                 140
Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
145                 150                 155                 160
Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe
                165                 170                 175
Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
            180                 185                 190
Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala
        195                 200                 205
His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
    210                 215                 220
Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val
225                 230                 235                 240
Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
                245                 250                 255
Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
            260                 265                 270
Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln
        275                 280                 285
Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
    290                 295                 300
Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
305                 310                 315                 320
Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335
Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro
            340                 345                 350
Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
        355                 360                 365
Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
    370                 375                 380
```

Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
385 390 395 400
Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
405 410 415
Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
420 425 430
His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
435 440 445

<210> 162
<211> 1341
<212> DNA
<213> 小家鼠

<400> 162
gaggtccagc tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cacattcact gactacaaca tgcactggat gaagcagaac 120
caaggaaaga gcctagaatg gataggagaa attaatccta acagtggtgg tgctggctac 180
aaccagcagt tcaaaggcaa ggccacattg actgtagaca agtcctccag gacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
tacgttggta attacgagga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctcccact ctcctggtaa a 1341

<210> 163
<211> 466
<212> PRT
<213> 小家鼠

<400> 163
Met Gly Trp Ser Trp Thr Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
1 5 10 15
Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
20 25 30

```
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45
Thr Asp Tyr Asn Met His Trp Met Lys Gln Asn Gln Gly Lys Ser Leu
    50                  55                  60
Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65                  70                  75                  80
Gln Gln Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg
                85                  90                  95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110
Tyr Tyr Cys Ala Arg Leu Gly Tyr Val Gly Asn Tyr Glu Asp Trp Tyr
        115                 120                 125
Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130                 135                 140
Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145                 150                 155                 160
Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175
Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180                 185                 190
His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195                 200                 205
Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210                 215                 220
Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225                 230                 235                 240
Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245                 250                 255
Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
            260                 265                 270
Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
        275                 280                 285
Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
    290                 295                 300
Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320
Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335
Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
            340                 345                 350
Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
        355                 360                 365
Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
    370                 375                 380
Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385                 390                 395                 400
Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
                405                 410                 415
Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
            420                 425                 430
```

Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
435 440 445
Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
450 455 460
Gly Lys
465

<210> 164
<211> 1398
<212> DNA
<213> 小家鼠

<400> 164
atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccagctgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatacac attcactgac tacaacatgc actggatgaa gcagaaccaa 180
ggaaagagcc tagaatggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
cagcagttca aaggcaaggc cacattgact gtagacaagt cctccaggac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
gttggtaatt acgaggactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420
tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480
actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
tctgacctct acactctgag cagctcagtg actgtccctc ccagcacctg gcccagcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080
agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaa 1398

<210> 165
<211> 214
<212> PRT
<213> 小家鼠

<400> 165
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15
Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe Lys Leu Leu Ile

```
        35                  40                  45
Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205
Phe Asn Arg Asn Glu Cys
    210
```

<210> 166
<211> 645
<212> DNA
<213> 小家鼠

<400> 166

```
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300
gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                  645
```

<210> 167
<211> 234
<212> PRT
<213> 小家鼠

<400> 167

```
Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
```

```
 1               5                  10                  15
Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
            20                  25                  30
Ala Ser Leu Gly Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp
        35                  40                  45
Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe
    50                  55                  60
Lys Leu Leu Ile Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser
65                  70                  75                  80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr
                85                  90                  95
Asn Leu Glu Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp
            100                 105                 110
Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
        115                 120                 125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130                 135                 140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210                 215                 220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 168
<211> 705
<212> DNA
<213> 小家鼠

<400> 168

```
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 120
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 180
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 360
gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                  705
```

<210> 169
<211> 447
<212> PRT
<213> 小家鼠

<400> 169

```
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu Asp Trp Ile
        35                  40                  45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
            100                 105                 110
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr Pro
        115                 120                 125
Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser
    130                 135                 140
Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
145                 150                 155                 160
Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe
                165                 170                 175
Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
            180                 185                 190
Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala
        195                 200                 205
His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
    210                 215                 220
Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val
225                 230                 235                 240
Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
                245                 250                 255
Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
            260                 265                 270
Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln
        275                 280                 285
Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
    290                 295                 300
Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
305                 310                 315                 320
Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335
Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro
            340                 345                 350
```

Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
355 360 365
Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
370 375 380
Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
385 390 395 400
Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
405 410 415
Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
420 425 430
His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
435 440 445

<210> 170
<211> 1344
<212> DNA
<213> 小家鼠

<400> 170
gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagaac 120
caaggaaaga ccctagactg gataggagaa attaatccta acagtggtgg tgctggctac 180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360
gtctcctcag ccaaaacgac accccatct gtctatccac tggccctgg atctgctgcc 420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctcccact ctcctggtaa atga 1344

<210> 171
<211> 466
<212> PRT
<213> 小家鼠

<400> 171

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Met Gly Trp Ser Trp Thr Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
 1               5                  10                  15
Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45
Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu
    50                  55                  60
Asp Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65                  70                  75                  80
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
                85                  90                  95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110
Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
        115                 120                 125
Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130                 135                 140
Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145                 150                 155                 160
Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175
Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180                 185                 190
His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195                 200                 205
Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210                 215                 220
Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225                 230                 235                 240
Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245                 250                 255
Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
            260                 265                 270
Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
        275                 280                 285
Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
    290                 295                 300
Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320
Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335
Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
            340                 345                 350
Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
        355                 360                 365
Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
    370                 375                 380
Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385                 390                 395                 400
```

Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
405 410 415
Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
420 425 430
Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
435 440 445
Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
450 455 460
Gly Lys
465

<210> 172
<211> 1401
<212> DNA
<213> 小家鼠

<400> 172
atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccaactgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaaccaa 180
ggaaagaccc tagactggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
gatgatatct acgacgactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420
tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480
actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
tctgacctct acactctgag cagctcagtg actgtccctc ccagcacctg gcccagcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080
agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaatg a 1401

<210> 173
<211> 214
<212> PRT
<213> 小家鼠

<400> 173
Asp Ile Gln Met Thr Gln Ile Thr Ser Ser Leu Ser Ala Ser Leu Gly

```
 1               5                  10                  15
Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe Lys Leu Leu Ile
        35                  40                  45
Phe Tyr Thr Ser Arg Leu Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205
Phe Asn Arg Asn Glu Cys
    210
```

<210> 174
<211> 642
<212> DNA
<213> 小家鼠

<400> 174

```
gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60
atcagttgca gggcaagtca agacattagc aattatttaa attggtatca gcagaaacca 120
gatggaactt ttaaactcct tatcttctac acatcaagat tattttcagg agtcccatca 180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300
gggaccaagg tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt                    642
```

<210> 175
<211> 234
<212> PRT

<213> 小家鼠

<400> 175

```
Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
 1               5                  10                  15
Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Ile Thr Ser Ser Leu Ser
            20                  25                  30
Ala Ser Leu Gly Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp
        35                  40                  45
Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe
    50                  55                  60
Lys Leu Leu Ile Phe Tyr Thr Ser Arg Leu Phe Ser Gly Val Pro Ser
65                  70                  75                  80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr
                85                  90                  95
Asn Leu Glu Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp
            100                 105                 110
Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
        115                 120                 125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130                 135                 140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145                 150                 155                 160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165                 170                 175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195                 200                 205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210                 215                 220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 176
<211> 702
<212> DNA
<213> 小家鼠

<400> 176

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atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagat tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 120
atcagttgca gggcaagtca agacattagc aattatttaa attggtatca gcagaaacca 180
gatggaactt ttaaactcct tatcttctac acatcaagat tattttcagg agtcccatca 240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 360
gggaccaagg tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
```

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag cacctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 702

<210> 177
<211> 450
<212> PRT
<213> 小家鼠

<400> 177
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Thr
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Asn Met His Trp Val Lys Gln Thr Gln Gly Lys Thr Leu Glu Trp Ile
35 40 45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
100 105 110
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr Ala
115 120 125
Pro Ser Val Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser
130 135 140
Ser Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
145 150 155 160
Thr Leu Thr Trp Asn Ser Gly Ser Leu Ser Ser Asp Val His Thr Phe
165 170 175
Pro Ala Leu Leu Gln Ser Gly Leu Tyr Thr Leu Ser Ser Ser Val Thr
180 185 190
Val Thr Thr Trp Pro Ser Gln Thr Ile Thr Cys Asn Val Ala His Pro
195 200 205
Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Ser Pro
210 215 220
Thr His Lys Pro Cys Pro Pro Cys Pro Ala Pro Asn Leu Leu Gly Gly
225 230 235 240
Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile
245 250 255
Ser Leu Ser Pro Met Val Thr Cys Val Val Val Asp Val Ser Glu Asp
260 265 270
Asp Pro Asp Val His Val Ser Trp Phe Val Asn Asn Val Glu Val His
275 280 285
Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Ile Arg
290 295 300
Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys
305 310 315 320

Glu Phe Lys Cys Lys Val Asn Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335
Arg Thr Ile Ser Lys Pro Lys Gly Pro Val Arg Ala Pro Gln Val Tyr
340 345 350
Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu
355 360 365
Thr Cys Met Ile Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp
370 375 380
Thr Asn Asn Gly Gln Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val
385 390 395 400
Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu
405 410 415
Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
420 425 430
Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro
435 440 445
Gly Lys
450

<210> 178
<211> 1350
<212> DNA
<213> 小家鼠

<400> 178
gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctgggacttc agtgaagatg 60
tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagacc 120
caaggaaaga ccctagagtg gataggagaa attaatccta acagtggtgg tgctggctac 180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aaaattgggc 300
tacgatgata tctacgacga ctggtatttc gatgtctggg gcgcagggac cacggtcacc 360
gtctcctcag ccaaaacaac agccccatcg gtctatccac tggcccctgt gtgtggagat 420
acaactggct cctcggtgac tctaggatgc ctggtcaagg gttatttccc tgagccagtg 480
accttgacct ggaactctgg atccctgtcc agtgatgtgc acaccttccc agctctcctg 540
cagtctggcc tctacaccct cagcagctca gtgactgtaa ccacctggcc cagccagacc 600
atcacctgca atgtggccca cccggcaagc agcaccaaag tggacaagaa aattgagccc 660
agagggtccc caacacataa accctgtcct ccatgcccag ctcctaacct cttgggtgga 720
ccatccgtct tcatcttccc tccaaagatc aaggatgtac tcatgatctc cctgagcccc 780
atggtcacgt gtgtggtggt ggatgtgagc gaggatgacc cagatgtcca tgtcagctgg 840
ttcgtgaaca acgtggaagt acacacagct cagacacaaa cccatagaga ggattacaac 900
agtactatcc gggtggtcag tgccctcccc atccagcacc aggactggat gagtggcaag 960
gagttcaaat gcaaggtcaa caacaaagcc ctcccagcgc ccatcgagag aaccatctca 1020
aaacccaaag ggccagtaag agctccacag gtatatgtct tgcctccacc agaagaagag 1080
atgactaaga aacaggtcac tctgacctgc atgatcacag acttcatgcc tgaagacatt 1140
tacgtggagt ggaccaacaa cgggcaaaca gagctaaact acaagaacac tgaaccagtc 1200
ctggactctg atggttctta cttcatgtac agcaagctga gagtggaaaa gaagaactgg 1260
gtggaaagaa atagctactc ctgttcagtg gtccacgagg gtctgcacaa tcaccacacg 1320
actaagagct tctcccggac tccgggtaaa 1350

<210> 179
<211> 469
<212> PRT
<213> 小家鼠

<400> 179

```
Met Gly Trp Ser Trp Thr Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
 1               5                  10                  15
Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20                  25                  30
Pro Gly Thr Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45
Thr Asp Tyr Asn Met His Trp Val Lys Gln Thr Gln Gly Lys Thr Leu
    50                  55                  60
Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65                  70                  75                  80
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
                85                  90                  95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110
Tyr Tyr Cys Ala Lys Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
        115                 120                 125
Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130                 135                 140
Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr
145                 150                 155                 160
Thr Gly Ser Ser Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165                 170                 175
Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ser Leu Ser Ser Asp Val
            180                 185                 190
His Thr Phe Pro Ala Leu Leu Gln Ser Gly Leu Tyr Thr Leu Ser Ser
        195                 200                 205
Ser Val Thr Val Thr Thr Trp Pro Ser Gln Thr Ile Thr Cys Asn Val
    210                 215                 220
Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg
225                 230                 235                 240
Gly Ser Pro Thr His Lys Pro Cys Pro Pro Cys Pro Ala Pro Asn Leu
                245                 250                 255
Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val
            260                 265                 270
Leu Met Ile Ser Leu Ser Pro Met Val Thr Cys Val Val Val Asp Val
        275                 280                 285
Ser Glu Asp Asp Pro Asp Val His Val Ser Trp Phe Val Asn Asn Val
    290                 295                 300
Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser
305                 310                 315                 320
Thr Ile Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met
                325                 330                 335
Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Ala Leu Pro Ala
            340                 345                 350
```

Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Pro Val Arg Ala Pro
355 360 365
Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln
370 375 380
Val Thr Leu Thr Cys Met Ile Thr Asp Phe Met Pro Glu Asp Ile Tyr
385 390 395 400
Val Glu Trp Thr Asn Asn Gly Gln Thr Glu Leu Asn Tyr Lys Asn Thr
405 410 415
Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu
420 425 430
Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser
435 440 445
Val Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser
450 455 460
Arg Thr Pro Gly Lys
465

<210> 180
<211> 1407
<212> DNA
<213> 小家鼠

<400> 180
atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccaactgc aacagtctgg acctgaacta atgaagcctg ggacttcagt gaagatgtcc 120
tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagacccaa 180
ggaaagaccc tagagtggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaaa attgggctac 360
gatgatatct acgacgactg gtatttcgat gtctggggcg cagggaccac ggtcaccgtc 420
tcctcagcca aaacaacagc cccatcggtc tatccactgg cccctgtgtg tggagataca 480
actggctcct cggtgactct aggatgcctg gtcaagggtt atttccctga gccagtgacc 540
ttgacctgga actctggatc cctgtccagt gatgtgcaca ccttcccagc tctcctgcag 600
tctggcctct acaccctcag cagctcagtg actgtaacca cctggcccag ccagaccatc 660
acctgcaatg tggcccaccc ggcaagcagc accaaagtgg acaagaaaat tgagcccaga 720
gggtccccaa cacataaacc ctgtcctcca tgcccagctc ctaacctctt gggtggacca 780
tccgtcttca tcttccctcc aaagatcaag gatgtactca tgatctccct gagccccatg 840
gtcacgtgtg tggtggtgga tgtgagcgag gatgacccag atgtccatgt cagctggttc 900
gtgaacaacg tggaagtaca cacagctcag acacaaaccc atagagagga ttacaacagt 960
actatccggg tggtcagtgc cctccccatc cagcaccagg actggatgag tggcaaggag 1020
ttcaaatgca aggtcaacaa caaagccctc ccagcgccca tcgagagaac catctcaaaa 1080
cccaaagggc cagtaagagc tccacaggta tatgtcttgc ctccaccaga agaagagatg 1140
actaagaaac aggtcactct gacctgcatg atcacagact tcatgcctga agacatttac 1200
gtggagtgga ccaacaacgg gcaaacagag ctaaactaca agaacactga accagtcctg 1260
gactctgatg gttcttactt catgtacagc aagctgagag tggaaaagaa gaactgggtg 1320
gaaagaaata gctactcctg ttcagtggtc cacgagggtc tgcacaatca ccacacgact 1380
aagagcttct cccggactcc gggtaaa 1407

<210> 181

<211> 214
<212> PRT
<213> 小家鼠

<400> 181

```
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1               5                  10                  15
Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe Lys Leu Leu Ile
        35                  40                  45
Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110
Pro Thr Val Ser Ile Phe Pro Leu Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205
Phe Asn Arg Asn Glu Cys
    210
```

<210> 182
<211> 645
<212> DNA
<213> 小家鼠

<400> 182

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gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 60
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 120
gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 240
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 300
gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacta 360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
```

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 183
<211> 234
<212> PRT
<213> 小家鼠

<400> 183
Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
1 5 10 15
Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
20 25 30
Ala Ser Leu Gly Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp
35 40 45
Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe
50 55 60
Lys Leu Leu Ile Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr
85 90 95
Asn Leu Glu Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp
100 105 110
Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
115 120 125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Leu Ser Ser Glu Gln
130 135 140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145 150 155 160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
165 170 175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
180 185 190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
195 200 205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
210 215 220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230

<210> 184
<211> 705
<212> DNA
<213> 小家鼠

<400> 184
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagggtctcc 120
atcagttgca gggcaagtca agacattagc aattatttaa actggtatca gcagaaacca 180

gatggaactt ttaaactcct tatcttctac acatcaagat tactctcagg agtcccatca 240
aggttcagtg gcagtgggtc tggaacagat tattctctca ccatttacaa cctggagcaa 300
gaagattttg ccacttactt ttgccaacag ggagatacgc ttccgtacac tttcggaggg 360
gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacta 420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 705

<210> 185
<211> 447
<212> PRT
<213> 小家鼠

<400> 185
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30
Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu Glu Trp Ile
        35   40   45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Ala Tyr
65   70   75   80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
            100   105   110
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr Pro
        115   120   125
Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser
    130   135   140
Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
145   150   155   160
Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe
                165   170   175
Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
            180   185   190
Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala
        195   200   205
His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
    210   215   220
Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val
225   230   235   240
Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
                245   250   255
Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
            260   265   270

Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln
275 280 285
Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
290 295 300
Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
305 310 315 320
Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro
340 345 350
Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
355 360 365
Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
370 375 380
Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
385 390 395 400
Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
405 410 415
Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
420 425 430
His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
435 440 445

<210> 186
<211> 1344
<212> DNA
<213> 小家鼠

<400> 186
gaggtccaac tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata tacattcact gactacaaca tgcactgggt gaagcagaac 120
caaggaaaga ccctagaatg gataggagaa attaatccta acagtggtgg tgctggctac 180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccac cacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
tacgatgata tctacgacga ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360
gtctcctcag ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200

gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctcccact ctcctggtaa atga 1344

<210> 187
<211> 466
<212> PRT
<213> 小家鼠

<400> 187
Met Gly Trp Ser Trp Thr Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
1 5 10 15
Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
20 25 30
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45
Thr Asp Tyr Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Thr Leu
50 55 60
Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65 70 75 80
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr
85 90 95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
100 105 110
Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
115 120 125
Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
130 135 140
Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145 150 155 160
Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
165 170 175
Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
180 185 190
His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
195 200 205
Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
210 215 220
Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225 230 235 240
Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
245 250 255
Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
260 265 270
Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
275 280 285
Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
290 295 300
Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305 310 315 320

Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
325 330 335
Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
340 345 350
Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
355 360 365
Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
370 375 380
Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385 390 395 400
Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
405 410 415
Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
420 425 430
Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
435 440 445
Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
450 455 460
Gly Lys
465

<210> 188
<211> 1401
<212> DNA
<213> 小家鼠

<400> 188
atgggatgga gctggacctt tctcttcctc ctgtcaggaa ctgcaggtgt cctctctgag 60
gtccaactgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatatac attcactgac tacaacatgc actgggtgaa gcagaaccaa 180
ggaaagaccc tagaatggat aggagaaatt aatcctaaca gtggtggtgc tggctacaac 240
cagaagttca agggcaaggc cacattgact gtagacaagt cctccaccac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
gatgatatct acgacgactg gtacttcgat gtctggggcg cagggaccac ggtcaccgtc 420
tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480
actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
tctgacctct acactctgag cagctcagtg actgtccctc ccagcacctg gcccagcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960
tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080
agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320

actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaatg a 1401

<210> 189
<211> 213
<212> PRT
<213> 小家鼠

<400> 189
Gln Ile Val Leu Ser Gln Ser Pro Ala Phe Leu Ser Val Ser Pro Gly
1 5 10 15
Asp Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Ile Ser Tyr Ile
20 25 30
His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Arg Ser Trp Ile Tyr
35 40 45
Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Gly Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asp Pro Leu Thr
85 90 95
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
100 105 110
Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
115 120 125
Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
130 135 140
Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
145 150 155 160
Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
165 170 175
Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
180 185 190
Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
195 200 205
Asn Arg Asn Glu Cys
210

<210> 190
<211> 642
<212> DNA
<213> 小家鼠

<400> 190
caaattgttc tctcccagtc tccagcattc ctgtctgtat ctccagggga taaggtcaca 60
atgacttgca gggccagctc aagtataagt tacatacact ggtttcagca gaagccagga 120
tcctccccca gatcctggat ttatgccaca tccaacctgg cttctggagt ccctggtcgc 180
ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgag 240
gatgctgcca cttattactg ccagcagtgg agtagtgacc cactcacgtt cggtgctggg 300

accaagctgg agctgaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc 360
agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420
aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480
agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg 540
accaaggacg agtatgaacg acataacagc tatacctgtg aggccactca caagacatca 600
acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag 642

<210> 191
<211> 235
<212> PRT
<213> 小家鼠

<400> 191
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
 1   5   10   15
Val Ile Met Ser Arg Gly Gln Ile Val Leu Ser Gln Ser Pro Ala Phe
            20   25   30
Leu Ser Val Ser Pro Gly Asp Lys Val Thr Met Thr Cys Arg Ala Ser
        35   40   45
Ser Ser Ile Ser Tyr Ile His Trp Phe Gln Gln Lys Pro Gly Ser Ser
    50   55   60
Pro Arg Ser Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro
65   70   75   80
Gly Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile
                85   90   95
Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
            100   105   110
Ser Ser Asp Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
        115   120   125
Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
    130   135   140
Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
145   150   155   160
Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
                165   170   175
Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
            180   185   190
Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
        195   200   205
Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
    210   215   220
Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225   230   235

<210> 192
<211> 708
<212> DNA
<213> 小家鼠

<400> 192
atggatttc aagtgcagat tttcagcttc ctgctaatca gtgcttcagt cataatgtcc 60
agaggacaaa ttgttctctc ccagtctcca gcattcctgt ctgtatctcc aggggataag 120
gtcacaatga cttgcagggc cagctcaagt ataagttaca tacactggtt tcagcagaag 180
ccaggatcct cccccagatc ctggatttat gccacatcca acctggcttc tggagtccct 240
ggtcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagagtggag 300
gctgaggatg ctgccactta ttactgccag cagtggagta gtgacccact cacgttcggt 360
gctgggacca agctggagct gaaacgggct gatgctgcac caactgtatc catcttccca 420
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 480
taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc 540
ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 600
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660
acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag 708

<210> 193
<211> 445
<212> PRT
<213> 小家鼠

<400> 193
Glu Val Gln Leu Gln Gln Ser Gly Ala Asp Leu Val Gln Pro Gly Ala
 1   5   10   15
Ser Val Lys Val Ser Cys Thr Ala Ser Gly Phe Asp Ile Lys Asp Tyr
            20   25   30
Tyr Ile His Trp Met Lys Gln Arg Pro Asp Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
    50   55   60
Pro Gly Lys Ala Thr Phe Thr Thr Asp Thr Ser Ser Asn Thr Ala Tyr
65   70   75   80
Leu Gln Leu Arg Gly Leu Thr Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
                85   90   95
Gly Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
            100   105   110
Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser
        115   120   125
Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
    130   135   140
Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val
145   150   155   160
Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
                165   170   175
Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
            180   185   190
Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro
        195   200   205
Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
    210   215   220
Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
225   230   235   240

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Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
                245                 250                 255
Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
            260                 265                 270
Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln
        275                 280                 285
Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
    290                 295                 300
Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
305                 310                 315                 320
Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335
Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
            340                 345                 350
Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr
        355                 360                 365
Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln
    370                 375                 380
Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
385                 390                 395                 400
Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu
                405                 410                 415
Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
            420                 425                 430
His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445
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<210> 194
<211> 1338
<212> DNA
<213> 小家鼠

<400> 194

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gaagttcagc tgcaacagtc tggggcagac cttgtgcagc caggggcctc agtcaaggtg 60
tcctgcacag cttctggctt cgacattaag gactactata tacactggat gaaacagagg 120
cctgaccagg gcctggagtg gattggaagg gttgatcctg acaatggtga gactgaattt 180
gccccgaagt tcccgggcaa ggccactttt acaacagaca catcctccaa cacagcctac 240
ctacaactca gaggcctgac atctgaggac actgccatct attactgtgg gagagaagac 300
tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt cactgtctct 360
gcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact 420
aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg 480
acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct 540
gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc 600
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc 720
ttcccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt 780
gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg 840
gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca 900
gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 960
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gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga 1020
ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1080
gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag 1140
tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc 1200
tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact 1260
ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320
cactctcctg gtaaatga 1338

<210> 195
<211> 464
<212> PRT
<213> 小家鼠

<400> 195
Met Lys Cys Ser Trp Val Ile Phe Phe Leu Met Ala Val Val Thr Gly
 1   5   10   15
Val Asn Ser Glu Val Gln Leu Gln Gln Ser Gly Ala Asp Leu Val Gln
            20   25   30
Pro Gly Ala Ser Val Lys Val Ser Cys Thr Ala Ser Gly Phe Asp Ile
        35   40   45
Lys Asp Tyr Tyr Ile His Trp Met Lys Gln Arg Pro Asp Gln Gly Leu
    50   55   60
Glu Trp Ile Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala
65   70   75   80
Pro Lys Phe Pro Gly Lys Ala Thr Phe Thr Thr Asp Thr Ser Ser Asn
                85   90   95
Thr Ala Tyr Leu Gln Leu Arg Gly Leu Thr Ser Glu Asp Thr Ala Ile
            100   105   110
Tyr Tyr Cys Gly Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro
        115   120   125
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr
    130   135   140
Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
145   150   155   160
Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
                165   170   175
Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
            180   185   190
Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
        195   200   205
Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
    210   215   220
Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
225   230   235   240
Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
                245   250   255
Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
            260   265   270
Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
        275   280   285

Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
290 295 300
Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
305 310 315 320
Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
325 330 335
Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
340 345 350
Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
355 360 365
Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
370 375 380
Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
385 390 395 400
Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
405 410 415
Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
420 425 430
Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
435 440 445
Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
450 455 460

<210> 196
<211> 1395
<212> DNA
<213> 小家鼠

<400> 196
atgaaatgca gctgggtcat cttcttcctg atggcagtgg ttacaggggt caattcagaa 60
gttcagctgc aacagtctgg ggcagacctt gtgcagccag gggcctcagt caaggtgtcc 120
tgcacagctt ctggcttcga cattaaggac tactatatac actggatgaa acagaggcct 180
gaccagggcc tggagtggat tggaagggtt gatcctgaca atggtgagac tgaatttgcc 240
ccgaagttcc cgggcaaggc acttttaca acagacacat cctccaacac agcctaccta 300
caactcagag gcctgacatc tgaggacact gccatctatt actgtgggag agaagactac 360
gatggtacct acacctggtt tccttattgg ggccaaggga ctctggtcac tgtctctgca 420
gccaaaacga caccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac 480
tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc 540
tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac 600
ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc 660
acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg 720
gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 780
cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg 840
gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag 900
gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 960
agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 1020
aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg 1080
aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 1140
agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg 1200

aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 1260
tacttcatct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 1320
acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380
tctcctggta aatga 1395

<210> 197
<211> 214
<212> PRT
<213> 小家鼠

<400> 197
Asp Leu Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1 5 10 15
Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
 20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
 35 40 45
Phe Tyr Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
Ser Gly Ser Gly Thr Asn Tyr Ser Leu Thr Ile Thr Asn Leu Glu Gln
65 70 75 80
Asp Asp Ala Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
 85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
 100 105 110
Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
 115 120 125
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
 130 135 140
Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145 150 155 160
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
 165 170 175
Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
 180 185 190
Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
 195 200 205
Phe Asn Arg Asn Glu Cys
 210

<210> 198
<211> 645
<212> DNA
<213> 小家鼠

<400> 198
gatctccaga tgacacagac tacttcctcc ctgtctgcct ctctgggaga cagagtcacc 60
atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120
gatggaactg ttaagctcct gatcttctac acatcaacat tacagtcagg agtcccatcg 180

aggttcagtg gcagtgggtc tggaacaaat tattctctca ccattaccaa cctggagcaa 240
gatgatgctg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg 300
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 199
<211> 234
<212> PRT
<213> 小家鼠

<400> 199
Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
 1   5   10   15
Gly Ser Arg Cys Asp Leu Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
            20   25   30
Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp
        35   40   45
Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
    50   55   60
Lys Leu Leu Ile Phe Tyr Thr Ser Thr Leu Gln Ser Gly Val Pro Ser
65   70   75   80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asn Tyr Ser Leu Thr Ile Thr
                85   90   95
Asn Leu Glu Gln Asp Asp Ala Ala Thr Tyr Phe Cys Gln Gln Gly Asp
            100   105   110
Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
        115   120   125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
    130   135   140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145   150   155   160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
                165   170   175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180   185   190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
        195   200   205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
    210   215   220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225   230

<210> 200
<211> 705
<212> DNA

<213> 小家鼠

<400> 200
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg ttccagatgt 60
gatctccaga tgacacagac tacttcctcc ctgtctgcct ctctgggaga cagagtcacc 120
atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 180
gatggaactg ttaagctcct gatcttctac acatcaacat tacagtcagg agtcccatcg 240
aggttcagtg gcagtgggtc tggaacaaat tattctctca ccattaccaa cctggagcaa 300
gatgatgctg ccacttactt ttgccaacag ggtgatacgc ttccgtacac gttcggaggg 360
gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 705

<210> 201
<211> 447
<212> PRT
<213> 小家鼠

<400> 201
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30
Asn Met His Trp Met Lys Gln Asn Gln Gly Lys Ser Leu Glu Trp Ile
        35   40   45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn Gln Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Leu Gly Tyr Tyr Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
            100   105   110
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr Pro
        115   120   125
Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser
    130   135   140
Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
145   150   155   160
Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe
                165   170   175
Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr
            180   185   190
Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala
        195   200   205
His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp
    210   215   220

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Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val
225                 230                 235                 240
Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr
                245                 250                 255
Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu
            260                 265                 270
Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln
        275                 280                 285
Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser
    290                 295                 300
Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys
305                 310                 315                 320
Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335
Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro
            340                 345                 350
Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met
        355                 360                 365
Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn
    370                 375                 380
Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr
385                 390                 395                 400
Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn
                405                 410                 415
Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu
            420                 425                 430
His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445
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<210> 202
<211> 1344
<212> DNA
<213> 小家鼠

<400> 202

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gaggtccagt tgcaacagtc tggacctgaa ctaatgaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cacattcact gactacaaca tgcactggat gaagcagaac 120
caaggaaaga gcctagagtg gataggagag attaatccta acagtggtgg ttctggttac 180
aaccagaagt tcaaaggcaa ggccacattg actgtagaca agtcctccag cacagcctac 240
atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagattgggc 300
tactatggta actacgagga ctggtatttc gatgtctggg gcgcagggac cacggtcacc 360
gtctcctctg ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc 420
caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480
acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540
cagtctgacc tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc 600
gagaccgtca cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt 660
gtgcccaggg attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc 720
ttcatcttcc ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg 780
tgtgttgtgg tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat 840
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gatgtggagg tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc 900
cgctcagtca gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa 960
tgcagggtca acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa 1020
ggcagaccga aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag 1080
gataaagtca gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag 1140
tggcagtgga atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca 1200
gatggctctt acttcatcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga 1260
aatactttca cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc 1320
ctctcccact ctcctggtaa atga 1344

<210> 203
<211> 466
<212> PRT
<213> 小家鼠

<400> 203
Met Gly Trp Ser Trp Thr Phe Leu Phe Leu Leu Ser Gly Thr Ser Gly
 1   5   10   15
Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Met Lys
            20   25   30
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35   40   45
Thr Asp Tyr Asn Met His Trp Met Lys Gln Asn Gln Gly Lys Ser Leu
    50   55   60
Glu Trp Ile Gly Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn
65   70   75   80
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85   90   95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
            100   105   110
Tyr Tyr Cys Ala Arg Leu Gly Tyr Tyr Gly Asn Tyr Glu Asp Trp Tyr
        115   120   125
Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys
    130   135   140
Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
145   150   155   160
Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
                165   170   175
Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
            180   185   190
His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
        195   200   205
Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
    210   215   220
Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
225   230   235   240
Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
                245   250   255
Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile
            260   265   270

Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp
275 280 285
Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His
290 295 300
Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305 310 315 320
Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys
325 330 335
Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu
340 345 350
Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr
355 360 365
Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
370 375 380
Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp
385 390 395 400
Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
405 410 415
Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln
420 425 430
Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
435 440 445
Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
450 455 460
Gly Lys
465

<210> 204
<211> 1401
<212> DNA
<213> 小家鼠

<400> 204
atgggatgga gctggacctt tctcttcctc ctgtcaggaa cttcgggtgt cctctctgag 60
gtccagttgc aacagtctgg acctgaacta atgaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctggatacac attcactgac tacaacatgc actggatgaa gcagaaccaa 180
ggaaagagcc tagagtggat aggagagatt aatcctaaca gtggtggttc tggttacaac 240
cagaagttca aaggcaaggc cacattgact gtagacaagt cctccagcac agcctacatg 300
gagctccgca gcctgacatc tgaggactct gcagtctatt actgtgcaag attgggctac 360
tatggtaact acgaggactg gtatttcgat gtctggggcg cagggaccac ggtcaccgtc 420
tcctctgcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 480
actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 540
gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 600
tctgacctct acactctgag cagctcagtg actgtccctc ccagcacctg gcccagcgag 660
accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 720
cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 780
atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 840
gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 900
gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 960

tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 1020
agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1080
agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1140
aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1200
cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1260
ggctcttact tcatctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1320
actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1380
tcccactctc ctggtaaatg a 1401

<210> 205
<211> 215
<212> PRT
<213> 小家鼠

<400> 205
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
 1   5   10   15
Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Thr Ser Ser
            20   25   30
Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
        35   40   45
Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
    50   55   60
Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu
65   70   75   80
Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Phe Phe Pro
                85   90   95
Ser Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala
            100   105   110
Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser
        115   120   125
Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp
    130   135   140
Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val
145   150   155   160
Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met
                165   170   175
Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser
            180   185   190
Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys
        195   200   205
Ser Phe Asn Arg Asn Glu Cys
    210   215

<210> 206
<211> 645
<212> DNA
<213> 小家鼠

<400> 206
cagattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60
atgacctgca gggccagctc aagtgtaact tccagttact tgaactggta ccagcagaag 120
ccaggatctt cccccaaact ctggatttat agcacatcca acctggcttc aggagtccca 180
gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagtgtggag 240
gctgaggatg ctgccactta ttactgccag cagtatgatt ttttcccatc gacgttcggt 300
ggaggcacca agctggaaat caagcgggct gatgctgcac caactgtatc catcttccca 360
ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 420
taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc 480
ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc 540
acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 600
acatcaactt cacccatcgt caagagcttc aacaggaatg agtgt 645

<210> 207
<211> 237
<212> PRT
<213> 小家鼠

<400> 207
Met Asp Ser Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Leu
 1   5   10   15
Val Lys Met Ser Arg Gly Gln Ile Val Leu Thr Gln Ser Pro Ala Ile
            20   25   30
Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
        35   40   45
Ser Ser Val Thr Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
    50   55   60
Ser Ser Pro Lys Leu Trp Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly
65   70   75   80
Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
                85   90   95
Thr Ile Ser Ser Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
            100   105   110
Gln Tyr Asp Phe Phe Pro Ser Thr Phe Gly Gly Gly Thr Lys Leu Glu
        115   120   125
Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser
    130   135   140
Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn
145   150   155   160
Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser
                165   170   175
Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys
            180   185   190
Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu
        195   200   205
Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser
    210   215   220
Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225   230   235

<210> 208
<211> 711
<212> DNA
<213> 小家鼠

<400> 208
atggattctc aagtgcagat tttcagcttc cttctaatca gtgccttagt caaaatgtcc 60
agaggacaga ttgttctcac ccagtctcca gcaatcatgt ctgcatctcc aggggagaag 120
gtcaccatga cctgcagggc cagctcaagt gtaacttcca gttacttgaa ctggtaccag 180
cagaagccag gatcttcccc caaactctgg atttatagca catccaacct ggcttcagga 240
gtcccagctc gcttcagtgg cagtgggtct gggacctctt actctctcac aatcagcagt 300
gtggaggctg aggatgctgc cacttattac tgccagcagt atgatttttt cccatcgacg 360
ttcggtggag gcaccaagct ggaaatcaag cgggctgatg ctgcaccaac tgtatccatc 420
ttcccaccat ccagtgagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac 480
aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat 540
ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc 600
accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact 660
cacaagacat caacttcacc catcgtcaag agcttcaaca ggaatgagtg t 711

<210> 209
<211> 445
<212> PRT
<213> 小家鼠

<400> 209
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30
Tyr Met Asn Trp Val Lys Gln Ser His Gly Glu Ser Leu Glu Trp Ile
        35   40   45
Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asn Thr Ala Tyr
65   70   75   80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
            100   105   110
Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser
        115   120   125
Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
    130   135   140
Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val
145   150   155   160
Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
                165   170   175
Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
            180   185   190

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Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro
        195                 200                 205
Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
    210                 215                 220
Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
225                 230                 235                 240
Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
                245                 250                 255
Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
            260                 265                 270
Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln
        275                 280                 285
Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
    290                 295                 300
Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
305                 310                 315                 320
Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335
Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
            340                 345                 350
Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr
        355                 360                 365
Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln
    370                 375                 380
Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
385                 390                 395                 400
Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu
                405                 410                 415
Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
            420                 425                 430
His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445
```

<210> 210
<211> 1335
<212> DNA
<213> 小家鼠

<400> 210
gaggtccagc tgcaacaatc tggacctgag ctggtgaagc ctggggcttc agtgaagatg 60
tcctgtaagg cttctggata cacattcact gactactaca tgaactgggt gaagcagagc 120
catggagaga gccttgagtg gattggagat attaatcctt acaacgatga tactacctac 180
aaccacaagt tcaagggcaa ggccacattg actgtagaca aatcctccaa cacagcctac 240
atgcagctca acagcctgac atctgaggac tctgcagtct attactgtgc aagagagacg 300
gccgttatta ctacgaatgc tatggactac tggggtcaag gaacctcagt caccgtctcc 360
tcagccaaaa cgacacccccc atctgtctat ccactggccc ctggatctgc tgcccaaact 420
aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg 480
acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct 540
gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc 600

gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 660
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc 720
ttcccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt 780
gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg 840
gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca 900
gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 960
gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga 1020
ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1080
gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag 1140
tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc 1200
tcttacttca tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact 1260
ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1320
cactctcctg gtaaa 1335

<210> 211
<211> 464
<212> PRT
<213> 小家鼠

<400> 211
Met Gly Trp Asn Trp Ile Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
 1   5   10   15
Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys
            20   25   30
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35   40   45
Thr Asp Tyr Tyr Met Asn Trp Val Lys Gln Ser His Gly Glu Ser Leu
    50   55   60
Glu Trp Ile Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn
65   70   75   80
His Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asn
                85   90   95
Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val
            100   105   110
Tyr Tyr Cys Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp
        115   120   125
Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr
    130   135   140
Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
145   150   155   160
Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
                165   170   175
Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
            180   185   190
Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
        195   200   205
Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
    210   215   220
Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
225   230   235   240

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Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
                245                 250                 255
Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
            260                 265                 270
Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
        275                 280                 285
Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
    290                 295                 300
Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
305                 310                 315                 320
Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
                325                 330                 335
Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
            340                 345                 350
Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
        355                 360                 365
Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
    370                 375                 380
Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
385                 390                 395                 400
Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
                405                 410                 415
Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser
            420                 425                 430
Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
        435                 440                 445
Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
    450                 455                 460
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<210> 212
<211> 1392
<212> DNA
<213> 小家鼠

<400> 212

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atgggatgga actggatctt tctcttcctc ttgtcaggaa ctgcaggtgt ctactctgag 60
gtccagctgc aacaatctgg acctgagctg gtgaagcctg gggcttcagt gaagatgtcc 120
tgtaaggctt ctggatacac attcactgac tactacatga actgggtgaa gcagagccat 180
ggagagagcc ttgagtggat tggagatatt aatccttaca acgatgatac tacctacaac 240
cacaagttca agggcaaggc cacattgact gtagacaaat cctccaacac agcctacatg 300
cagctcaaca gcctgacatc tgaggactct gcagtctatt actgtgcaag agagacggcc 360
gttattacta cgaatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 420
gccaaaacga caccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac 480
tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc 540
tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac 600
ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc 660
acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg 720
gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 780
cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg 840
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gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag 900
gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 960
agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 1020
aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg 1080
aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 1140
agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg 1200
aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 1260
tacttcatct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 1320
acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1380
tctcctggta aa 1392

<210> 213
<211> 215
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 213
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Val Thr Ser Ser
20 25 30
Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Phe Phe Pro
85 90 95
Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205
Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 214
<211> 645
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 214
gacatccagc tgacccagag ccccagcttc ctttccgcat ccgttggtga ccgagtaaca 60
atcacatgcc gcgcctcatc ttcagttaca tcttcttatc ttaattggta tcaacaaaaa 120
ccaggaaaag cacctaaact tcttatatac tctacatcta atctcgcatc aggagttccc 180
tctcgatttt caggatctgg atcaggcaca gaatttacac ttactatatc atcactccaa 240
ccagaagact tcgccactta ttactgccaa caatacgatt tttttccaag cacattcgga 300
ggaggtacaa aagtagaaat caagcgtacg gtggctgcac catctgtctt catcttcccg 360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420
tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 600
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 645

<210> 215
<211> 237
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 215
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1   5   10   15
Leu Pro Gly Ala Arg Cys Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe
            20   25   30
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35   40   45
Ser Ser Val Thr Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
    50   55   60
Lys Ala Pro Lys Leu Leu Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly
65   70   75   80
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu
                85   90   95
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
            100   105   110
Gln Tyr Asp Phe Phe Pro Ser Thr Phe Gly Gly Gly Thr Lys Val Glu
        115   120   125
Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
    130   135   140
Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
145   150   155   160

Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala
165 170 175
Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys
180 185 190
Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp
195 200 205
Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
210 215 220
Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 216
<211> 711
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 216
atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct cccaggtgcc 60
agatgtgaca tccagctgac ccagagcccc agcttccttt ccgcatccgt tggtgaccga 120
gtaacaatca catgccgcgc ctcatcttca gttacatctt cttatcttaa ttggtatcaa 180
caaaaaccag gaaaagcacc taaacttctt atatactcta catctaatct cgcatcagga 240
gttccctctc gattttcagg atctggatca ggcacagaat ttacacttac tatatcatca 300
ctccaaccag aagacttcgc cacttattac tgccaacaat acgatttttt tccaagcaca 360
ttcggaggag gtacaaaagt agaaatcaag cgtacggtgg ctgcaccatc tgtcttcatc 420
ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat 480
aacttctatc ccagagaggc caaagtacag tggaaggtgg ataacgccct ccaatcgggt 540
aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 600
accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc 660
catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg t 711

<210> 217
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 217
Glu 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 Asp Tyr
20 25 30
Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45
Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe

50 55 60
Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala 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 His 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 Phe Arg Val Val Ser
290 295 300
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg 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 Met Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln 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 Pro Gly Lys
435 440 445

<210> 218
<211> 1341
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 218
gaggtgcagc tggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaaggtt 60
agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc 120
cctggacaaa gacttgaatg gatgggagac attaaccctt ataacgacga cactacatac 180
aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatc aaccgcctat 240
atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact 300
gccgttatta ctactaacgc tatggattac tggggtcaag gaaccactgt taccgtctct 360
agtgcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa a 1341

<210> 219
<211> 466
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 219
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
 1   5   10   15
Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20   25   30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35   40   45
Thr Asp Tyr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu

```
    50                  55                  60
Glu Trp Met Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn
65                  70                  75                  80
His Lys Phe Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser
                85                  90                  95
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110
Tyr Tyr Cys Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp
        115                 120                 125
Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140
Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145                 150                 155                 160
Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175
Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205
Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220
Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240
Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
```

450 455 460
Gly Lys
465

<210> 220
<211> 1398
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 220
atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60
gtgcagctgg tgcagagcgg cgccgaggtc aagaaacctg gagcaagcgt aaaggttagt 120
tgcaaagcat ctggatacac atttaccgac tactacatga attgggtacg acaagccccc 180
ggacaaagac ttgaatggat gggagacatt aacccttata acgacgacac tacatacaat 240
cataaattta aaggaagagt tacaattaca agagatacat ccgcatcaac cgcctatatg 300
gaactttcct cattgagatc tgaagacact gctgtttatt actgtgcaag agaaactgcc 360
gttattacta ctaacgctat ggattactgg ggtcaaggaa ccactgttac cgtctctagt 420
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 480
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 540
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 600
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 660
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 720
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 780
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacgtgc 840
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 900
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 960
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 1020
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1080
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1140
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1200
gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1260
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1320
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380
tccctgtctc cgggtaaa 1398

<210> 221
<211> 215
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 221
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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Asp Arg Val Thr Ile Thr Cys Ser Val Ser Ser Thr Ile Ser Ser Asn
            20                  25                  30
His Leu His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu
        35                  40                  45
Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
                85                  90                  95
Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205
Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> 222
<211> 645
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 222

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gacatccaga tgacccagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca 60
ataacatgca gcgtatcatc aactatatca tcaaatcatc ttcattggtt ccaacagaaa 120
cccggcaaag cacctaaatc acttatatac ggcacatcaa atctcgcatc aggcgttcct 180
tcaagatttt caggctctgg ctcaggcacc gactttactc ttacaatatc ctccctccaa 240
cccgaagact tcgcaaccta ttactgtcaa caatggtcct catatccact cacatttggc 300
ggcggcacaa aagtagaaat taaacgtacg gtggctgcac catctgtctt catcttcccg 360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420
tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 600
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt                  645
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<210> 223

<211> 237
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 223
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1   5   10   15
Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20   25   30
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Val Ser
        35   40   45
Ser Thr Ile Ser Ser Asn His Leu His Trp Phe Gln Gln Lys Pro Gly
    50   55   60
Lys Ala Pro Lys Ser Leu Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly
65   70   75   80
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85   90   95
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
            100   105   110
Gln Trp Ser Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu
        115   120   125
Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
    130   135   140
Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
145   150   155   160
Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala
                165   170   175
Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys
            180   185   190
Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp
        195   200   205
Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
    210   215   220
Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225   230   235

<210> 224
<211> 711
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 224
atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc 60

agatgtgaca tccagatgac ccagtctcca tcctccctct cagcatccgt aggcgataga 120
gttacaataa catgcagcgt atcatcaact atatcatcaa atcatcttca ttggttccaa 180
cagaaacccg gcaaagcacc taaatcactt atatacggca catcaaatct cgcatcaggc 240
gttccttcaa gattttcagg ctctggctca ggcaccgact ttactcttac aatatcctcc 300
ctccaacccg aagacttcgc aacctattac tgtcaacaat ggtcctcata tccactcaca 360
tttggcggcg gcacaaaagt agaaattaaa cgtacggtgg ctgcaccatc tgtcttcatc 420
ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat 480
aacttctatc ccagagaggc caaagtacag tggaaggtgg ataacgccct ccaatcgggt 540
aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 600
accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc 660
catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg t 711

<210> 225
<211> 451
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 225
Glu 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 Asp Phe Asn Ile Lys Asp Phe
            20   25   30
Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe
    50   55   60
Gln Asp Lys Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr Trp Tyr Phe
            100   105   110
Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        115   120   125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
    130   135   140
Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145   150   155   160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165   170   175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180   185   190
Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
        195   200   205
Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
    210   215   220
Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala

225 230 235 240
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270
Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
290 295 300
Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
305 310 315 320
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
325 330 335
Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400
Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445
Pro Gly Lys
450

<210> 226
<211> 1353
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 226
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgactt caacattaaa gacttctatc tacactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gattggaagg attgatcctg agaatggtga tactttatat 180
gacccgaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg 300
gattatttcc acgatggtac ctcctactgg tacttcgatg tctggggccg tggcaccctg 360
gtcaccgtct ctagtgcctc caccaagggc ccatcggtct tccccctggc gccctgctcc 420
aggagcacct ccgagagcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa 480
ccggtgacgg tgtcgtggaa ctcaggcgct ctgaccagcg gcgtgcacac cttcccagct 540
gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcaac 600

ttcggcaccc agacctacac ctgcaacgta gatcacaagc ccagcaacac caaggtggac 660
aagacagttg agcgcaaatg ttgtgtcgag tgcccaccgt gcccagcacc acctgtggca 720
ggaccgtcag tcttcctctt cccccccaaaa cccaaggaca ccctcatgat ctcccggacc 780
cctgaggtca cgtgcgtggt ggtggacgtg agccacgaag accccgaggt ccagttcaac 840
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccacggga ggagcagttc 900
aacagcacgt tccgtgtggt cagcgtcctc accgttgtgc accaggactg gctgaacggc 960
aaggagtaca agtgcaaggt ctccaacaaa ggcctcccag cccccatcga gaaaaccatc 1020
tccaaaacca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 1080
gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta ccccagcgac 1140
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacacctccc 1200
atgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg 1260
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1320
acgcagaaga gcctctccct gtctccgggt aaa 1353

<210> 227
<211> 470
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 227
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
 1   5   10   15
Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20   25   30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Asn Ile
        35   40   45
Lys Asp Phe Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50   55   60
Glu Trp Ile Gly Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp
65   70   75   80
Pro Lys Phe Gln Asp Lys Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85   90   95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100   105   110
Tyr Tyr Cys Ala Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr
        115   120   125
Trp Tyr Phe Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
    130   135   140
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145   150   155   160
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
                165   170   175
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
            180   185   190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
        195   200   205
Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr

210 215 220
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
225 230 235 240
Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
245 250 255
Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
260 265 270
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
275 280 285
Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
290 295 300
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
305 310 315 320
Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
325 330 335
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
340 345 350
Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
355 360 365
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
370 375 380
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385 390 395 400
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
405 410 415
Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
420 425 430
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
435 440 445
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
450 455 460
Ser Leu Ser Pro Gly Lys
465 470

<210> 228
<211> 1410
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 228
atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60
gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg gggcctcagt gaaggtctcc 120
tgcaaggctt ctgacttcaa cattaaagac ttctatctac actgggtgcg acaggcccct 180
ggacaagggc ttgagtggat tggaaggatt gatcctgaga atggtgatac tttatatgac 240
ccgaagttcc aggacaaggt caccatgacc acagacacgt ccaccagcac agcctacatg 300
gagctgagga gcctgagatc tgacgacacg gccgtgtatt actgtgcgag agaggcggat 360

tatttccacg atggtacctc ctactggtac ttcgatgtct ggggccgtgg caccctggtc 420
accgtctcta gtgcctccac caagggccca tcggtcttcc ccctggcgcc ctgctccagg 480
agcacctccg agagcacagc ggccctgggc tgcctggtca aggactactt ccccgaaccg 540
gtgacggtgt cgtggaactc aggcgctctg accagcggcg tgcacacctt cccagctgtc 600
ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc cagcaacttc 660
ggcacccaga cctacacctg caacgtagat cacaagccca gcaacaccaa ggtggacaag 720
acagttgagc gcaaatgttg tgtcgagtgc ccaccgtgcc cagcaccacc tgtggcagga 780
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccccct 840
gaggtcacgt gcgtggtggt ggacgtgagc cacgaagacc ccgaggtcca gttcaactgg 900
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cacgggagga gcagttcaac 960
agcacgttcc gtgtggtcag cgtcctcacc gttgtgcacc aggactggct gaacggcaag 1020
gagtacaagt gcaaggtctc caacaaaggc ctcccagccc ccatcgagaa aaccatctcc 1080
aaaaccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 1140
atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctaccc cagcgacatc 1200
gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac acctcccatg 1260
ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 1320
cagcaggggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1380
cagaagagcc tctccctgtc tccgggtaaa 1410

<210> 229
<211> 213
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 229
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Ile Ser Tyr Ile
            20   25   30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        35   40   45
Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50   55   60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65   70   75   80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asp Pro Leu Thr
                85   90   95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
            100   105   110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115   120   125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130   135   140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145   150   155   160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165   170   175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205
Asn Arg Gly Glu Cys
210

<210> 230
<211> 639
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 230
gacatccagt tgacccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgca gggccagctc aagtataagt tacatacact ggtatcagca aaaaccaggg 120
aaagccccta agctcctgat ctatgccaca tccaacctgg cttctggggt cccatcaagg 180
ttcagcggca gtggatctgg gacagaattc actctcacaa tcagcagcct gcagcctgaa 240
gattttgcaa cttattactg tcagcagtgg agtagtgacc cactcacgtt cggcggaggg 300
accaaggtgg agatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct 360
gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420
agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480
agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540
agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600
agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639

<210> 231
<211> 235
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 231
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe
20 25 30
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45
Ser Ser Ile Ser Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
50 55 60
Pro Lys Leu Leu Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro
65 70 75 80
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp
100 105 110
Ser Ser Asp Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
210 215 220
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 232
<211> 705
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 232
atggacatga gggtccccgc tcagctcctg gggctcctgc tgctctggct cccaggtgcc 60
agatgtgaca tccagttgac ccagtctcca tccttcctgt ctgcatctgt aggagacaga 120
gtcaccatca cttgcagggc cagctcaagt ataagttaca tacactggta tcagcaaaaa 180
ccagggaaag cccctaagct cctgatctat gccacatcca acctggcttc tggggtccca 240
tcaaggttca gcggcagtgg atctgggaca gaattcactc tcacaatcag cagcctgcag 300
cctgaagatt ttgcaactta ttactgtcag cagtggagta gtgacccact cacgttcggc 360
ggagggacca aggtggagat caaacgtacg gtggctgcac catctgtctt catcttcccg 420
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 480
tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 540
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 600
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 660
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 705

<210> 233
<211> 447
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 233

Glu 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 Phe Asp Ile Lys Asp Tyr
20 25 30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
50 55 60
Pro Gly Lys Val Thr Met Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala 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 His 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 Phe Arg Val Val Ser
290 295 300
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg 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 Met Leu Asp Ser

385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln 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 Pro Gly Lys
435 440 445

<210> 234
<211> 1341
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 234
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tcctgcaagg cttctggatt cgacattaag gactactata tacactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatcggaagg gttgatcctg acaatggtga gactgaattt 180
gccccgaagt tcccgggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac 300
tacgatggta cctacacctg gtttccttat tggggccaag ggactctggt caccgtctct 360
agtgcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgccccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa a 1341

<210> 235
<211> 466
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 235

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Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asp Ile
        35                  40                  45
Lys Asp Tyr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60
Glu Trp Ile Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala
65                  70                  75                  80
Pro Lys Phe Pro Gly Lys Val Thr Met Thr Thr Asp Thr Ser Ile Ser
                85                  90                  95
Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110
Tyr Tyr Cys Ala Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro
        115                 120                 125
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140
Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145                 150                 155                 160
Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175
Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205
Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220
Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240
Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
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385 390 395 400
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
405 410 415
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
420 425 430
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
435 440 445
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
450 455 460
Gly Lys
465

<210> 236
<211> 1398
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

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gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg gggcctcagt gaaggtctcc 120
tgcaaggctt ctggattcga cattaaggac tactatatac actgggtgcg acaggcccct 180
ggacaagggc ttgagtggat cggaagggtt gatcctgaca atggtgagac tgaatttgcc 240
ccgaagttcc cgggcaaggt caccatgacc acagacacgt ccatcagcac agcctacatg 300
gagctgagca ggctgagatc tgacgacacg gccgtgtatt actgtgcgag agaagactac 360
gatggtacct acacctggtt tccttattgg ggccaaggga ctctggtcac cgtctctagt 420
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 480
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 540
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 600
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 660
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 720
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 780
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacgtgc 840
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 900
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 960
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 1020
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1080
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1140
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1200
gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1260
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1320
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380
tccctgtctc cgggtaaa 1398

<210> 237
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<212> PRT

<213> 小家鼠

<400> 237
Gly Thr Ser Asn Leu Ala Ser
 1   5

<210> 238
<211> 8
<212> PRT
<213> 小家鼠

<400> 238
Gln Gln Trp Thr Thr Thr Tyr Thr
 1   5

<210> 239
<211> 11
<212> PRT
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<400> 239
Arg Ala Ser Gln Asp Ile Ser Ser Tyr Leu Asn
 1   5   10

<210> 240
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Ser Thr Ser Arg Leu Asn Ser
 1   5

<210> 241
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Gln Gln Asp Ile Lys His Pro Thr
 1   5

<210> 242
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Lys Ala Ser Gln Asp Val Phe Thr Ala Val Ala
 1   5   10

<210> 243
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<213> 小家鼠

<400> 243
Trp Ala Ser Thr Arg His Thr
 1   5

<210> 244
<211> 9
<212> PRT
<213> 小家鼠

<400> 244
Gln Gln Tyr Ser Ser Tyr Pro Leu Thr
 1   5

<210> 245
<211> 5
<212> PRT
<213> 小家鼠

<400> 245
Asp Tyr Asn Met His
 1   5

<210> 246
<211> 17
<212> PRT
<213> 小家鼠

<400> 246
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
 1   5   10   15
Gly

<210> 247

<211> 14
<212> PRT
<213> 小家鼠

<400> 247
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
 1   5   10

<210> 248
<211> 5
<212> PRT
<213> 小家鼠

<400> 248
Asp Tyr Asn Met His
 1   5

<210> 249
<211> 17
<212> PRT
<213> 小家鼠

<400> 249
Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn Gln Lys Phe Lys
 1   5   10   15
Gly

<210> 250
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<212> PRT
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<400> 250
Leu Val Tyr Asp Gly Ser Tyr Glu Asp Trp Tyr Phe Asp Val
 1   5   10

<210> 251
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<213> 小家鼠

<400> 251
Asp Tyr Asn Met His
 1   5

<210> 252
<211> 17
<212> PRT
<213> 小家鼠

<400> 252
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Gln Phe Lys
 1   5   10   15
Gly

<210> 253
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<212> PRT
<213> 小家鼠

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Leu Gly Tyr Val Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
 1   5   10

<210> 254
<211> 5
<212> PRT
<213> 小家鼠

<400> 254
Asp Tyr Asn Met His
 1   5

<210> 255
<211> 17
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<400> 255
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
 1   5   10   15
Gly

<210> 256
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<400> 256
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
 1   5   10

<210> 257
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<213> 小家鼠

<400> 257
Asp Tyr Asn Met His
 1   5

<210> 258
<211> 17
<212> PRT
<213> 小家鼠

<400> 258
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
 1   5   10   15
Gly

<210> 259
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Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
 1   5   10

<210> 260
<211> 5
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<213> 小家鼠

<400> 260
Asp Tyr Asn Met His
 1   5

<210> 261
<211> 17
<212> PRT

<213> 小家鼠

<400> 261
Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe Lys
 1   5   10   15
Gly

<210> 262
<211> 14
<212> PRT
<213> 小家鼠

<400> 262
Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
 1   5   10

<210> 263
<211> 5
<212> PRT
<213> 小家鼠

<400> 263
Asp Tyr Asn Met His
 1   5

<210> 264
<211> 17
<212> PRT
<213> 小家鼠

<400> 264
Glu Ile Asn Pro Asn Ser Gly Gly Ser Gly Tyr Asn Gln Lys Phe Lys
 1   5   10   15
Gly

<210> 265
<211> 14
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<400> 265
Leu Gly Tyr Tyr Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
 1   5   10

<210> 266
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<213> 小家鼠

<400> 266
Asp Tyr Tyr Ile His
 1   5

<210> 267
<211> 17
<212> PRT
<213> 小家鼠

<400> 267
Arg Ile Asp Pro Asp Asn Gly Glu Ser Thr Tyr Val Pro Lys Phe Gln
 1   5   10   15
Gly

<210> 268
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<400> 268
Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val Asp Tyr
 1   5   10

<210> 269
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<213> 小家鼠

<400> 269
Asp Tyr Ile Met His
 1   5

<210> 270
<211> 17
<212> PRT
<213> 小家鼠

<400> 270
Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe Lys

1 5 10 15
Gly

<210> 271
<211> 11
<212> PRT
<213> 小家鼠

<400> 271
Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr
1 5 10

<210> 272
<211> 5
<212> PRT
<213> 小家鼠

<400> 272
Asp Tyr Tyr Met His
1 5

<210> 273
<211> 17
<212> PRT
<213> 小家鼠

<400> 273
Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe Gln
1 5 10 15
Gly

<210> 274
<211> 10
<212> PRT
<213> 小家鼠

<400> 274
Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr
1 5 10

<210> 275
<211> 10
<212> PRT

<213> 小家鼠

<400> 275
Arg Ala Ser Ser Ser Val Tyr Tyr Met His
 1   5   10

<210> 276
<211> 7
<212> PRT
<213> 小家鼠

<400> 276
Ala Thr Ser Asn Leu Ala Ser
 1   5

<210> 277
<211> 9
<212> PRT
<213> 小家鼠

<400> 277
Gln Gln Trp Ser Ser Asp Pro Leu Thr
 1   5

<210> 278
<211> 12
<212> PRT
<213> 小家鼠

<400> 278
Ser Val Ser Ser Thr Ile Ser Ser Asn His Leu His
 1   5   10

<210> 279
<211> 7
<212> PRT
<213> 小家鼠

<400> 279
Gly Thr Ser Asn Leu Ala Ser
 1   5

<210> 280
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<213> 小家鼠

<400> 280
Gln Gln Trp Ser Ser Tyr Pro Leu Thr
 1   5

<210> 281
<211> 10
<212> PRT
<213> 小家鼠

<400> 281
Arg Ala Ser Ser Ser Ile Ser Tyr Ile His
 1   5   10

<210> 282
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<400> 282
Ala Thr Ser Asn Leu Ala Ser
 1   5

<210> 283
<211> 9
<212> PRT
<213> 小家鼠

<400> 283
Gln Gln Trp Ser Ser Asp Pro Leu Thr
 1   5

<210> 284
<211> 12
<212> PRT
<213> 小家鼠

<400> 284
Arg Ala Ser Ser Ser Val Thr Ser Ser Tyr Leu Asn
 1   5   10

<210> 285
<211> 7
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<213> 小家鼠

<400> 285
Ser Thr Ser Asn Leu Ala Ser
 1   5

<210> 286
<211> 9
<212> PRT
<213> 小家鼠

<400> 286
Gln Gln Tyr Asp Phe Phe Pro Ser Thr
 1   5

<210> 287
<211> 5
<212> PRT
<213> 小家鼠

<400> 287
Asp Tyr Phe Ile His
 1   5

<210> 288
<211> 17
<212> PRT
<213> 小家鼠

<400> 288
Arg Leu Asp Pro Glu Asp Gly Glu Ser Asp Tyr Ala Pro Lys Phe Gln
 1   5   10   15
Asp

<210> 289
<211> 12
<212> PRT
<213> 小家鼠

<400> 289
Glu Asp Tyr Asp Gly Thr Tyr Thr Phe Phe Pro Tyr
 1   5   10

<210> 290

<211> 5
<212> PRT
<213> 小家鼠

<400> 290
Asp Phe Tyr Leu His
 1   5

<210> 291
<211> 17
<212> PRT
<213> 小家鼠

<400> 291
Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe Gln
 1   5   10   15
Asp

<210> 292
<211> 16
<212> PRT
<213> 小家鼠

<400> 292
Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr Trp Tyr Phe Asp Val
 1   5   10   15

<210> 293
<211> 5
<212> PRT
<213> 小家鼠

<400> 293
Asp Tyr Tyr Ile His
 1   5

<210> 294
<211> 17
<212> PRT
<213> 小家鼠

<400> 294
Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe Pro
 1   5   10   15
Gly

<210> 295
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<212> PRT
<213> 小家鼠

<400> 295
Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr
 1   5   10

<210> 296
<211> 5
<212> PRT
<213> 小家鼠

<400> 296
Asp Tyr Tyr Met Asn
 1   5

<210> 297
<211> 17
<212> PRT
<213> 小家鼠

<400> 297
Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe Lys
 1   5   10   15
Gly

<210> 298
<211> 11
<212> PRT
<213> 小家鼠

<400> 298
Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp
 1   5   10

<210> 299
<211> 130
<212> PRT
<213> 小家鼠

<400> 299
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Met Leu Ile Ser Val Thr
 1   5   10   15
Val Ile Leu Ser Ser Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Leu
            20   25   30
Met Ala Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Val Ser
        35   40   45
Ser Ser Ile Ser Ser Ser Asn Leu His Trp Ser Gln Gln Lys Ser Gly
    50   55   60
Thr Ser Pro Lys Leu Trp Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly
65   70   75   80
Val Pro Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
                85   90   95
Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
            100   105   110
Gln Trp Thr Thr Thr Tyr Thr Phe Gly Ser Gly Thr Lys Leu Glu Leu
        115   120   125
Lys Arg
    130

<210> 300
<211> 390
<212> DNA
<213> 小家鼠

<400> 300
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agtggagaaa ttgtgctcac ccagtctcca gcactcatgg ctgcatctcc aggggagaag 120
gtcaccatca cctgcagtgt cagctcgagt ataagttcca gcaacttaca ctggtcccag 180
cagaagtcag gaacctcccc caaactctgg atttatggca catccaacct tgcttctgga 240
gtccctgttc gcttcagtgg cagtggatct gggacctctt attctctcac aatcagcagc 300
atggaggctg aagatgctgc cacttattac tgtcaacagt ggactactac gtatacgttc 360
ggatcgggga ccaagctgga gctgaaacgt   390

<210> 301
<211> 141
<212> PRT
<213> 小家鼠

<400> 301
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Val Asn Ser Glu Val Gln Leu Arg Gln Ser Gly Ala Asp Leu Val Lys
            20   25   30
Pro Gly Ala Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
        35   40   45
Lys Asp Tyr Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
    50   55   60
Glu Trp Ile Gly Arg Ile Asp Pro Asp Asn Gly Glu Ser Thr Tyr Val

65 70 75 80
Pro Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn
85 90 95
Thr Ala Tyr Leu Gln Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Ile
100 105 110
Tyr Tyr Cys Gly Arg Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val
115 120 125
Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
130 135 140

<210> 302
<211> 423
<212> DNA
<213> 小家鼠

<400> 302
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gtgcagttgc ggcagtctgg ggcagacctt gtgaagccag gggcctcagt caagttgtcc 120
tgcacagctt ctggcttcaa cattaaagac tactatatac actgggtgaa gcagaggcct 180
gaacagggcc tggagtggat tggaaggatt gatcctgata atggtgaaag tacatatgtc 240
ccgaagttcc agggcaaggc cactataaca gcagacacat catccaacac agcctaccta 300
caactcagaa gcctgacatc tgaggacact gccatctatt attgtgggag agaggggctc 360
gactatggtg actactatgc tgtggactac tggggtcaag gaacctcggt cacagtctcg 420
agc 423

<210> 303
<211> 130
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 303
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
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Leu Pro Gly Ala Arg Cys Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe
20 25 30
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Val Ser
35 40 45
Ser Ser Ile Ser Ser Ser Asn Leu His Trp Tyr Gln Gln Lys Pro Gly
50 55 60
Lys Ala Pro Lys Leu Leu Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly
65 70 75 80
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu
85 90 95
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
100 105 110
Gln Trp Thr Thr Thr Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile

115 120 125
Lys Arg
130

<210> 304
<211> 390
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 304
atggatatgc gcgtgccggc gcagctgctg ggcctgctgc tgctgtggct gccgggcgcg 60
cgctgcgata ttcagctgac ccagagcccg agctttctga gcgcgagcgt gggcgatcgc 120
gtgaccatta cctgcagcgt gagcagcagc attagcagca gcaacctgca ttggtatcag 180
cagaaaccgg gcaaagcgcc gaaactgctg atttatggca ccagcaacct ggcgagcggc 240
gtgccgagcc gctttagcgg cagcggcagc ggcaccgaat ttaccctgac cattagcagc 300
ctgcagccgg aagattttgc gacctattat tgccagcagt ggaccaccac ctatacctt 360
ggccagggca ccaaactgga aattaaacgt 390

<210> 305
<211> 141
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 305
Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Pro Thr Gly
1 5 10 15
Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile
35 40 45
Lys Asp Tyr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60
Glu Trp Met Gly Arg Ile Asp Pro Asp Asn Gly Glu Ser Thr Tyr Val
65 70 75 80
Pro Lys Phe Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
85 90 95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
100 105 110
Tyr Tyr Cys Ala Arg Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val
115 120 125
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
130 135 140

<210> 306
<211> 423
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 306
atggattgga cctggagcat tctgtttctg gtggcggcgc cgaccggcgc gcatagcgaa 60
gtgcagctgg tgcagagcgg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc 120
tgcaaagcga gcggctttaa cattaaagat tattatattc attgggtgcg ccaggcgccg 180
ggccagggcc tggaatggat gggccgcatt gatccggata acggcgaaag cacctatgtg 240
ccgaaatttc agggccgcgt gaccatgacc accgatacca gcaccagcac cgcgtatatg 300
gaactgcgca gcctgcgcag cgatgatacc gcggtgtatt attgcgcgcg cgaaggcctg 360
gattatggcg attattatgc ggtggattat tggggccagg gcaccctggt gaccgtctcg 420
agc 423

<210> 307
<211> 127
<212> PRT
<213> 小家鼠

<400> 307
Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
 1   5   10   15
Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
            20   25   30
Ala Ser Leu Gly Asp Arg Val Asn Ile Ser Cys Arg Ala Ser Gln Asp
        35   40   45
Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
    50   55   60
Lys Leu Leu Ile Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser
65   70   75   80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser
                85   90   95
Asn Leu Ala Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ile
            100   105   110
Lys His Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg
        115   120   125

<210> 308
<211> 381
<212> DNA
<213> 小家鼠

<400> 308
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcaac 120
atcagctgca gggcaagtca ggacattagc agttatttaa actggtatca gcagaaacca 180
gatggaactg ttaaactcct gatctactcc acatcaagat taaactcagg agtcccatca 240
aggttcagtg gcagtgggtc tgggacagat tattctctca ctattagcaa cctggcacaa 300
gaagatattg ccacttactt ttgccaacag gatattaagc atccgacgtt cggtggaggc 360
accaagttgg agctgaaacg t 381

<210> 309
<211> 139
<212> PRT
<213> 小家鼠

<400> 309
Met Glu Trp Ile Trp Ile Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
 1   5   10   15
Val His Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys
            20   25   30
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Phe Thr Phe
        35   40   45
Thr Asp Tyr Ile Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu
    50   55   60
Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn
65   70   75   80
Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser
                85   90   95
Thr Ala Tyr Met Asp Leu Ser Ser Leu Thr Ser Glu Gly Ser Ala Val
            100   105   110
Tyr Tyr Cys Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr
        115   120   125
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130   135

<210> 310
<211> 417
<212> DNA
<213> 小家鼠

<400> 310
atggaatgga tctggatatt tctcttcctc ctgtcaggaa ctgcaggtgt ccactctgag 60
gtccagctgc agcagtctgg acctgagctg gtaaagcctg gggcttcagt gaagatgtcc 120
tgcaaggctt ctgggttcac attcactgac tacattatgc actgggtgaa gcagaagcct 180
gggcagggcc ttgagtggat tggatatatt aatccttaca atgatgatac tgaatacaat 240
gagaagttca aaggcaaggc cacactgact tcagacaaat cctccagcac agcctacatg 300
gatctcagca gtctgacctc tgagggctct gcggtctatt actgtgcaag atcgatttat 360
tactacgatg ccccgtttgc ttactggggc caagggactc tggtcacagt ctcgagc 417

<210> 311
<211> 127
<212> PRT

<213> 人工序列

<220>
<223> 人化抗體序列

<400> 311
Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
 1   5   10   15
Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
            20   25   30
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp
        35   40   45
Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
    50   55   60
Lys Leu Leu Ile Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser
65   70   75   80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85   90   95
Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Ile
            100   105   110
Lys His Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
        115   120   125

<210> 312
<211> 381
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 312
atgatgtcct ctgctcagtt ccttggtctc ctgttgctct gttttcaagg taccagatgt 60
gatatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtga ccgtgtcacc 120
atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca 180
gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca 240
cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct 300
gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtcaaggc 360
accaaggtgg agatcaaacg t   381

<210> 313
<211> 139
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 313

```
Met Glu Trp Ile Trp Ile Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
 1               5                  10                  15
Val His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30
Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
        35                  40                  45
Thr Asp Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60
Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn
65                  70                  75                  80
Glu Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser
                85                  90                  95
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110
Tyr Tyr Cys Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr
        115                 120                 125
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135
```

<210> 314
<211> 107
<212> PRT
<213> 小家鼠

<400> 314

```
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1               5                  10                  15
Asp Arg Val Asn Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45
Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Ala Gln
65                  70                  75                  80
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ile Lys His Pro Thr
                85                  90                  95
Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg
            100                 105
```

<210> 315
<211> 128
<212> PRT
<213> 小家鼠

<400> 315

```
Met Lys Ser Gln Thr Gln Val Phe Val Tyr Met Leu Leu Trp Leu Ser
 1               5                  10                  15
```

Gly Val Glu Gly Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser
            20   25   30
Thr Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp
        35   40   45
Val Phe Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro
    50   55   60
Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp
65   70   75   80
Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85   90   95
Asn Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Ser
            100   105   110
Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
        115   120   125

<210> 316
<211> 381
<212> DNA
<213> 小家鼠

<400> 316
atgaagtcac agacccaggt ctttgtatac atgttgctgt ggttgtctgg tgttgaagga 60
gacattgtga tgacccagtc tcacaaattc atgtccacgt cagtaggaga cagggtcacc 120
atcacctgca aggccagtca ggatgtcttt actgctgtag cctggtatca acagaaacca 180
ggacaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccctgat 240
cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcagtct 300
gaagacttgg cagattattt ctgtcaacaa tatagcagct atcctctcac gttcggtgct 360
gggaccaagt tggagctgaa a   381

<210> 317
<211> 138
<212> PRT
<213> 小家鼠

<400> 317
Met Gly Trp Asn Trp Ile Ile Phe Phe Leu Met Ala Val Val Thr Gly
 1   5   10   15
Val Asn Ser Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg
            20   25   30
Pro Gly Ala Leu Val Lys Leu Ser Cys Lys Ala Ser Gly Phe Asn Ile
        35   40   45
Lys Asp Tyr Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
    50   55   60
Glu Trp Ile Gly Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp
65   70   75   80
Pro Lys Phe Gln Gly Lys Ala Ser Ile Thr Thr Asp Thr Ser Ser Asn
                85   90   95
Thr Ala Tyr Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val
            100   105   110

Tyr Tyr Cys Ala Tyr Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr Trp
115 120 125
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
130 135

<210> 318
<211> 411
<212> DNA
<213> 小家鼠

<400> 318
atgggatgga actggatcat cttcttcctg atggcagtgg ttacaggggt caattcagag 60
gttcagctgc agcagtctgg ggctgagctt gtgaggccag gggccttagt caagttgtcc 120
tgcaaagctt ctggcttcaa tattaaagac tactatatgc actgggtgaa gcagaggcct 180
gaacagggcc tggagtggat tggaaggatt gatcctgaga atggtgatat tatatatgac 240
ccgaagttcc agggcaaggc cagtataaca acagacacat cctccaacac agcctacctg 300
cagctcagca gcctgacgtc tgaggacact gccgtctatt actgtgctta cgatgctggt 360
gaccccgcct ggtttactta ctggggccaa gggactctgg tcaccgtctc g 411

<210> 319
<211> 130
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 319
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45
Gln Asp Val Phe Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60
Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly Val
65 70 75 80
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110
Tyr Ser Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125
Lys Arg
130

<210> 320

<211> 390
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 320
atggatatgc gcgtgccggc gcagctgctg ggcctgctgc tgctgtggct gcgcggcgcg 60
cgctgcgata tccagatgac ccagagcccg agcagcctga gcgcgagcgt gggcgatcgc 120
gtgaccatta cctgcaaagc gagccaggat gtgtttaccg cggtggcgtg gtatcagcag 180
aaaccgggca aagcgccgaa actgctgatt tattgggcga gcacccgcca taccggcgtg 240
ccgagtcgct ttagcggcag cggcagcggc accgatttta ccctgaccat tagcagcctg 300
cagccggaag attttgcgac ctattattgc cagcagtata gcagctatcc gctgaccttt 360
ggcggcggca ccaaagtgga aattaaacgt 390

<210> 321
<211> 138
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 321
Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Pro Thr Gly
 1   5   10   15
Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20   25   30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile
        35   40   45
Lys Asp Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50   55   60
Glu Trp Ile Gly Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp
65   70   75   80
Pro Lys Phe Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85   90   95
Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100   105   110
Tyr Tyr Cys Ala Tyr Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr Trp
        115   120   125
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130   135

<210> 322
<211> 414
<212> DNA
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 322
atggattgga cctggagcat tctgtttctg gtggcggcgc cgaccggcgc gcatagcgaa 60
gtgcagctgg tgcagagcgg cgcggaagtg aaaaaaccgg gcgcgagcgt gaaagtgagc 120
tgcaaagcga gcggctttaa cattaaagat tattatatgc attgggtgcg ccaggcgccg 180
ggccagggcc tggaatggat cggccgcatt gatccggaaa acggcgatat tatttatgat 240
ccgaaatttc agggccgcgt gaccatgacc accgatacca gcaccagcac cgcgtatatg 300
gaactgcgca gcctgcgcag cgatgatacc gcggtgtatt attgcgcgta tgatgcgggc 360
gatccggcgt ggtttaccta ttggggccag ggcaccctgg tgaccgtctc gagc 414

<210> 323
<211> 106
<212> PRT
<213> 小家鼠

<400> 323
Thr Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
 1   5   10   15
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
            20   25   30
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
        35   40   45
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
    50   55   60
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
65   70   75   80
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
                85   90   95
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
            100   105

<210> 324
<211> 324
<212> PRT
<213> 小家鼠

<400> 324
Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
 1   5   10   15
Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
            20   25   30
Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
        35   40   45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
    50   55   60
Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
65   70   75   80

```
Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
                85                  90                  95
Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
            100                 105                 110
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
        115                 120                 125
Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
    130                 135                 140
Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
145                 150                 155                 160
Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
                165                 170                 175
Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
            180                 185                 190
Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
        195                 200                 205
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
    210                 215                 220
Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
225                 230                 235                 240
Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
                245                 250                 255
Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
            260                 265                 270
Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
        275                 280                 285
Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
    290                 295                 300
Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
305                 310                 315                 320
Ser Pro Gly Lys
```

<210> 325
<211> 106
<212> PRT
<213> 人類

<400> 325

```
Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1               5                  10                  15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
            20                  25                  30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
        35                  40                  45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
    50                  55                  60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65                  70                  75                  80
```

```
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
                85                  90                  95
Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
```

<210> 326
<211> 327
<212> PRT
<213> 人類

<400> 326

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1               5                  10                  15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300
```

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320
Leu Ser Leu Ser Leu Gly Lys
325

<210> 327
<211> 120
<212> PRT
<213> 小家鼠

<400> 327
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30
Ile Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Asp Leu Ser Ser Leu Thr Ser Glu Gly Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 328
<211> 120
<212> PRT
<213> 小家鼠

<400> 328
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30
Ile Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Asp Leu Ser Ser Leu Thr Ser Glu Gly Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 329
<211> 120
<212> PRT
<213> 小家鼠

<400> 329
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30
Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
50 55 60
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 330
<211> 226
<212> PRT
<213> 小家鼠

<400> 330
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30
Ile Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Asp Leu Ser Ser Leu Thr Ser Glu Gly Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Thr Val Ala Ala Pro Ser Val Phe
115 120 125

Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
130 135 140
Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
145 150 155 160
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
165 170 175
Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
180 185 190
Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
195 200 205
Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
210 215 220
Glu Cys
225

<210> 331
<211> 447
<212> PRT
<213> 小家鼠

<400> 331
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30
Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
50 55 60
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro 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 Phe Leu 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 Thr Leu 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 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 Lys
        435                 440                 445
```

<210> 332
<211> 107
<212> PRT
<213> 小家鼠

<400> 332

```
Asp Ile Gln Met Thr Gln Ile Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1               5                  10                  15
Asp Arg Val Ser Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Phe Lys Leu Leu Ile
        35                  40                  45
Phe Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Tyr Asn Leu Glu Gln
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Tyr
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 333
<211> 324
<212> PRT
<213> 小家鼠

<400> 333
Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
1 5 10 15
Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
20 25 30
Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
35 40 45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
50 55 60
Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
65 70 75 80
Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
85 90 95
Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
100 105 110
Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
115 120 125
Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
130 135 140
Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
145 150 155 160
Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
165 170 175
Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
180 185 190
Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
195 200 205
Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
210 215 220
Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
225 230 235 240
Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
245 250 255
Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
260 265 270
Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn
275 280 285
Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
290 295 300
Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
305 310 315 320
Ser Pro Gly Lys

<210> 334
<211> 213
<212> PRT
<213> 小家鼠

<400> 334
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1   5   10   15
Asp Arg Val Asn Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35   40   45
Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Ala Gln
65   70   75   80
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ile Lys His Pro Thr
                85   90   95
Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Thr Asp Ala Ala Pro
            100   105   110
Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
        115   120   125
Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
    130   135   140
Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
145   150   155   160
Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
                165   170   175
Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
            180   185   190
Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
        195   200   205
Asn Arg Asn Glu Cys
    210

<210> 335
<211> 444
<212> PRT
<213> 小家鼠

<400> 335
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
            20   25   30
Ile Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45

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Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Met Asp Leu Ser Ser Leu Thr Ser Glu Gly Ser Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val
        115                 120                 125
Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr
    130                 135                 140
Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr
145                 150                 155                 160
Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser
            180                 185                 190
Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala
        195                 200                 205
Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys
    210                 215                 220
Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe
225                 230                 235                 240
Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val
                245                 250                 255
Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe
            260                 265                 270
Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro
        275                 280                 285
Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro
    290                 295                 300
Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val
305                 310                 315                 320
Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
                325                 330                 335
Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys
            340                 345                 350
Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp
        355                 360                 365
Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro
    370                 375                 380
Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser
385                 390                 395                 400
Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala
                405                 410                 415
Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His
            420                 425                 430
His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440
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<210> 336
<211> 108
<212> PRT
<213> 小家鼠

<400> 336
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 Val Phe Thr Ala
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Trp Ala Ser Thr Arg His Thr 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 Ser Ser Tyr Pro Leu
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 337
<211> 324
<212> DNA
<213> 小家鼠

<400> 337
gatatccaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60
attacctgca aagcgagcca ggatgtgttt accgcggtgg cgtggtatca gcagaaaccg 120
ggcaaagcgc cgaaactgct gatttattgg gcgagcaccc gccataccgg cgtgccgagt 180
cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240
gaagattttg cgacctatta ttgccagcag tatagcagct atccgctgac ctttggcggc 300
ggcaccaaag tggaaattaa acgt   324

<210> 338
<211> 119
<212> PRT
<213> 小家鼠

<400> 338
Glu 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 Phe Asn Ile Lys Asp Tyr
            20   25   30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe

50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Tyr Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 339
<211> 357
<212> DNA
<213> 小家鼠

<400> 339
gaagtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg 60
agctgcaaag cgagcggctt taacattaaa gattattata tgcattgggt gcgccaggcg 120
ccgggccagg gcctggaatg gatcggccgc attgatccgg aaaacggcga tattatttat 180
gatccgaaat ttcagggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat 240
atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgcgc gtatgatgcg 300
ggcgatccgg cgtggtttac ctattggggc cagggcaccc tggtgaccgt ctcgagc 357

<210> 340
<211> 1395
<212> DNA
<213> 小家鼠

<400> 340
atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60
gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggt gaaggtctcc 120
tgcaaggctt ctggttttac cttcaccgac tatattatgc actgggtgcg tcaggccccc 180
ggtcaagggc ttgagtggat gggctatatc aacccttata atgatgacac cgaatacaac 240
gagaagttca agggccgtgt cacgattacc gcggacaaat ccacgagcac agcctacatg 300
gagctgagca gcctgcgctc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat 360
tactacgatg ccccgtttgc ttactggggc caagggactc tggtcaccgt ctctagtgcc 420
tccaccaagg gcccatcggt cttccccctg gcgccctgct ccaggagcac ctccgagagc 480
acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 540
aactcaggcg ctctgaccag cggcgtgcac accttcccag ctgtcctaca gtcctcagga 600
ctctactccc tcagcagcgt ggtgaccgtg ccctccagca acttcggcac ccagacctac 660
acctgcaacg tagatcacaa gcccagcaac accaaggtgg acaagacagt tgagcgcaaa 720
tgttgtgtcg agtgcccacc gtgcccagca ccacctgtgg caggaccgtc agtcttcctc 780
ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacgtgcgtg 840
gtggtggacg tgagccacga agaccccgag gtccagttca actggtacgt ggacggcgtg 900
gaggtgcata atgccaagac aaagccacgg gaggagcagt tcaacagcac gttccgtgtg 960
gtcagcgtcc tcaccgttgt gcaccaggac tggctgaacg gcaaggagta caagtgcaag 1020
gtctccaaca aaggcctccc agcccccatc gagaaaacca tctccaaaac caaagggcag 1080
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag 1140
gtcagcctga cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag 1200

agcaatgggc agccggagaa caactacaag accacacctc ccatgctgga ctccgacggc 1260
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc 1320
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc 1380
ctgtctccgg gtaaa 1395

<210> 341
<211> 213
<212> PRT
<213> 小家鼠

<400> 341
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Ile Lys His Pro Thr
                85   90   95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
            100   105   110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115   120   125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130   135   140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145   150   155   160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165   170   175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180   185   190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195   200   205
Asn Arg Gly Glu Cys
    210

<210> 342
<211> 639
<212> DNA
<213> 小家鼠

<400> 342
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtga ccgtgtcacc 60
atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca 180

cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtcaaggc 300
accaaggtgg agatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct 360
gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420
agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480
agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540
agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600
agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639

<210> 343
<211> 235
<212> PRT
<213> 小家鼠

<400> 343
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1   5   10   15
Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20   25   30
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35   40   45
Gln Asp Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50   55   60
Ala Pro Lys Leu Leu Ile Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val
65   70   75   80
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85   90   95
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100   105   110
Asp Ile Lys His Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        115   120   125
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130   135   140
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145   150   155   160
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165   170   175
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180   185   190
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195   200   205
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210   215   220
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225   230   235

<210> 344
<211> 705
<212> DNA

<213> 小家鼠

<400> 344
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcc 60
agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt aggtgaccgt 120
gtcaccatca cttgccgcgc aagtcaggat attagcagct atttaaattg gtatcagcag 180
aaaccaggga aagcccctaa gctcctgatc tattctactt cccgtttgaa tagtggggtc 240
ccatcacgct tcagtggcag tggctctggg acagatttca ctctcaccat cagcagtctg 300
caacctgaag attttgcaac ttactactgt caacaggata ttaaacaccc tacgttcggt 360
caaggcacca aggtggagat caaacgtacg gtggctgcac catctgtctt catcttcccg 420
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 480
tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 540
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 600
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 660
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 705

<210> 345
<211> 446
<212> PRT
<213> 小家鼠

<400> 345
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
            20   25   30
Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro 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 Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
        195   200   205
Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
    210   215   220

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Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225                 230                 235                 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
    290                 295                 300
Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320
Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335
Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu 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 Met 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 Lys
        435                 440                 445
```

<210> 346
<211> 1338
<212> DNA
<213> 小家鼠

<400> 346

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gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggttt taccttcacc gactatatta tgcactgggt gcgtcaggcc 120
cctggtcaag ggcttgagtg gatgggctat atcaaccctt ataatgatga caccgaatac 180
aacgagaagt tcaagggccg tgtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgcg ctctgaggac acggccgtgt attactgtgc gcgttcgatt 300
tattactacg atgccccgtt tgcttactgg ggccaaggga ctctggtcac cgtctctagt 360
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 420
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 600
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 660
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 720
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc 780
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 840
```

gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 900
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 960
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1020
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1140
gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1200
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320
tccctgtctc cgggtaaa 1338

<210> 347
<211> 465
<212> PRT
<213> 小家鼠

<400> 347
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
 1   5   10   15
Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20   25   30
Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
        35   40   45
Thr Asp Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50   55   60
Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn
65   70   75   80
Glu Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser
                85   90   95
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100   105   110
Tyr Tyr Cys Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr
        115   120   125
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130   135   140
Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
145   150   155   160
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165   170   175
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180   185   190
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195   200   205
Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
    210   215   220
Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
225   230   235   240
Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
                245   250   255
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            260   265   270

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
275 280 285
Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
290 295 300
Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
305 310 315 320
Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
325 330 335
Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
340 345 350
Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
355 360 365
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
370 375 380
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385 390 395 400
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
405 410 415
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
420 425 430
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
435 440 445
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
450 455 460
Lys
465

<210> 348
<211> 1395
<212> DNA
<213> 小家鼠

<400> 348
atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60
gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggt gaaggtctcc 120
tgcaaggctt ctggttttac cttcaccgac tatattatgc actgggtgcg tcaggcccct 180
ggtcaagggc ttgagtggat gggctatatc aacccttata atgatgacac cgaatacaac 240
gagaagttca agggccgtgt cacgattacc gcggacaaat ccacgagcac agcctacatg 300
gagctgagca gcctgcgctc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat 360
tactacgatg ccccgtttgc ttactggggc caagggactc tggtcaccgt ctctagtgcc 420
tccaccaagg gcccatcggt cttccccctg gcgccctgct ccaggagcac ctccgagagc 480
acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 540
aactcaggcg ctctgaccag cggcgtgcac accttcccag ctgtcctaca gtcctcagga 600
ctctactccc tcagcagcgt ggtgaccgtg ccctccagca acttcggcac ccagacctac 660
acctgcaacg tagatcacaa gcccagcaac accaaggtgg acaagacagt tgagcgcaaa 720
tgttgtgtcg agtgcccacc gtgcccagca ccacctgtgg caggaccgtc agtcttcctc 780
ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacgtgcgtg 840
gtggtggacg tgagccacga agaccccgag gtccagttca actggtacgt ggacggcgtg 900
gaggtgcata atgccaagac aaagccacgg gaggagcagt tcaacagcac gttccgtgtg 960

gtcagcgtcc tcaccgttgt gcaccaggac tggctgaacg gcaaggagta caagtgcaag 1020
gtctccaaca aaggcctccc agcccccatc gagaaaacca tctccaaaac caaagggcag 1080
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag 1140
gtcagcctga cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag 1200
agcaatgggc agccggagaa caactacaag accacacctc ccatgctgga ctccgacggc 1260
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc 1320
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc 1380
ctgtctccgg gtaaa 1395

<210> 349
<211> 417
<212> DNA
<213> 小家鼠

<400> 349
atggaatgga tctggatatt tctcttcctc ctgtcaggaa ctgcaggtgt ccactctgag 60
gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggt gaaggtctcc 120
tgcaaggctt ctggttttac cttcaccgac tatattatgc actgggtgcg tcaggcccct 180
ggtcaagggc ttgagtggat gggctatatc aacccttata atgatgacac cgaatacaac 240
gagaagttca agggccgtgt cacgattacc gcggacaaat ccacgagcac agcctacatg 300
gagctgagca gcctgcgctc tgaggacacg gccgtgtatt actgtgcgcg ttcgatttat 360
tactacgatg ccccgtttgc ttactggggc caagggactc tggtcacagt ctcgagc 417

<210> 350
<211> 218
<212> PRT
<213> 小家鼠

<400> 350
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1   5   10   15
Gln Arg Ala Thr Ile Ala Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20   25   30
Gly Thr Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45
Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Glu Ile Pro Ala
    50   55   60
Arg Phe Ser Gly Thr Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65   70   75   80
Pro Val Glu Glu Glu Asp Ile Thr Thr Tyr Tyr Cys Gln Gln Ser Asn
                85   90   95
Glu Asp Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100   105   110
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
        115   120   125
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
    130   135   140
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145   150   155   160
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr

```
                165                 170                 175
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
            180                 185                 190
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
        195                 200                 205
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
    210                 215
```

<210> 351
<211> 15
<212> PRT
<213> 小家鼠

<400> 351
```
Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Thr Ser Tyr Met Asn
 1               5                  10                  15
```

<210> 352
<211> 7
<212> PRT
<213> 小家鼠

<400> 352
```
Ala Ala Ser Asn Leu Glu Ser
 1               5
```

<210> 353
<211> 9
<212> PRT
<213> 小家鼠

<400> 353
```
Gln Gln Ser Asn Glu Asp Pro Phe Thr
 1               5
```

<210> 354
<211> 657
<212> DNA
<213> 小家鼠

<400> 354
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gacattgtgt tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 60
atcgcctgca aggccagcca aagtgttgat tatgatggta ctagttatat gaattggtac 120
caacagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct 180
gagatcccag ccaggtttag tggcactggg tctgggacag acttcaccct caacatccat 240
cctgtggagg aggaggatat cacaacctat tactgtcagc aaagtaatga ggatccgttc 300
```

acgttcggag gggggaccaa gttggaaata aaacgggctg atgctgcacc aactgtatcc 360
atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 420
aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 480
aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 540
agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 600
actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag 657

<210> 355
<211> 238
<212> PRT
<213> 小家鼠

<400> 355
Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15
Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
20 25 30
Val Ser Leu Gly Gln Arg Ala Thr Ile Ala Cys Lys Ala Ser Gln Ser
35 40 45
Val Asp Tyr Asp Gly Thr Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
50 55 60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
65 70 75 80
Glu Ile Pro Ala Arg Phe Ser Gly Thr Gly Ser Gly Thr Asp Phe Thr
85 90 95
Leu Asn Ile His Pro Val Glu Glu Glu Asp Ile Thr Thr Tyr Tyr Cys
100 105 110
Gln Gln Ser Asn Glu Asp Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu
115 120 125
Glu Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro
130 135 140
Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu
145 150 155 160
Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly
165 170 175
Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser
180 185 190
Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp
195 200 205
Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr
210 215 220
Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230 235

<210> 356
<211> 717
<212> DNA
<213> 小家鼠

<400> 356
atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60
gacattgtgt tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 120
atcgcctgca aggccagcca aagtgttgat tatgatggta ctagttatat gaattggtac 180
caacagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct 240
gagatcccag ccaggtttag tggcactggg tctgggacag acttcaccct caacatccat 300
cctgtggagg aggaggatat cacaacctat tactgtcagc aaagtaatga ggatccgttc 360
acgttcggag gggggaccaa gttggaaata aaacgggctg atgctgcacc aactgtatcc 420
atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 480
aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 540
aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 600
agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 660
actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag 717

<210> 357
<211> 442
<212> PRT
<213> 小家鼠

<400> 357
Gln Val Gln Leu Gln Gln Pro Gly Thr Glu Leu Val Arg Pro Gly Thr
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Thr Tyr
20 25 30
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Met Ile His Pro Ser Ala Ser Glu Ile Arg Leu Asp Gln Lys Phe
50 55 60
Lys Asp Lys Ala Thr Leu Thr Leu Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met His Leu Ser Gly Pro Thr Ser Val Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Gly Glu Trp Gly Ser Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro
115 120 125
Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly
130 135 140
Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn
145 150 155 160
Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr
180 185 190
Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Ser
195 200 205
Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro
210 215 220
Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro
225 230 235 240

```
Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys
                245                 250                 255
Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp
            260                 265                 270
Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu
        275                 280                 285
Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met
    290                 295                 300
His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser
305                 310                 315                 320
Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
                325                 330                 335
Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln
            340                 345                 350
Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe
        355                 360                 365
Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu
    370                 375                 380
Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe
385                 390                 395                 400
Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn
                405                 410                 415
Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr
            420                 425                 430
Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440
```

<210> 358
<211> 5
<212> PRT
<213> 小家鼠

<400> 358

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Thr Tyr Trp Met Asn
 1               5
```

<210> 359
<211> 17
<212> PRT
<213> 小家鼠

<400> 359

```
Met Ile His Pro Ser Ala Ser Glu Ile Arg Leu Asp Gln Lys Phe Lys
 1               5                  10                  15
Asp
```

<210> 360
<211> 9
<212> PRT
<213> 小家鼠

<400> 360
Ser Gly Glu Trp Gly Ser Met Asp Tyr
 1   5

<210> 361
<211> 1329
<212> DNA
<213> 小家鼠

<400> 361
caggtccaac tacagcagcc tgggactgag ctggtgaggc ctggaacttc agtgaagttg 60
tcctgtaagg cttctggcta catcttcacc acctactgga tgaactgggt gaaacagagg 120
cctggacaag gccttgagtg gattggcatg attcatcctt ccgcaagtga aattaggttg 180
gatcagaaat tcaaggacaa ggccacattg actcttgaca aatcctccag cacagcctat 240
atgcacctca gcggcccgac atctgtggat tctgcggtct attactgtgc aagatcaggg 300
gaatgggggt ctatggacta ctggggtcaa ggaacctcag tcaccgtctc ctcagccaaa 360
acgacacccc catctgtcta tccactggcc cctggatctg ctgcccaaac taactccatg 420
gtgaccctgg gatgcctggt caagggctat ttccctgagc cagtgacagt gacctggaac 480
tctggatccc tgtccagcgg tgtgcacacc ttcccagctg tcctgcagtc tgacctctac 540
actctgagca gctcagtgac tgtcccctcc agcacctggc ccagcgagac cgtcacctgc 600
aacgttgccc acccggccag cagcaccaag gtggacaaga aaattgtgcc cagggattgt 660
ggttgtaagc cttgcatatg tacagtccca gaagtatcat ctgtcttcat cttccccca 720
aagcccaagg atgtgctcac cattactctg actcctaagg tcacgtgtgt tgtggtagac 780
atcagcaagg atgatcccga ggtccagttc agctggtttg tagatgatgt ggaggtgcac 840
acagctcaga cgcaaccccg ggaggagcag ttcaacagca ctttccgctc agtcagtgaa 900
cttcccatca tgcaccagga ctggctcaat ggcaaggagt tcaaatgcag ggtcaacagt 960
gcagctttcc ctgccccat cgagaaaacc atctccaaaa ccaaaggcag accgaaggct 1020
ccacaggtgt acaccattcc acctcccaag gagcagatgg ccaaggataa agtcagtctg 1080
acctgcatga taacagactt cttccctgaa gacattactg tggagtggca gtggaatggg 1140
cagccagcgg agaactacaa gaacactcag cccatcatgg acacagatgg ctcttacttc 1200
atctacagca agctcaatgt gcagaagagc aactgggagg caggaaatac tttcacctgc 1260
tctgtgttac atgagggcct gcacaaccac catactgaga agagcctctc ccactctcct 1320
ggtaaatga   1329

<210> 362
<211> 461
<212> PRT
<213> 小家鼠

<400> 362
Met Gly Trp Ser Ser Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
 1   5   10   15
Val His Ser Gln Val Gln Leu Gln Gln Pro Gly Thr Glu Leu Val Arg
            20   25   30

```
Pro Gly Thr Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe
        35                  40                  45
Thr Thr Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
    50                  55                  60
Glu Trp Ile Gly Met Ile His Pro Ser Ala Ser Glu Ile Arg Leu Asp
65                  70                  75                  80
Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Leu Asp Lys Ser Ser Ser
                85                  90                  95
Thr Ala Tyr Met His Leu Ser Gly Pro Thr Ser Val Asp Ser Ala Val
            100                 105                 110
Tyr Tyr Cys Ala Arg Ser Gly Glu Trp Gly Ser Met Asp Tyr Trp Gly
        115                 120                 125
Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser
    130                 135                 140
Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
145                 150                 155                 160
Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175
Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190
Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
        195                 200                 205
Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro
    210                 215                 220
Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
225                 230                 235                 240
Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
                245                 250                 255
Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
            260                 265                 270
Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
        275                 280                 285
Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln
    290                 295                 300
Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
305                 310                 315                 320
Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
                325                 330                 335
Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            340                 345                 350
Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
        355                 360                 365
Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr
    370                 375                 380
Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln
385                 390                 395                 400
Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
                405                 410                 415
Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu
            420                 425                 430
```

```
Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
        435                 440                 445
His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
    450                 455                 460
```

<210> 363
<211> 1386
<212> DNA
<213> 小家鼠

<400> 363

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atgggatgga gctctatcat cctcttcttg gtagcaacag ctacaggtgt ccactcccag 60
gtccaactac agcagcctgg gactgagctg gtgaggcctg gaacttcagt gaagttgtcc 120
tgtaaggctt ctggctacat cttcaccacc tactggatga actgggtgaa acagaggcct 180
ggacaaggcc ttgagtggat tggcatgatt catccttccg caagtgaaat taggttggat 240
cagaaattca aggacaaggc cacattgact cttgacaaat cctccagcac agcctatatg 300
cacctcagcg gcccgacatc tgtggattct gcggtctatt actgtgcaag atcaggggaa 360
tgggggtcta tggactactg gggtcaagga acctcagtca ccgtctcctc agccaaaacg 420
acacccccat ctgtctatcc actggccccc ggatctgctg cccaaactaa ctccatggtg 480
accctgggat gcctggtcaa gggctatttc cctgagccag tgacagtgac ctggaactct 540
ggatccctgt ccagcggtgt gcacaccttc ccagctgtcc tgcagtctga cctctacact 600
ctgagcagct cagtgactgt cccctccagc acctggccca gcgagaccgt cacctgcaac 660
gttgcccacc cggccagcag caccaaggtg gacaagaaaa ttgtgcccag ggattgtggt 720
tgtaagcctt gcatatgtac agtcccagaa gtatcatctg tcttcatctt cccccaaaag 780
cccaaggatg tgctcaccat tactctgact cctaaggtca cgtgtgttgt ggtagacatc 840
agcaaggatg atcccgaggt ccagttcagc tggtttgtag atgatgtgga ggtgcacaca 900
gctcagacgc aaccccggga ggagcagttc aacagcactt tccgctcagt cagtgaactt 960
cccatcatgc accaggactg gctcaatggc aaggagttca aatgcagggt caacagtgca 1020
gctttccctg cccccatcga gaaaaccatc tccaaaacca aaggcagacc gaaggctcca 1080
caggtgtaca ccattccacc tcccaaggag cagatggcca aggataaagt cagtctgacc 1140
tgcatgataa cagacttctt ccctgaagac attactgtgg agtggcagtg gaatgggcag 1200
ccagcggaga actacaagaa cactcagccc atcatggaca cagatggctc ttacttcatc 1260
tacagcaagc tcaatgtgca gaagagcaac tgggaggcag gaaatacttt cacctgctct 1320
gtgttacatg agggcctgca caaccaccat actgagaaga gcctctccca ctctcctggt 1380
aaatga                                                          1386
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<210> 364
<211> 106
<212> PRT
<213> 小家鼠

<400> 364

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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 Arg Ala Ser Gln Asp Ile Ser Ser Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ser Thr Ser Arg Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
```

```
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Ile Lys His Pro Thr
                85                  90                  95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 365
<211> 318
<212> DNA
<213> 小家鼠

<400> 365
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggtga ccgtgtcacc 60
atcacttgcc gcgcaagtca ggatattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctattct acttcccgtt tgaatagtgg ggtcccatca 180
cgcttcagtg gcagtggctc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag gatattaaac accctacgtt cggtcaaggc 300
accaaggtgg agatcaaa 318

<210> 366
<211> 120
<212> PRT
<213> 小家鼠

<400> 366
```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
            20                  25                  30
Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
    50                  55                  60
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 367
<211> 360
<212> DNA
<213> 小家鼠

<400> 367
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggttt taccttcacc gactatatta tgcactgggt gcgtcaggcc 120
cctggtcaag ggcttgagtg gatgggctat atcaaccctt ataatgatga caccgaatac 180
aacgagaagt tcaagggccg tgtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgcg ctctgaggac acggccgtgt attactgtgc gcgttcgatt 300
tattactacg atgccccgtt tgcttactgg ggccaaggga ctctggtcac cgtctctagt 360

<210> 368
<211> 108
<212> PRT
<213> 小家鼠

<400> 368
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 Val Phe Thr Ala
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Trp Ala Ser Thr Arg His Thr 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 Ser Ser Tyr Pro Leu
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 369
<211> 324
<212> DNA
<213> 小家鼠

<400> 369
gatatccaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60
attacctgca aagcgagcca ggatgtgttt accgcggtgg cgtggtatca gcagaaaccg 120
ggcaaagcgc cgaaactgct gatttattgg gcgagcaccc gccataccgg cgtgccgagt 180
cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240
gaagattttg cgacctatta ttgccagcag tatagcagct atccgctgac ctttggcggc 300
ggcaccaaag tggaaattaa acgt   324

<210> 370
<211> 119
<212> PRT
<213> 小家鼠

<400> 370
Glu 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 Phe Asn Ile Lys Asp Tyr
            20   25   30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Arg Ile Asp Pro Glu Asn Gly Asp Ile Ile Tyr Asp Pro Lys Phe
    50   55   60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Tyr Asp Ala Gly Asp Pro Ala Trp Phe Thr Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 371
<211> 357
<212> DNA
<213> 小家鼠

<400> 371
gaagtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg 60
agctgcaaag cgagcggctt taacattaaa gattattata tgcattgggt gcgccaggcg 120
ccgggccagg gcctggaatg gatcggccgc attgatccgg aaaacggcga tattatttat 180
gatccgaaat ttcagggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat 240
atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgcgc gtatgatgcg 300
ggcgatccgg cgtggtttac ctattggggc cagggcaccc tggtgaccgt ctcgagc   357

<210> 372
<211> 108
<212> PRT
<213> 小家鼠

<400> 372
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Ser Val Ser Ser Ser Ile Ser Ser Ser
            20   25   30
Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
        35   40   45
Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50   55   60
Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65   70   75   80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Thr Thr Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 373
<211> 324
<212> DNA
<213> 小家鼠

<400> 373
gatattcagc tgacccagag cccgagcttt ctgagcgcga gcgtgggcga tcgcgtgacc 60
attacctgca gcgtgagcag cagcattagc agcagcaacc tgcattggta tcagcagaaa 120
ccgggcaaag cgccgaaact gctgatttat ggcaccagca acctggcgag cggcgtgccg 180
agccgcttta gcggcagcgg cagcggcacc gaatttaccc tgaccattag cagcctgcag 240
ccggaagatt ttgcgaccta ttattgccag cagtggacca ccacctatac ctttggccag 300
ggcaccaaac tggaaattaa acgt 324

<210> 374
<211> 122
<212> PRT
<213> 小家鼠

<400> 374
Glu 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 Phe Asn Ile Lys Asp Tyr
20 25 30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Arg Ile Asp Pro Asp Asn Gly Glu Ser Thr Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 375
<211> 366
<212> DNA
<213> 小家鼠

<400> 375
gaagtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg 60
agctgcaaag cgagcggctt taacattaaa gattattata ttcattgggt gcgccaggcg 120
ccgggccagg gcctggaatg gatgggccgc attgatccgg ataacggcga aagcacctat 180

gtgccgaaat ttcagggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat 240
atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgcgc gcgcgaaggc 300
ctggattatg gcgattatta tgcggtggat tattggggcc agggcaccct ggtgaccgtc 360
tcgagc 366

<210> 376
<211> 107
<212> PRT
<213> 小家鼠

<400> 376
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35 40 45
Tyr Tyr Thr Ser Arg Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Thr Leu Pro Tyr
                85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100 105

<210> 377
<211> 321
<212> DNA
<213> 小家鼠

<400> 377
gacatccaga tgacccagtc tccatcctcc ctctccgcat ccgtaggcga ccgcgtaacc 60
ataacatgta gagcatctca agatatttcc aactatttga attggtacca acaaaaaccc 120
ggcaaagcac ctaaactcct catttactat acatcaagac tcctctccgg cgttccatca 180
cgattctcag gctccggctc cggcacagat ttcacactca ctatttcctc cctccaacca 240
gaagattttg caacctatta ctgtcaacaa ggcgatacac tcccatacac attcggcggc 300
ggcacaaaag ttgaaattaa a 321

<210> 378
<211> 123
<212> PRT
<213> 小家鼠

<400> 378
Glu 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 Asp Tyr
            20 25 30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
100 105 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 379
<211> 369
<212> DNA
<213> 小家鼠

<400> 379
gaggtgcagc tggtgcagag cggcgccgag gtaaaaaaac caggagcaag cgttaaagtt 60
tcttgtaaag caagcggata tacatttaca gattacaaca tgcattgggt aagacaagcg 120
ccaggacaag gattggaatg gatgggcgaa attaacccta atagtggagg agcaggctac 180
aatcaaaaat tcaaagggag agttacaatg acaacagaca caagcacttc aacagcatat 240
atggaactgc gatcacttag aagcgacgat acagctgtat actattgcgc acgacttggg 300
tatgatgata tatatgatga ctggtatttc gatgtttggg gccagggaac aacagttacc 360
gtctctagt 369

<210> 380
<211> 108
<212> PRT
<213> 小家鼠

<400> 380
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Val Thr Ser Ser
20 25 30
Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Phe Phe Pro
85 90 95
Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 381
<211> 324
<212> DNA
<213> 小家鼠

<400> 381
gacatccagc tgacccagag ccccagcttc ctttccgcat ccgttggtga ccgagtaaca 60
atcacatgcc gcgcctcatc ttcagttaca tcttcttatc ttaattggta tcaacaaaaa 120
ccaggaaaag cacctaaact tcttatatac tctacatcta atctcgcatc aggagttccc 180
tctcgatttt caggatctgg atcaggcaca gaatttacac ttactatatc atcactccaa 240
ccagaagact tcgccactta ttactgccaa caatacgatt tttttccaag cacattcgga 300
ggaggtacaa aagtagaaat caag 324

<210> 382
<211> 121
<212> PRT
<213> 小家鼠

<400> 382
Glu 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 Asp Tyr
            20   25   30
Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35   40   45
Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe
    50   55   60
Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
            100   105   110
Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 383
<211> 363
<212> DNA
<213> 小家鼠

<400> 383
gaggtgcagc tggtgcagag cggcgccgag gtcaagaaac ctggagcaag cgtaaaggtt 60
agttgcaaag catctggata cacatttacc gactactaca tgaattgggt acgacaagcc 120
cctggacaaa gacttgaatg gatgggagac attaaccctt ataacgacga cactacatac 180
aatcataaat ttaaaggaag agttacaatt acaagagata catccgcatc aaccgcctat 240
atggaacttt cctcattgag atctgaagac actgctgttt attactgtgc aagagaaact 300
gccgttatta ctactaacgc tatggattac tggggtcaag gaaccactgt taccgtctct 360
agt 363

<210> 384
<211> 108
<212> PRT
<213> 小家鼠

<400> 384
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 Ser Val Ser Ser Thr Ile Ser Ser Asn
            20   25   30
His Leu His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu
        35   40   45
Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50   55   60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65   70   75   80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
                85   90   95
Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 385
<211> 324
<212> DNA
<213> 小家鼠

<400> 385
gacatccaga tgacccagtc tccatcctcc ctctcagcat ccgtaggcga tagagttaca 60
ataacatgca gcgtatcatc aactatatca tcaaatcatc ttcattggtt ccaacagaaa 120
cccggcaaag cacctaaatc acttatatac ggcacatcaa atctcgcatc aggcgttcct 180
tcaagatttt caggctctgg ctcaggcacc gactttactc ttacaatatc ctccctccaa 240
cccgaagact tcgcaaccta ttactgtcaa caatggtcct catatccact cacatttggc 300
ggcggcacaa aagtagaaat taaa   324

<210> 386
<211> 125
<212> PRT
<213> 小家鼠

<400> 386
Glu 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 Asp Phe Asn Ile Lys Asp Phe
            20   25   30
Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe
    50   55   60

Gln Asp Lys Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr Trp Tyr Phe
100 105 110
Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 387
<211> 375
<212> DNA
<213> 小家鼠

<400> 387
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgactt caacattaaa gacttctatc tacactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gattggaagg attgatcctg agaatggtga tactttatat 180
gacccgaagt tccaggacaa ggtcaccatg accacagaca cgtccaccag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggcg 300
gattatttcc acgatggtac ctcctactgg tacttcgatg tctggggccg tggcaccctg 360
gtcaccgtct ctagt 375

<210> 388
<211> 106
<212> PRT
<213> 小家鼠

<400> 388
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Ile Ser Tyr Ile
20 25 30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45
Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asp Pro Leu Thr
85 90 95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 389
<211> 318
<212> DNA
<213> 小家鼠

<400> 389
gacatccagt tgacccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgca gggccagctc aagtataagt tacatacact ggtatcagca aaaaccaggg 120
aaagccccta agctcctgat ctatgccaca tccaacctgg cttctggggt cccatcaagg 180
ttcagcggca gtggatctgg gacagaattc actctcacaa tcagcagcct gcagcctgaa 240
gattttgcaa cttattactg tcagcagtgg agtagtgacc cactcacgtt cggcggaggg 300
accaaggtgg agatcaaa 318

<210> 390
<211> 121
<212> PRT
<213> 小家鼠

<400> 390
Glu 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 Phe Asp Ile Lys Asp Tyr
20 25 30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
50 55 60
Pro Gly Lys Val Thr Met Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 391
<211> 363
<212> DNA
<213> 小家鼠

<400> 391
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggatt cgacattaag gactactata tacactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatcggaagg gttgatcctg acaatggtga gactgaattt 180
gccccgaagt tcccgggcaa ggtcaccatg accacagaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagaagac 300
tacgatggta cctacacctg gtttccttat tggggccaag gactctggt caccgtctct 360
agt 363

<210> 392
<211> 448
<212> PRT

<213> 人工序列

<220>
<223> 人化抗體序列

<400> 392

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Glu 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 Asp Tyr
            20                  25                  30
Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
            100                 105                 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125
Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
    130                 135                 140
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190
Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
        195                 200                 205
Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
    210                 215                 220
Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
225                 230                 235                 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270
Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
    290                 295                 300
Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320
Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335
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Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
385 390 395 400
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 393
<211> 446
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 393
Glu 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 Asp Tyr
20 25 30
Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45
Gly Asp Ile Asn Pro Tyr Asn Asp Asp Thr Thr Tyr Asn His Lys Phe
50 55 60
Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Thr Ala Val Ile Thr Thr Asn Ala Met Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val

```
            180                 185                 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
    210                 215                 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala 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 His 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 Phe Arg Val Val Ser
    290                 295                 300
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335
Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350
Pro Ser Arg 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 Met Leu Asp Ser
385                 390                 395                 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415
Trp Gln Gln 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 Pro Gly
        435                 440                 445
```

<210> 394
<211> 450
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

```
<400> 394
Glu 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 Asp Phe Asn Ile Lys Asp Phe
            20                  25                  30
```

```
Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45
Gly Arg Ile Asp Pro Glu Asn Gly Asp Thr Leu Tyr Asp Pro Lys Phe
    50                  55                  60
Gln Asp Lys Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Ala Asp Tyr Phe His Asp Gly Thr Ser Tyr Trp Tyr Phe
            100                 105                 110
Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
    130                 135                 140
Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190
Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
        195                 200                 205
Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
    210                 215                 220
Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
225                 230                 235                 240
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270
Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
    290                 295                 300
Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
                325                 330                 335
Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400
Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430
```

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445
Pro Gly
450

<210> 395
<211> 446
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 395
Glu 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 Phe Asp Ile Lys Asp Tyr
20 25 30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Val Asp Pro Asp Asn Gly Glu Thr Glu Phe Ala Pro Lys Phe
50 55 60
Pro Gly Lys Val Thr Met Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Asp Tyr Asp Gly Thr Tyr Thr Trp Phe Pro Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala 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 His 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 Phe Arg Val Val Ser
    290                 295                 300
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335
Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350
Pro Ser Arg 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 Met Leu Asp Ser
385                 390                 395                 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415
Trp Gln Gln 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 Pro Gly
        435                 440                 445
```

<210> 396
<211> 445
<212> PRT
<213> 人工序列

<220>
<223> 人化抗體序列

<400> 396

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
            20                  25                  30
Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn Glu Lys Phe
    50                  55                  60
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro 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 Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
    210                 215                 220
Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225                 230                 235                 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
    290                 295                 300
Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320
Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335
Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu 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 Met 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
```

【發明申請專利範圍】

【請求項1】

一種單株抗體，其與人類殼硬蛋白(sclerostin)之部分結合，且對人類殼硬蛋白具有小於或等於1×10^{-10} M的結合親合力，其中該部分由SEQ ID NO: 1之胺基酸57-64、73-86、111-117及138-144所組成，且具有所有以下三者：

(a) 胺基酸57與111之間之二硫鍵；

(b) 胺基酸82與142之間之二硫鍵；及

(c) 胺基酸86與144之間之二硫鍵。

【請求項2】

如請求項1之單株抗體，其為$F(ab')_2$、Fab、Fab'或Fv片段。

【請求項3】

如請求項1之單株抗體，其為人化(humanized)抗體或人類抗體。

【請求項4】

如請求項1至3中任一項之單株抗體，其以小於或等於1×10^{-11} M或小於或等於1×10^{-12} M的結合親合力與人類殼硬蛋白結合。

【請求項5】

如請求項1至3中任一項之單株抗體，其以大於對雞蛋白溶菌酶(lysozyme)之親合力至少50、100、250、500、1000或10,000倍之親合力結合至殼硬蛋白。

【請求項6】

一種如請求項1至5中任一項之單株抗體的用途，其係用於製備用於增加哺乳動物中之骨形成、骨礦質密度、骨礦質含量、骨質、骨

品質及骨強度中之至少一者，或在以細胞為基礎之礦質化分析中阻斷殼硬蛋白的藥物。

【請求項7】

一種如請求項1至5中任一項之單株抗體的用途，其係用於製備用於治療骨質疏鬆症(osteoporosis)或骨質減少(osteopenia)的藥物。

【請求項8】

一種如請求項1至5中任一項之單株抗體的用途，其係用於製備用於矯形外科程序、牙科程序、植入手術、關節置換、骨移植、骨整容手術或骨修復之結果(諸如骨折康復、骨不連合康復、延遲連合康復或面部重整)的藥物。

【發明圖式】

A.

```
  1 AQVLTQTPAS VSAAVGGTVT INCQSSQSVY DNNWLAWFQQ KPGQPPKLLI
 51 YDASDLASGV PSRFSGSGSG TQFTLTISGV QCADAATYYC QGAYNDVIYA
101 FGGGTEVVVK RTDAAPTVSI FPPSSEQLTS GGASVVCFLN NFYPKDINVK
151 WKIDGSERQN GVLNSWTDQD SKDSTYSMSS TLTLTKDEYE RHNSYTCEAT
201 HKTSTSPIVK SFNRNEC
```

B.

```
  1 QSLEESGGRL VTPGTPLTLT CTASGFSLSS YWMNWVRQAP GEGLEWIGTI
 51 DSGGRTDYAS WAKGRFTISR TSTTMDLKMT SLTTGDTARY FCARNWNLWG
101 QGTLVTVSSA STKGPSVYPL APGSAAQTNS MVTLGCLVKG YFPEPVTVTW
151 NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT CNVAHPASST
201 KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT LTPKVTCVVV
251 DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS ELPIMHQDWL
301 NGKEFKCRVN SAAFPAPIEK TISKTKGRPK APQVYTIPPP KEQMAKDKVS
351 LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMNTNGSY FVYSKLNVQK
401 SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK
```

【圖 1】

A.

```
  1 QIVLTQSPTI VSASPGEKVT LICSASSSVS FVDWFQQKPG TSPKRWIYRT
 51 SNLGFGVPAR FSGGGSGTSH SLTISRMEAE DAATYYCQQR STYPPTFGAG
101 TKLELKRADA APTVSIFPPS SEQLTSGGAS VVCFLNNFYP KDINVKWKID
151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
201 TSPIVKSFNR NEC
```

B.

```
  1 QVTLKESGPG ILQPSQTLSL TCSFSGFSLS TSGMGVGWIR HPSGKNLEWL
 51 AHIWWDDVKR YNPVLKSRLT ISKDTSNSQV FLKIANVDTA DTATYYCARI
101 EDFDYDEEYY AMDYWGQGTS VIVSSAKTTP PSVYPLAPGS AAQTNSMVTL
151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW
201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
251 DVLTITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
301 TFRSVSELPI MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIM
401 DTDGSYFVYS KLNVQKSNWE AGNTFTCSVL HEGLHNHHTE KSLSHSPGK
```

【圖 2】

A.

```
  1 DIVLTQSPAS LTVSLGLRAT ISCKASQSVD YDGDSYMNWY QQKPGQPPKL
 51 LIYAASNLES GIPARFSGNG SGTDFTLNIH PVEEEDAVTY YCQQSNEDPW
101 TFGGGTKLEI KRADAAPTVS IFPPSSEQLT SGGASVVCFL NNFYPKDINV
151 KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS STLTLTKDEY ERHNSYTCEA
201 THKTSTSPIV KSFNRNEC
```

B.

```
  1 EVQLQQSGPE LVKPGTSVKM SCKASGYTFT DCYMNWVKQS HGKSLEWIGD
 51 INPFNGGTTY NQKFKGKATL TVDKSSSTAY MQLNSLTSDD SAVYYCARSH
101 YYFDGRVPWD AMDYWGQGTS VTVSSAKTTP PSVYPLAPGS AAQTNSMVTL
151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW
201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
251 DVLTITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
301 TFRSVSELPI MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIM
401 DTDGSYFIYS KLNVQKSNWE AGNTFTCSVL HEGLHNHHTE KSLSHSPGK
```

【圖 3】

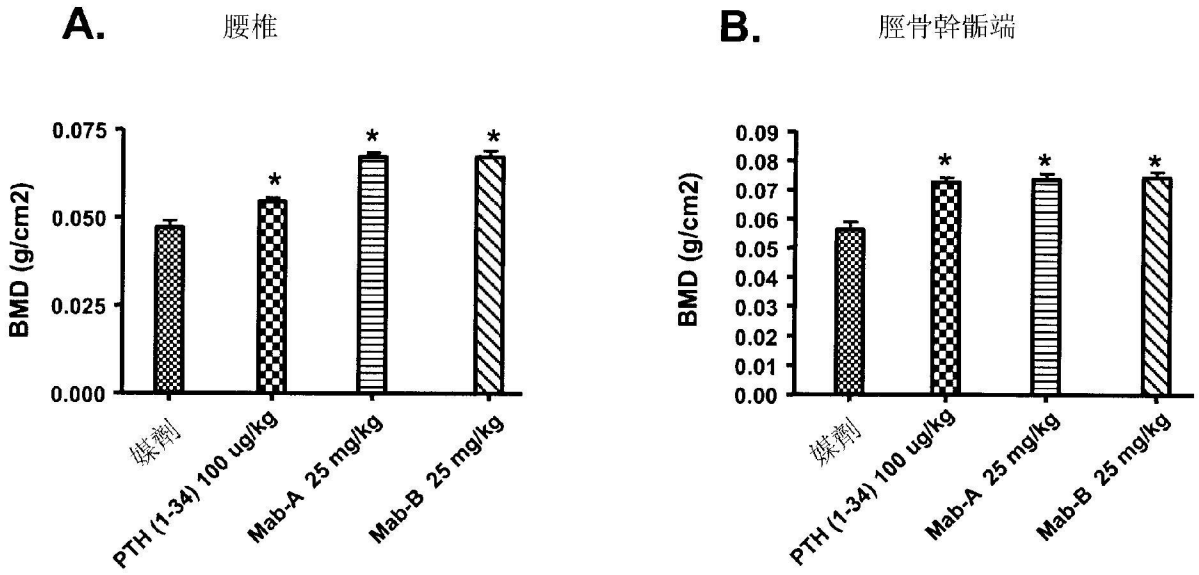
A.

```
  1 DVQMIQSPSS LSASLGDIVT MTCQASQGTS INLNWFQQKP GKAPKLLIYG
 51 SSNLEDGVPS RFSGSRYGTD FTLTISSLED EDLATYFCLQ HSYLPYTFGG
101 GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC
```

B.

```
  1 EVQLQQSGPE LVTPGASVKI SCKASGYTFT DHYMSWVKQS HGKSLEWIGD
 51 INPYSGETTY NQKFKGTATL TVDKSSSIAY MEIRGLTSED SAVYYCARDD
101 YDASPFAYWG QGTLVTVSAA KTTPPSVYPL APGSAAQTNS MVTLGCLVKG
151 YFPEPVTVTW NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT
201 CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT
251 LTPKVTCVVV DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS
301 ELPIMHQDWL NGKEFKCRVN SPAFPAPIEK TISKTKGRPK APQVYTIPPP
351 KEQMAKDKVS LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMDTDGSY
401 FIYSKLNVQK SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK
```

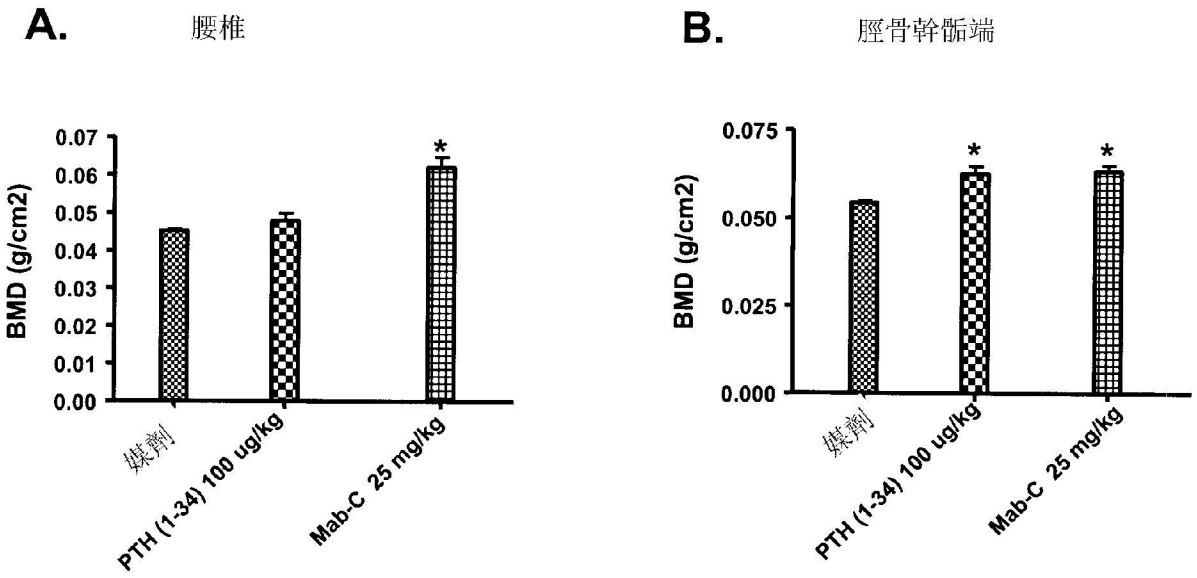
【圖 4】



＊ =在統計學上顯著不同於媒劑

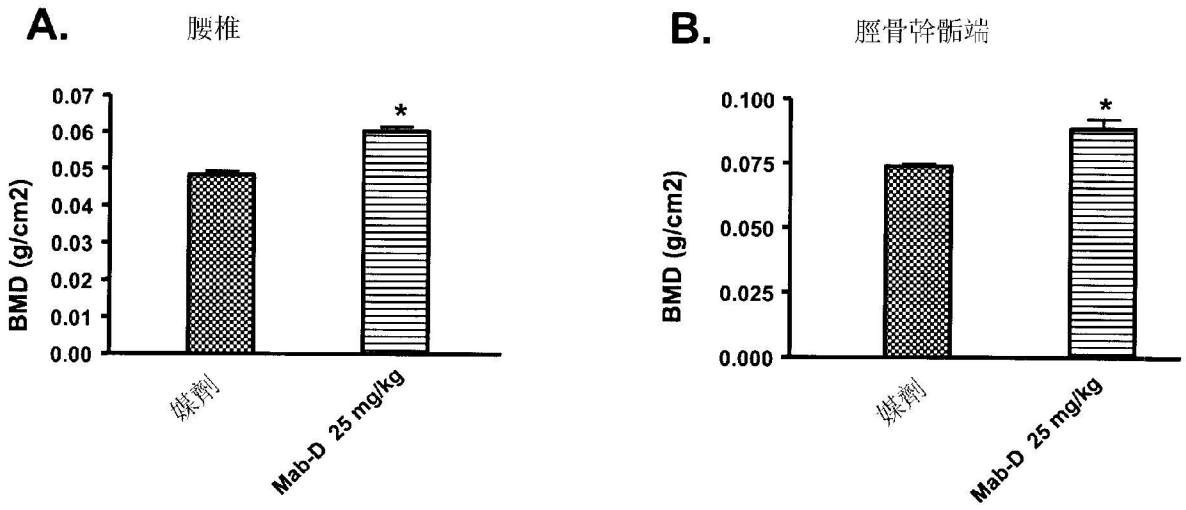
誤差條形圖=平均值+/−標準差

【圖 5】



＊ =在統計學上顯著不同於媒劑
誤差條形圖=平均值+/-標準差

【圖 6】



＊ =在統計學上顯著不同於媒劑

誤差條形圖=平均值+/-標準差

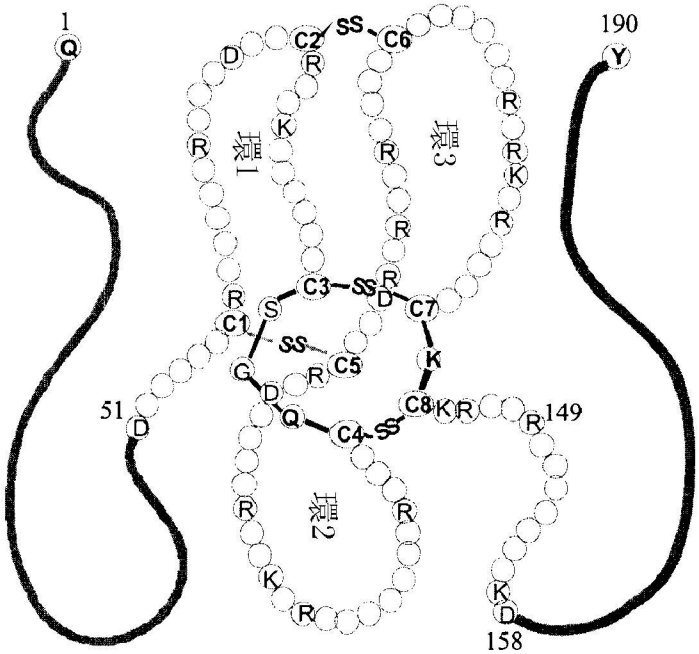
【圖 7】

```
1   QGWQAFKNDA TEIIPELGEY PEPPPELENN KTMNRAENGG RPPHHPFETK

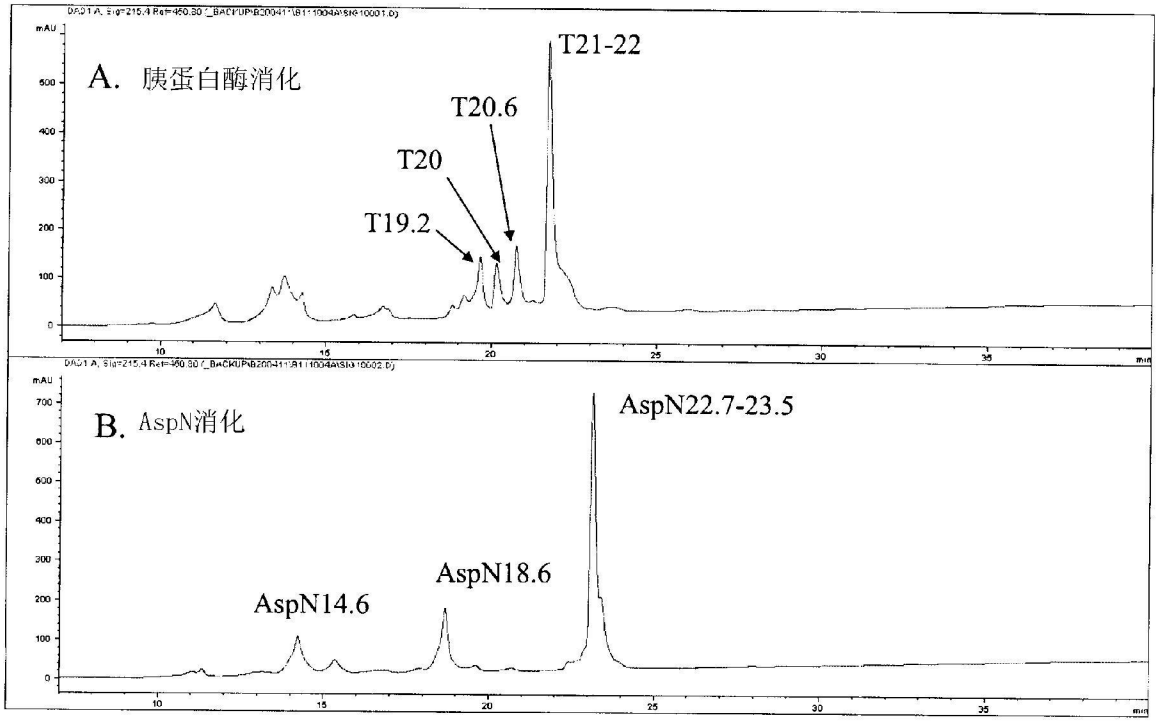
51  DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR LLPNAIGRGK
          C1                C2             C3   C4
101 WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTRF
               C5                 C6                  C7 C8
151 HNQSELKDFG TEAARPQKGR KPRPRARSAK ANQAELENAY
```

```
1   CAGGGGTGGC AGGCGTTCAA GAATGATGCC ACGGAAATCA TCCCCGAGCT
51  CGGAGAGTAC CCCGAGCCTC CACCGGAGCT GGAGAACAAC AAGACCATGA
101 ACCGGGCGGA GAACGGAGGG CGGCCTCCCC ACCACCCCTT TGAGACCAAA
151 GACGTGTCCG AGTACAGCTG CCGCGAGCTG CACTTCACCC GCTACGTGAC
201 CGATGGGCCG TGCCGCAGCG CCAAGCCGGT CACCGAGCTG GTGTGCTCCG
251 GCCAGTGCGG CCCGGCGCGC CTGCTGCCCA ACGCCATCGG CCGCGGCAAG
301 TGGTGGCGAC CTAGTGGGCC CGACTTCCGC TGCATCCCCG ACCGCTACCG
351 CGCGCAGCGC GTGCAGCTGC TGTGTCCCGG TGGTGAGGCG CCGCGCGCGC
401 GCAAGGTGCG CCTGGTGGCC TCGTGCAAGT GCAAGCGCCT CACCCGCTTC
451 CACAACCAGT CGGAGCTCAA GGACTTCGGG ACCGAGGCCG CTCGGCCGCA
501 GAAGGGCCGG AAGCCGCGGC CCCGCGCCCG GAGCGCCAAA GCCAACCAGG
551 CCGAGCTGGA GAACGCCTAC
```

【圖8】



【圖9】


A. 胰蛋白酶消化
T21-22
T20.6
T20
T19.2
B. AspN消化
AspN22.7-23.5
AspN18.6
AspN14.6

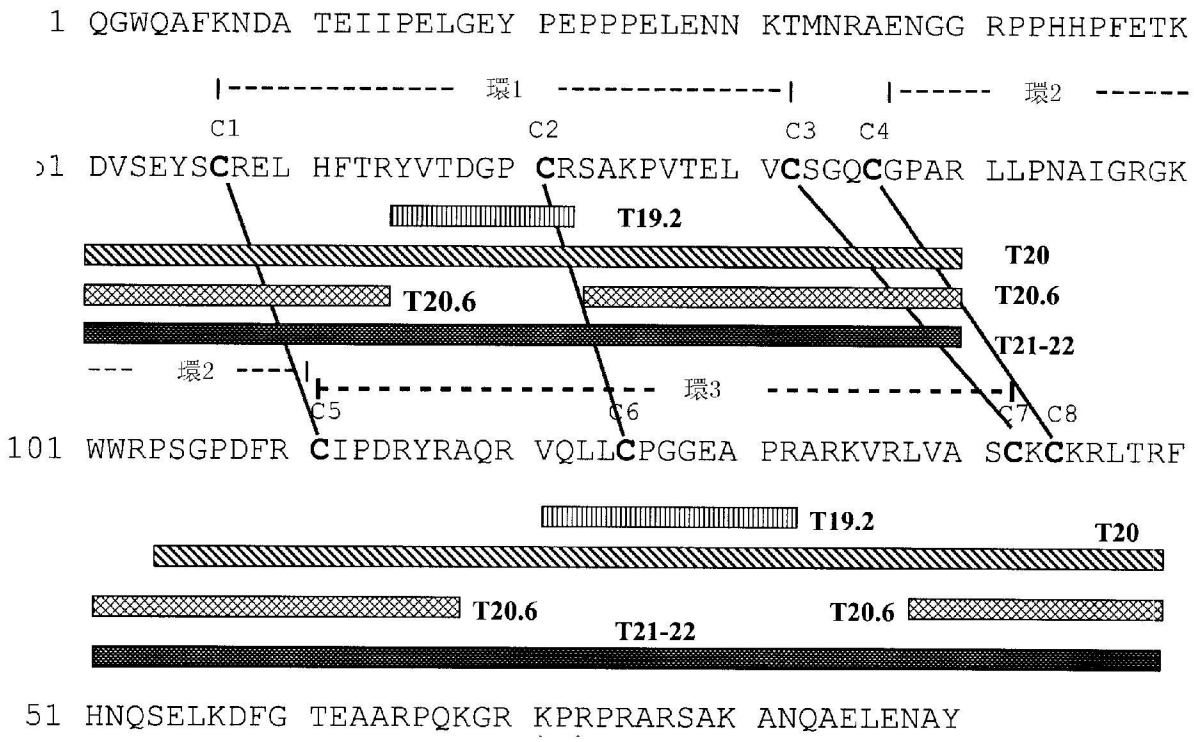
【圖 10】

肽	序列位置	觀察質量	序列
T19.2	65-72	2146.34	1. YVTDGP CR (910) C2
	121-132	(2145.8)	2. VQLLCPGGEA PR (1239) C6
T20		9620.8 (MALDI); 9638.41 (ESI-MS)	
	51-90	(4419.1)	1. DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR
	104-149	(5226.2)	2. PSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLT R
T20.6		7105.7 (MALDI); 7122.0 (ESI-MS)	
	51-64	3944.5	1. DVSEYSCREL HFTR (1740.9) C1
	101-117		2. WWRPSGPPFR CIPDRYR (2206.6) C5
	73-90	3177.0	3. SAKPVTELVC SGQCGPAR (1802.2) C3,C4
	138-149		4. LVASCKCKRL TR (1378.5) C7,C8
T21-22		10,147 (MALDI); 10170.3 (ESI-MS)	
	51-90	(4419.1)	1. DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR
	101-149	(5754.8)	2. WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTR

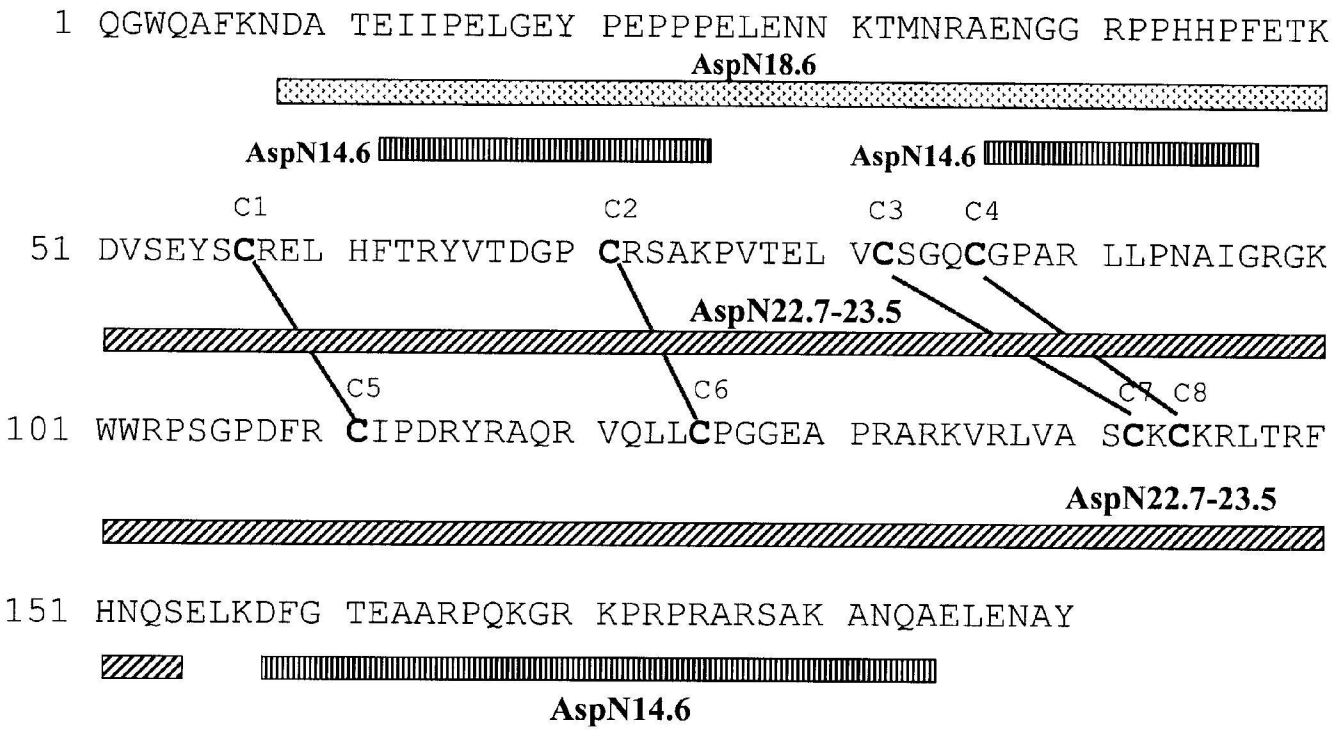
【圖 11】

肽	序列位置	觀察質量	序列
AspN14.6	34-47	1245.5	ENGGRPPHHPF
	12-25	1585.4	EIIPELGFYP EPPP
	158-184	2964.5	DFGTEAARPQ KGRKPRPRAR SAKANQA
AspN18.6	9-50		DATEIIPELG EYPEPPPELE NNKTMNRAEN GGRPPHHPFE TK (糖肽)
AspN22.7-23.5	51-154	11,740	DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR LLPNAIGRGK WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTRF HNQS

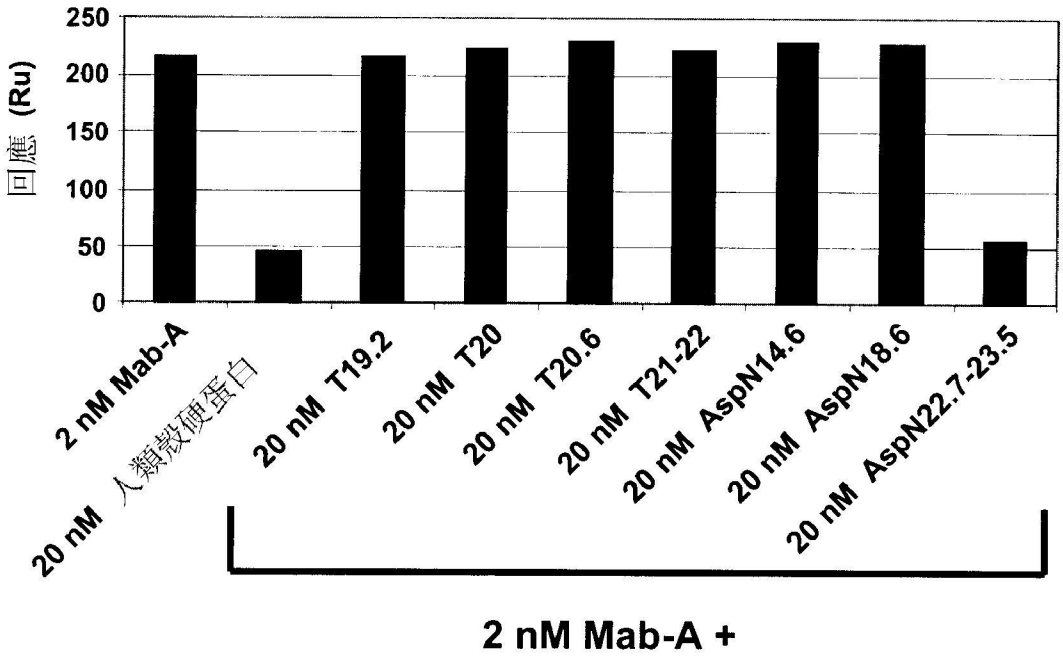
【圖 12】


1 QGWQAFKNDA TEIIPELGEY PEPPPELENN KTMNRAENGG RPPHHPFETK
環1
環2
C1
C2
C3
C4
›1 DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR LLPNAIGRGK
T19.2
T20
T20.6
T20.6
T21-22
環2
環3
C5
C6
C7
C8
101 WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTRF
T19.2
T20
T20.6
T20.6
T21-22
51 HNQSELKDFG TEAARPQKGR KPRPRARSAK ANQAELENAY

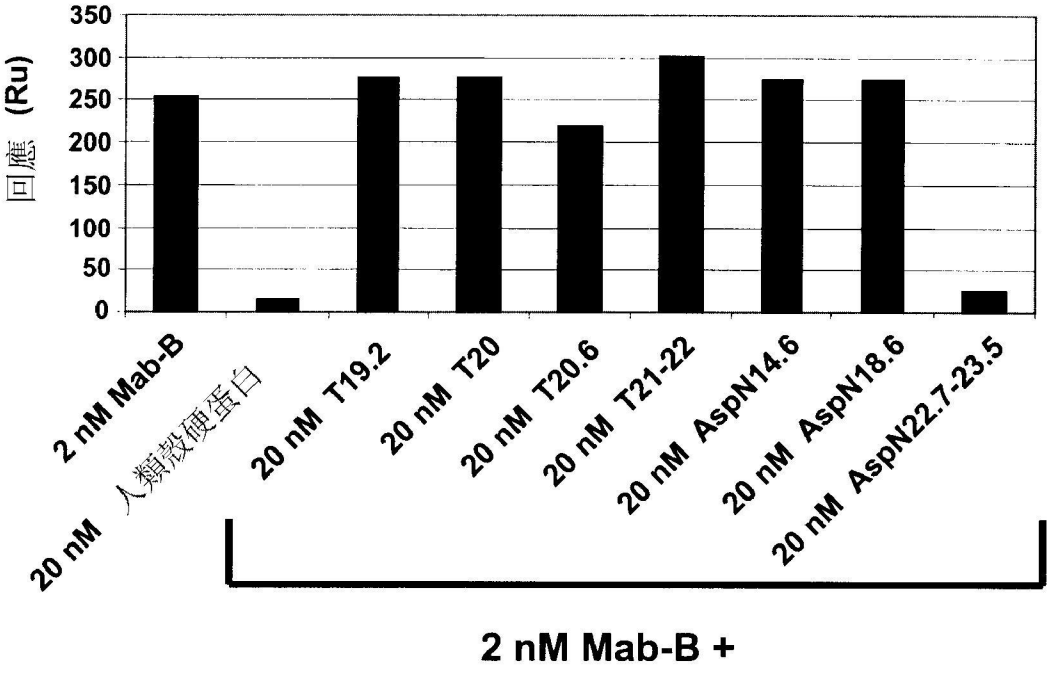
【圖 13】


1 QGWQAFKNDA TEIIPELGEY PEPPPELENN KTMNRAENGG RPPHHPFETK
AspN18.6
AspN14.6
AspN14.6
C1
C2
C3
C4
51 DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR LLPNAIGRGK
AspN22.7-23.5
C5
C6
C7
C8
101 WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTRF
AspN22.7-23.5
151 HNQSELKDFG TEAARPQKGR KPRPRARSAK ANQAELENAY
AspN14.6

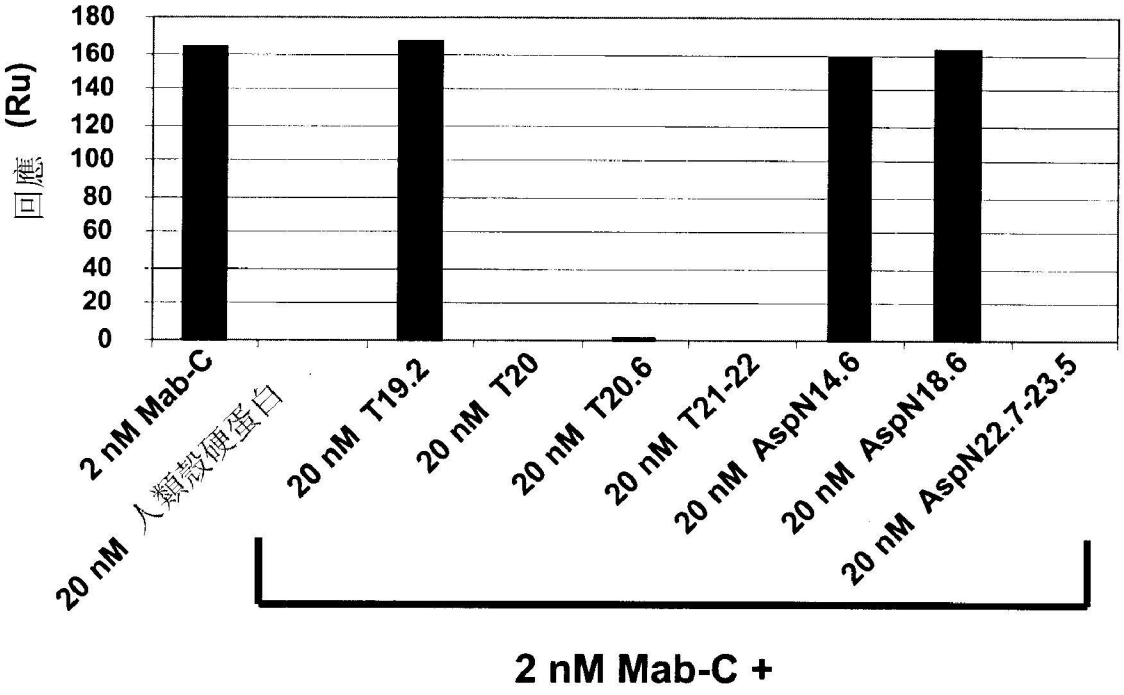
【圖 14】


250
200
150
100
50
0
回應 (Ru)
2 nM Mab-A
20 nM 人類殼硬蛋白
20 nM T19.2
20 nM T20
20 nM T20.6
20 nM T21-22
20 nM AspN14.6
20 nM AspN18.6
20 nM AspN22.7-23.5
2 nM Mab-A +

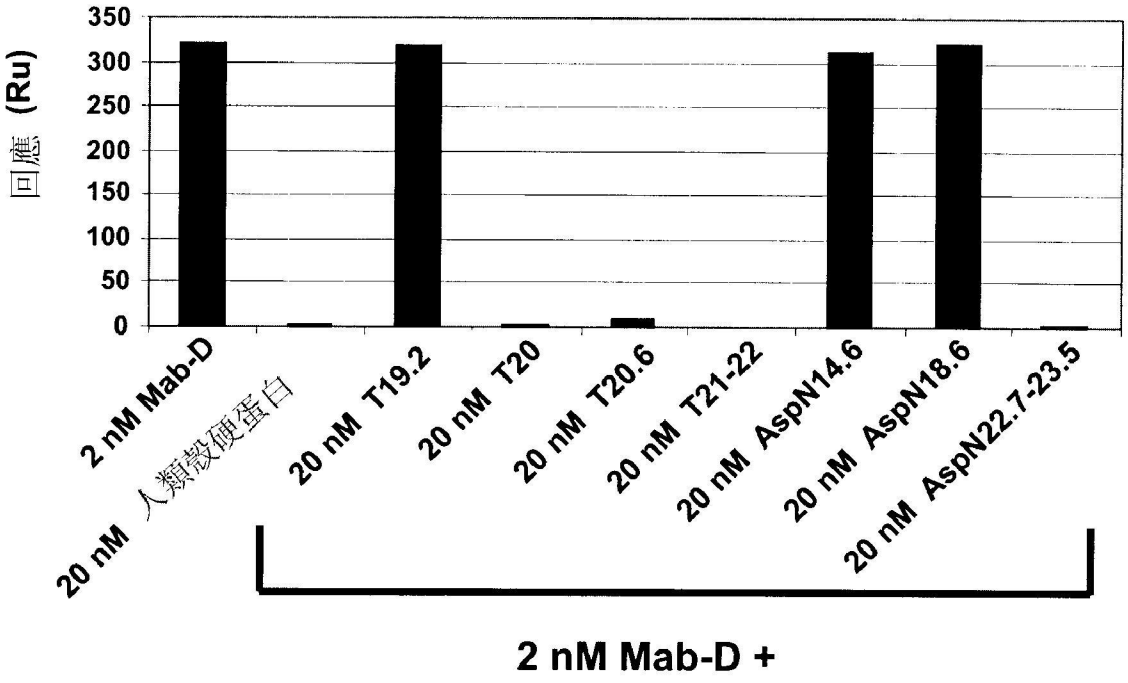
【圖 15】


回應 (Ru)
350
300
250
200
150
100
50
0
2 nM Mab-B
20 nM 人類散硬蛋白
20 nM T19.2
20 nM T20
20 nM T20.6
20 nM T21-22
20 nM AspN14.6
20 nM AspN18.6
20 nM AspN22.7-23.5
2 nM Mab-B +

【圖 16】

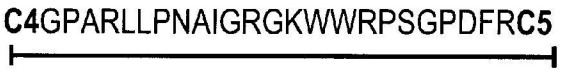

回應 (Ru)
180
160
140
120
100
80
60
40
20
0
2 nM Mab-C
20 nM 人類熱休克蛋白
20 nM T19.2
20 nM T20
20 nM T20.6
20 nM T21-22
20 nM AspN14.6
20 nM AspN18.6
20 nM AspN22.7-23.5
2 nM Mab-C +

【圖 17】

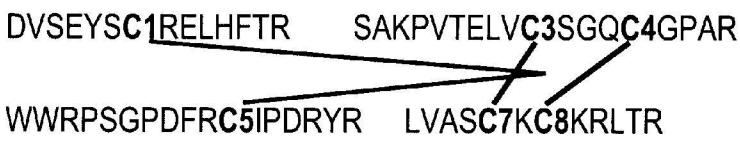

回應 (Ru)
350
300
250
200
150
100
50
0
2 nM Mab-D
20 nM 人類殼硬蛋白
20 nM T19.2
20 nM T20
20 nM T20.6
20 nM T21-22
20 nM AspN14.6
20 nM AspN18.6
20 nM AspN22.7-23.5
2 nM Mab-D +

【圖 18】

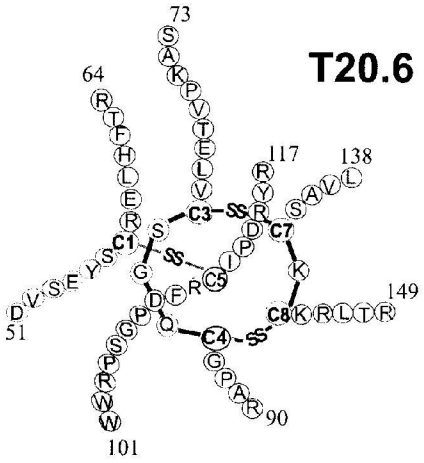
A. Mab-A及Mab-B之環2抗原決定基

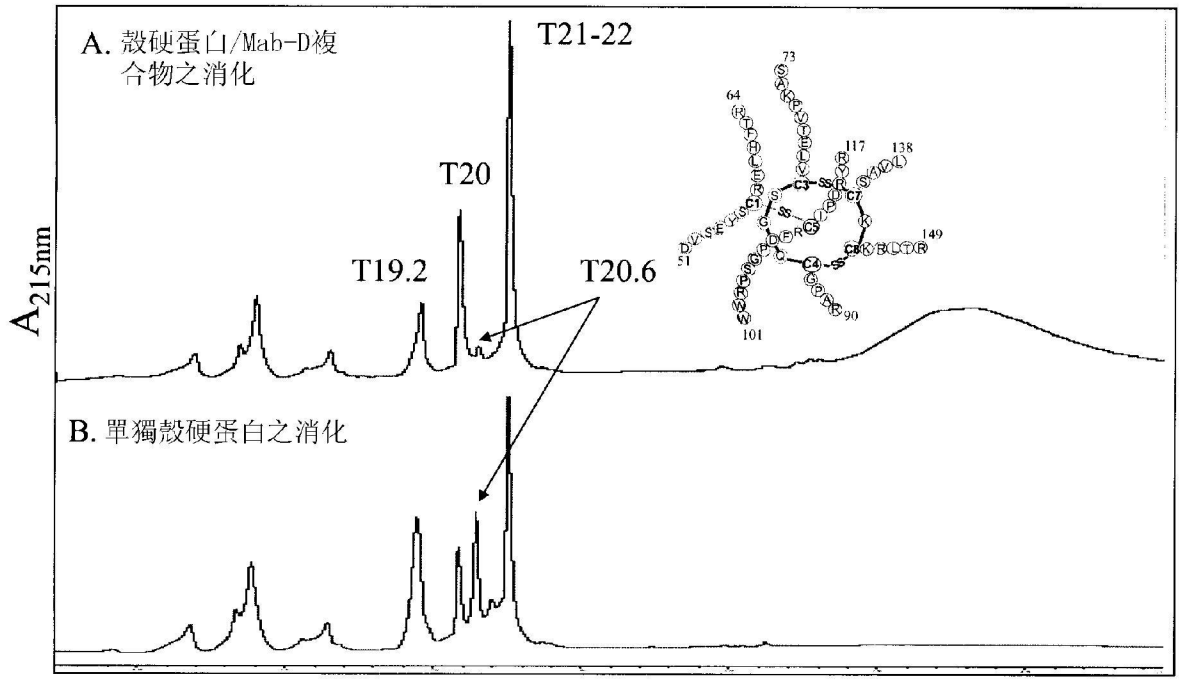


B. Mab-C及Mab-D之T20.6抗原決定基



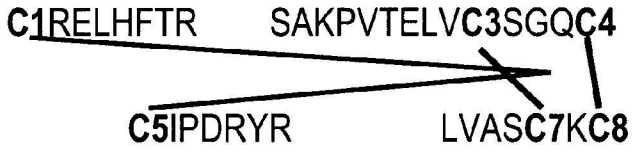
【圖 19】



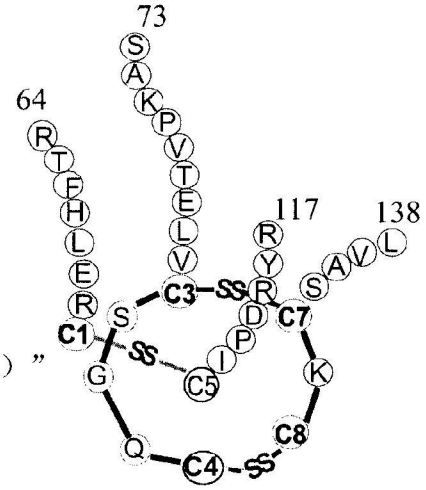

A. 殼硬蛋白/Mab-D複合物之消化
T21-22
T20
T19.2
T20.6
A215nm
B. 單獨殼硬蛋白之消化
73
64
117
138
149
51
90
101
C1
C2
C3
C4
C5
C6
C7
C8

【圖 20】

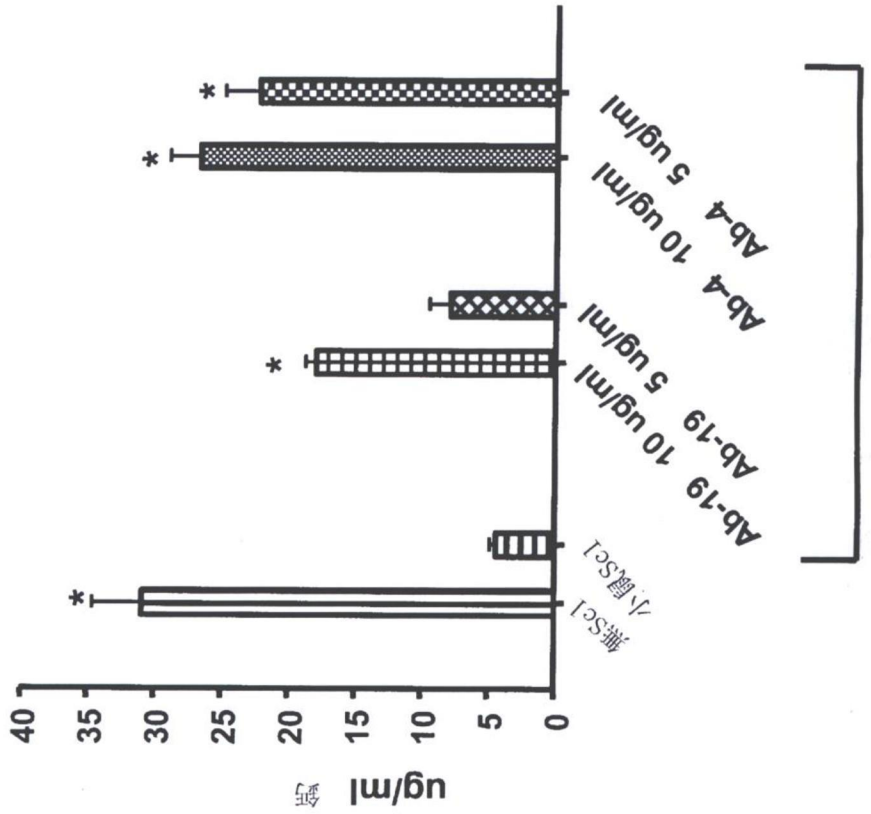
Mab-D之“T20.6衍生物1（胱胺酸結 + 4個臂）”抗原決定基



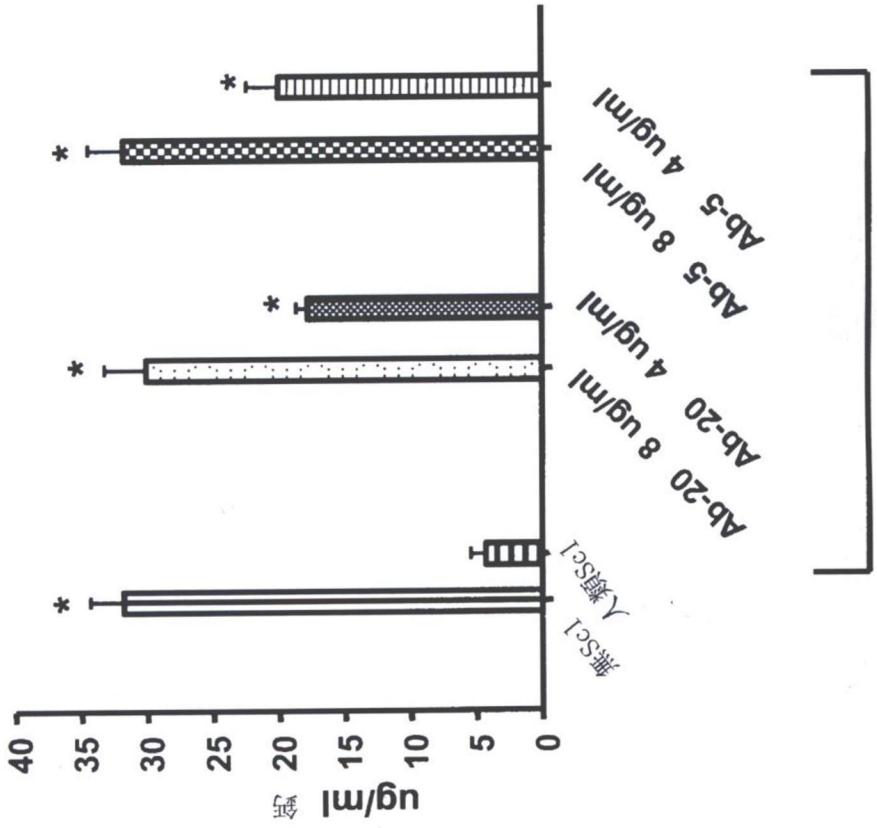
“T20.6衍生物1（胱胺酸結 + 4個臂）”



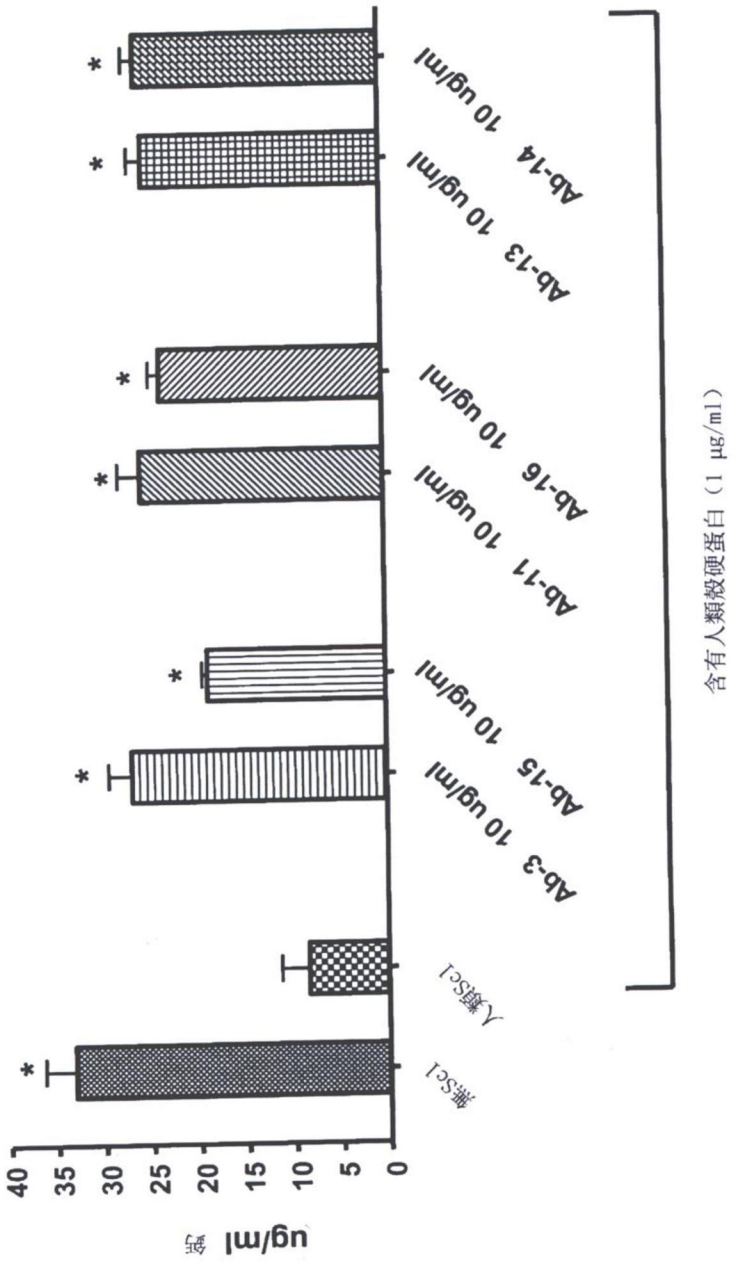
【圖21】


ug/ml 鈣
40
35
30
25
20
15
10
5
0
無Scl
小鼠Scl
Ab-19 10 ug/ml
Ab-19 5 ug/ml
Ab-4 10 ug/ml
Ab-4 5 ug/ml
含有小鼠殼硬蛋白（1 μg/ml）
* =在統計學上顯著不同於小鼠Scl組
誤差條形圖=平均值+/- SEM

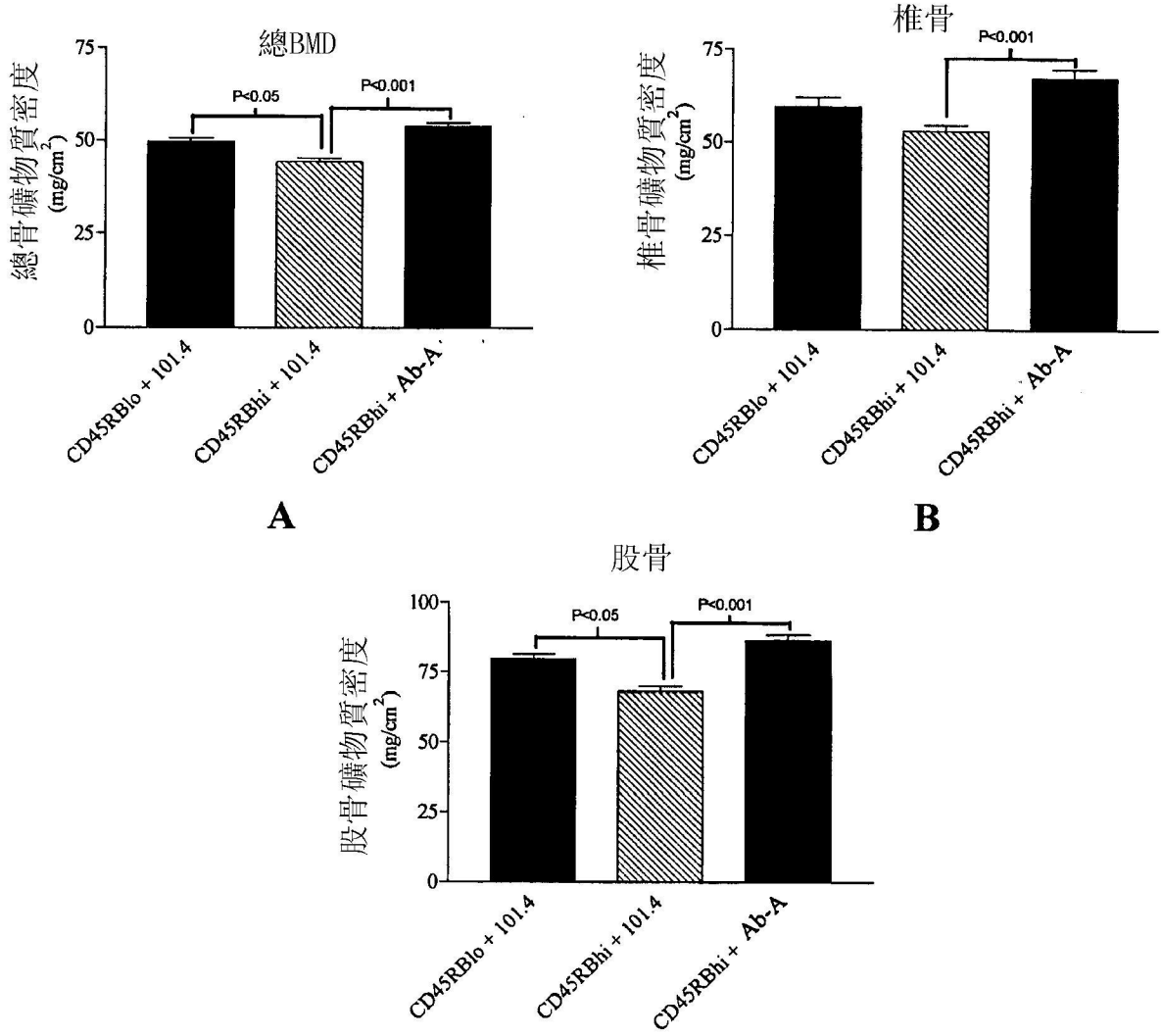
【圖 22】


40
35
30
25
20
15
10
5
0
ug/ml 鈣
無Sc1
人類Sc1
Ab-20 8 ug/ml
Ab-20 4 ug/ml
Ab-5 8 ug/ml
Ab-5 4 ug/ml
含有人類殼硬蛋白（1 μg/ml）
* =在統計學上顯著不同於人類Sc1組
誤差條形圖=平均值+/-SEM

【圖23】


ug/ml 數
40
35
30
25
20
15
10
5
0
無Sc1
人類Sc1
Ab-3 10 ug/ml
Ab-15 10 ug/ml
Ab-11 10 ug/ml
Ab-16 10 ug/ml
Ab-13 10 ug/ml
Ab-14 10 ug/ml
含有人類殺硬蛋白（1 μg/ml）
* = 在統計學上顯著不同於人類Sc1組
誤差條形圖=平均值+/-SEM

【圖 24】


總BMD
總骨礦物質密度 (mg/cm²)
75
50
25
0
P<0.05
P<0.001
CD45RBlo + 101.4
CD45RBhi + 101.4
CD45RBhi + Ab-A
A
椎骨
椎骨礦物質密度 (mg/cm²)
P<0.001
B
股骨
股骨礦物質密度 (mg/cm²)
100
C

【圖25】