I683827

(19)中華民國智慧財產局

(12)發明說明書公告本　**(11)證書號數：TW I683827 B**

(45)公告日： 中華民國 109 (2020) 年 02 月 01 日

(21)申請案號：102142528　(22)申請日： 中華民國 102 (2013) 年 11 月 21 日

(51)Int. Cl.：　*C07K16/18 (2006.01)*　*C07K16/46 (2006.01)*

A61K39/395 (2006.01)

(30)優先權：2012/11/21　美國　61/729,148

2013/03/13　美國　61/779,439

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(56)參考文獻：

WO　2006/119107A2　WO　2009/089004A1

WO　2012/118903A1

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申請專利範圍項數：11 項　圖式數：14　共 971 頁

(54)名稱

異二聚免疫球蛋白

(57)摘要

本申請案係有關異二聚抗體及使用方法。

The present application is directed to heterodimeric antibodies and methods of use.

指定代表圖：

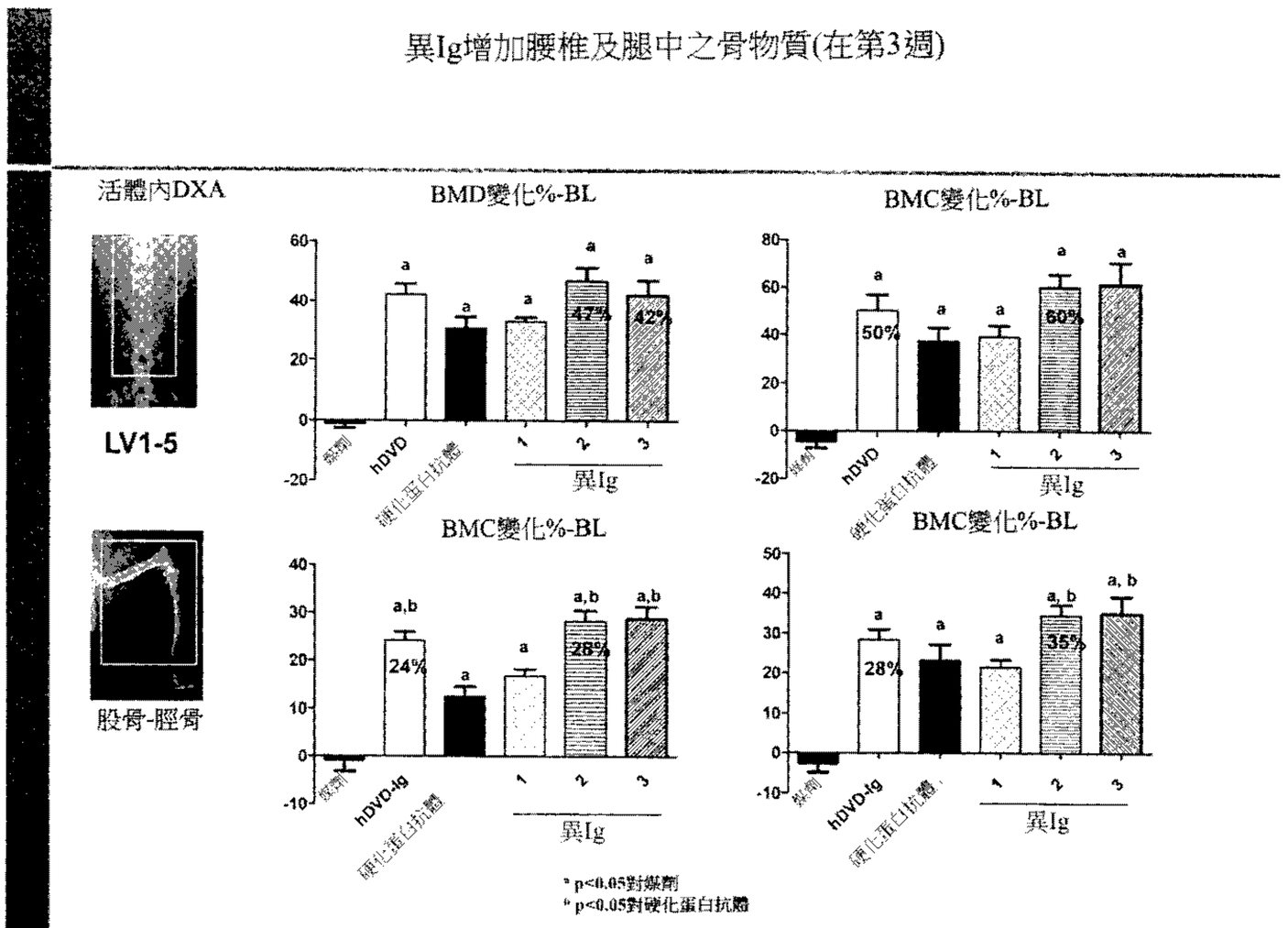


圖 2

公告本

I683827

發明摘要

申請案號：

申請日：

※IPC 分類：C07K；A61K

【發明名稱】

異二聚免疫球蛋白

HETERODIMERIC IMMUNOGLOBULINS

【中文】

本申請案係有關異二聚抗體及使用方法。

【英文】

The present application is directed to heterodimeric antibodies and methods of use.

【代表圖】

【本案指定代表圖】：第（　2　）圖。

【本代表圖之符號簡單說明】：

無

【本案若有化學式時，請揭示最能顯示發明特徵的化學式】：

無

發明專利說明書

（本說明書格式、順序，請勿任意更動）

【發明名稱】

異二聚免疫球蛋白

HETERODIMERIC IMMUNOGLOBULINS

[相關申請案之交互參照]

本申請案主張2012年11月21日申請之美國臨時申請案第61/729,148號及2013年3月13日申請之美國臨時申請案第61/779,439號之優先權益，該等臨時申請案之揭露內容以全文引用的方式併入本文中。

【技術領域】

本發明大體上係關於製備及使用用於治療與低骨礦物質密度相關之病症之異二聚抗體的方法。

[以引用的方式併入電子提交材料]

以全文引用的方式併入本文中的是與此同時提交且如下鑒別之電腦可讀核苷酸/胺基酸序列表：2013年11月13日創建之名爲「47233B_SeqListing.txt」之具有960,666個位元組的ASCII(文本)檔案。

[以引用方式之併入]

以下申請案據此以全文引用的方式併入：2006年4月25日申請之美國專利申請案第11/410,540號，其主張2006年4月17日申請之美國臨時專利申請案第60/792,645號、2006年3月13日申請之美國臨時專利申請案第60/782,244號、2006年2月24日申請之美國臨時專利申請案第60/776,847號及2005年5月3日申請之美國臨時專利申請案第60/677,583號之優先權；及2006年4月25日申請之美國專利申請案第11/411,003號(以美國專利第7,592,429號頒佈)，其主張2006年4月17日

申請之美國臨時專利申請案第60/792,645號、2006年3月13日申請之美國臨時專利申請案第60/782,244號、2006年2月24日申請之美國臨時專利申請案第60/776,847號及2005年5月3日申請之美國臨時專利申請案第60/677,583號之優先權。以下申請案據此亦以引用的方式併入：2008年9月17日申請之美國專利申請案第12/212,327號，其主張2007年9月17日申請之美國臨時專利申請案第60/973,024號之優先權；及2010年6月29日申請之美國專利申請案第12/811,171號，其根據美國法典第371篇爲2008年12月15日申請之國際專利申請案第PCT/US08/86864號之美國國家階段申請案，其主張2007年12月14日申請之美國臨時專利申請案第61/013,917號之優先權。

【先前技術】

開發作爲人類疾病之治療劑之雙特異性抗體具有巨大臨床潛力。雙特異性抗體可同時識別兩種不同抗原，中和不同病原性介體，募集不同類型之效應細胞，且調節信號路徑。然而，產生雙特異性抗體已極具挑戰性。廣泛應用雙特異性抗體已因難以開發用於產生展現有利半衰期、高穩定性、缺乏免疫原性以及大規模製造及純化之可行性之雙特異性抗體的平台而受阻。諸如DVD-Ig(雙可變域Ig)(Nature Biotechnology 25, 1290-1297 (2007))；交叉Ig[Schaefer W等人 (2011) PNAS 108(27): 11187-11192]；二合一Ig(Science 2009, 323, 1610)；BiTE®抗體[PNAS 92(15):7021-7025; 1995]之有前途之雙特異性抗體形式允許產生雙特異性抗體，但其具有不同種類之缺點。

【發明內容】

本文描述自兩種不同先前存在抗體產生異二聚抗體之方法。

在一個態樣中，本文描述一種在以下各域中包含一或多個取代之異二聚抗體或其片段：第一CH_3域、第二CH_3域、CH_1域、C_L域、V_H域及V_L域，其中該一或多個取代引入在靜電方面不利於同二聚體形成且

在靜電方面有利於異二聚體形成的帶電荷胺基酸。

在一些變化形式中，第一CH3域或第二CH3域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型人類IgG胺基酸序列中在CH3域中之相應位置處之一或多個帶正電荷胺基酸(例如離胺酸、組胺酸及精胺酸)經一或多個帶負電荷胺基酸(例如天冬胺酸及麩胺酸)置換。或者，第一CH3域或第二CH3域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型人類IgG胺基酸序列中在CH3域中之相應位置處之一或多個帶負電荷胺基酸經一或多個帶正電荷胺基酸置換。

在一些變化形式中，CH1域或CL域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型IgG胺基酸序列中之一或多個帶正電荷胺基酸經一或多個帶負電荷胺基酸置換。或者，CH1域或CL域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型IgG胺基酸序列中之一或多個帶負電荷胺基酸經一或多個帶正電荷胺基酸置換。

在一些變化形式中，本文所述之異二聚抗體之VH域或VL域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型IgG胺基酸序列中之一或多個帶正電荷胺基酸經一或多個帶負電荷胺基酸置換。或者，VH域或VL域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型IgG胺基酸序列中之一或多個帶負電荷胺基酸經一或多個帶正電荷胺基酸置換。

在另一態樣中，本文描述一種包含重鏈之異二聚抗體或其片段，該重鏈包含(a)在選自由AHo位置42-50組成之群之AHo位置處的在該位置處引入帶電荷胺基酸之第一胺基酸取代，(b)在選自由位置126-213(EU編號)組成之群之位置處的在該位置處引入帶電荷胺基酸之第二胺基酸取代，(c)在選自由位置352-360(EU編號)組成之群之位置處的在該位置處引入帶電荷胺基酸之第三胺基酸取代，及(d)在選自由位置395-403(EU編號)組成之群之位置處的引入帶電荷胺基酸之第四

胺基酸取代，其中(a)之該帶電荷胺基酸與(b)之該帶電荷胺基酸具有相同電荷，且其中(c)及(d)之該等帶電荷胺基酸具有(a)及(b)之該等帶電荷胺基酸之相反電荷。

在一些實施例中，第一胺基酸取代在AHo位置46處，第二胺基酸取代在EU位置183處，第三胺基酸取代在EU位置356處且第四胺基酸取代在EU位置399處。在一些實施例中，AHo位置46處之麩醯胺酸經麩胺酸置換，EU位置183處之絲胺酸經麩胺酸置換，EU位置356處之麩胺酸經離胺酸置換，且EU位置399處之天冬胺酸經離胺酸置換。

在另一態樣中，本文描述一種包含重鏈之抗體或其片段，該重鏈包含(a)在選自由AHo位置35-43組成之群之AHo位置處的在該位置處引入帶電荷胺基酸之第一胺基酸取代，(b)在選自由位置126-213(EU編號)組成之群之位置處的在該位置處引入帶電荷胺基酸之第二胺基酸取代，(c)在選自由位置388-398(EU編號)組成之群之位置處的在該位置處引入帶電荷胺基酸之第三胺基酸取代，及(d)在選自由位置404-413(EU編號)組成之群之位置處的引入帶電荷胺基酸之第四胺基酸取代，其中(c)及(d)之該等帶電荷胺基酸具有(a)及(b)之該等帶電荷胺基酸之相反電荷。在一些實施例中，AHo位置46處之麩醯胺酸經離胺酸置換，EU位置183處之絲胺酸經離胺酸置換，EU位置392處之離胺酸經天冬胺酸置換且EU位置409處之離胺酸經天冬胺酸置換。

在另一態樣中，本文描述一種包含輕鏈之抗體或片段，該輕鏈包含(a)在選自由AHo位置42-50組成之群之AHo位置處的在該位置處引入帶電荷胺基酸之第一胺基酸取代，及(b)在選自由位置126-213(EU編號)組成之群之位置處的在該位置處引入帶電荷胺基酸之第二胺基酸取代。在一些實施例中，AHo位置46處之麩醯胺酸經麩胺酸置換且EU位置176處之絲胺酸經麩胺酸置換。

在另一態樣中，本文描述一種包含重鏈之抗體，該重鏈包含(a)在

選自由AHo位置42-50組成之群之AHo位置處的在該位置處引入帶電荷胺基酸之第一胺基酸取代，(b)在選自由位置126-213(EU編號)組成之群之位置處的在該位置處引入帶電荷胺基酸之第二胺基酸取代，(c)在選自由位置352-360(EU編號)組成之群之位置處的在該位置處引入帶電荷胺基酸之第三胺基酸取代，及(d)在選自由位置395-403(EU編號)組成之群之位置處的引入帶電荷胺基酸之第四胺基酸取代，其中(a)及(b)之該等帶電荷胺基酸具有負電荷且(c)及(d)之該等帶電荷胺基酸具有正電荷。在一些實施例中，第一胺基酸取代在AHo位置46處，第二胺基酸取代在EU位置183處，第三胺基酸取代在EU位置356處且第四胺基酸取代在EU位置399處。在一些實施例中，抗體包含在AHo位置46及EU位置176處包含帶正電荷胺基酸之輕鏈。

在另一態樣中，本文描述一種包含第一重鏈及第二重鏈以及第一輕鏈及第二輕鏈之異二聚抗體，其中該第一重鏈在AHo位置46及EU位置183、356及399處包含胺基酸取代，其中該第二重鏈在AHo位置46及EU位置183、392及409處包含胺基酸取代，且其中該第一輕鏈及該第二輕鏈在AHo位置46及EU位置176處包含胺基酸取代，其中該等胺基酸取代在該等位置處引入帶電荷胺基酸。在一些實施例中，第一重鏈之AHo位置46處之麩醯胺酸經麩胺酸置換，第二重鏈之AHo位置46處之麩醯胺酸經離胺酸置換，第一輕鏈之AHo位置46處之麩醯胺酸經離胺酸置換，第二輕鏈之AHo位置46處之麩醯胺酸經麩胺酸置換，第一重鏈之EU位置183處之絲胺酸經麩胺酸置換，第一重鏈之EU位置356處之麩胺酸經離胺酸置換，第一重鏈之EU位置399處之麩胺酸經離胺酸置換，第二重鏈之EU位置183處之絲胺酸經離胺酸置換，第二重鏈之EU位置392處之離胺酸經天冬胺酸置換，且第二重鏈之EU位置409處之離胺酸經天冬胺酸置換。

在本文所述之一些或任何實施例中，抗體結合硬化蛋白

(sclerostin)之包含SEQ ID NO: 1之胺基酸86-111的區域。

本文亦描述一種結合硬化蛋白之包含SEQ ID NO: 1之胺基酸86-111的區域之異二聚抗體，其中該抗體包含含有硬化蛋白結合部分之第一重鏈及第一輕鏈以及包含DKK1結合部分之第二重鏈及第二輕鏈，其中該第一重鏈在AHo位置46及EU位置183、356及399處包含胺基酸取代，其中該第二重鏈在AHo位置46及EU位置183、392及409處包含胺基酸取代，其中該第一輕鏈及該第二輕鏈在AHo位置46及EU位置176處包含胺基酸取代，且其中該等胺基酸取代在該等位置處引入帶電荷胺基酸。

在另一態樣中，本文描述一種結合硬化蛋白之包含SEQ ID NO: 1之胺基酸86-111的區域之異二聚抗體，該抗體包含含有硬化蛋白結合部分之第一重鏈及第一輕鏈以及含有DKK1結合部分之第二重鏈及第二輕鏈，其中該第一重鏈在EU位置183、356及399處包含胺基酸取代，其中該第二重鏈在EU位置183、392及409處包含胺基酸取代，且其中該第一輕鏈及該第二輕鏈在EU位置176處包含胺基酸取代，其中該等胺基酸取代在該等位置處引入帶電荷胺基酸。

本發明之另一態樣係關於一種結合硬化蛋白及DKK-1之異二聚抗體，其包含第一重鏈，該第一重鏈包含本文所述之任一硬化蛋白抗體之重鏈可變區胺基酸序列且在該第一重鏈之EU位置183、356及399處包含胺基酸取代；第二重鏈，該第二重鏈包含本文所述之任一DKK-1抗體之重鏈可變區胺基酸序列且在該第二重鏈之EU位置183、392及409處包含胺基酸取代；第一輕鏈，該第一輕鏈包含本文所述之任一硬化蛋白抗體之輕鏈可變區胺基酸序列且在該第一輕鏈之EU位置176處包含胺基酸取代；及第二輕鏈，該第二輕鏈包含本文所述之任何DKK-1抗體之輕鏈可變區胺基酸序列且在該第二輕鏈之EU位置176處包含胺基酸取代；其中該等胺基酸取代在該等位置處引入帶電荷胺基酸。

本發明之另一態樣係關於一種結合硬化蛋白及DKK-1之異二聚抗體，其包含第一重鏈，該第一重鏈包含選自由SEQ ID NO: 378及366組成之群之可變區胺基酸序列且在該第一重鏈之EU位置183、356及399處包含胺基酸取代；第二重鏈，該第二重鏈包含選自由SEQ ID NO: 1003及974組成之群之可變區胺基酸序列且在該第二重鏈之EU位置183、392及409處包含胺基酸取代；第一輕鏈，該第一輕鏈包含選自由SEQ ID NO: 376及364組成之群之可變區胺基酸序列且在該第一輕鏈之EU位置176處包含胺基酸取代；及第二輕鏈，該第二輕鏈包含選自由SEQ ID NO: 1002及978組成之群之可變區胺基酸序列且在該第二輕鏈之EU位置176處包含胺基酸取代；其中該等胺基酸取代在該等位置處引入帶電荷胺基酸。

在一些實施例中，結合硬化蛋白及DKK1之異二聚抗體包含含有SEQ ID NO: 1038中所述之胺基酸序列之第一重鏈；含有SEQ ID NO: 1034中所述之胺基酸序列之第二重鏈；含有SEQ ID NO: 1039中所述之胺基酸序列之第一輕鏈及含有SEQ ID NO: 1035中所述之胺基酸序列之第二輕鏈。

在一些實施例中，結合硬化蛋白及DKK1之異二聚抗體包含含有SEQ ID NO: 1038中所述之胺基酸序列之第一重鏈；含有SEQ ID NO: 1036中所述之胺基酸序列之第二重鏈；含有SEQ ID NO: 1039中所述之胺基酸序列之第一輕鏈及含有SEQ ID NO: 1037中所述之胺基酸序列之第二輕鏈。

在一些實施例中，結合硬化蛋白及DKK1之異二聚抗體包含含有SEQ ID NO: 1040中所述之胺基酸序列之第一重鏈；含有SEQ ID NO: 1034中所述之胺基酸序列之第二重鏈；含有SEQ ID NO: 1041中所述之胺基酸序列之第一輕鏈及含有SEQ ID NO: 1035中所述之胺基酸序列之第二輕鏈。

在一些實施例中，結合硬化蛋白及DKK1之異二聚抗體包含含有SEQ ID NO: 1040中所述之胺基酸序列之第一重鏈；含有SEQ ID NO: 1036中所述之胺基酸序列之第二重鏈；含有SEQ ID NO: 1041中所述之胺基酸序列之第一輕鏈及含有SEQ ID NO: 1037中所述之胺基酸序列之第二輕鏈。

在一些實施例中，結合硬化蛋白及DKK1之異二聚抗體包含含有SEQ ID NO: 1046中所述之胺基酸序列之第一重鏈；含有SEQ ID NO: 1042中所述之胺基酸序列之第二重鏈；含有SEQ ID NO: 1047中所述之胺基酸序列之第一輕鏈及含有SEQ ID NO: 1043中所述之胺基酸序列之第二輕鏈。

在一些實施例中，結合硬化蛋白及DKK1之異二聚抗體包含含有SEQ ID NO: 1046中所述之胺基酸序列之第一重鏈；含有SEQ ID NO: 1044中所述之胺基酸序列之第二重鏈；含有SEQ ID NO: 1047中所述之胺基酸序列之第一輕鏈及含有SEQ ID NO: 1045中所述之胺基酸序列之第二輕鏈。

在一些實施例中，結合硬化蛋白及DKK1之異二聚抗體包含含有SEQ ID NO: 1048中所述之胺基酸序列之第一重鏈；含有SEQ ID NO: 1042中所述之胺基酸序列之第二重鏈；含有SEQ ID NO: 1049中所述之胺基酸序列之第一輕鏈及含有SEQ ID NO: 1043中所述之胺基酸序列之第二輕鏈。

在一些實施例中，結合硬化蛋白及DKK1之異二聚抗體包含含有SEQ ID NO: 1048中所述之胺基酸序列之第一重鏈；含有SEQ ID NO: 1044中所述之胺基酸序列之第二重鏈；含有SEQ ID NO: 1049中所述之胺基酸序列之第一輕鏈及含有SEQ ID NO: 1045中所述之胺基酸序列之第二輕鏈。

本發明亦涵蓋一種包含重鏈之異二聚抗體，該重鏈包含選自由

SEQ ID NO: 1038、SEQ ID NO: 1046、SEQ ID NO: 1040及SEQ ID NO: 1048組成之群之胺基酸序列。在一些實施例中，異二聚抗體視情況包含選自由SEQ ID NO: 1039、SEQ ID NO: 1047、SEQ ID NO: 1041及SEQ ID NO: 1049組成之群之輕鏈胺基酸序列。

本發明亦涵蓋一種包含重鏈之異二聚抗體，該重鏈包含選自由SEQ ID NO: 1034、SEQ ID NO: 1042、SEQ ID NO: 1036及SEQ ID NO: 1044組成之群之胺基酸序列。在一些實施例中，異二聚抗體視情況包含選自由SEQ ID NO: 1035、SEQ ID NO: 1043、SEQ ID NO: 1037及SEQ ID NO: 1045組成之群之輕鏈胺基酸序列。

在另一態樣中，本文描述一種結合硬化蛋白之包含SEQ ID NO: 1之胺基酸86-111的區域之抗體，其中該抗體在以下各域中包含取代：第一CH3域、第二CH3域、CH1域及CL域，其中該一或多個取代引入在靜電方面不利於同二聚體形成且在靜電方面有利於異二聚體形成的帶電荷胺基酸。

本文亦描述一種結合硬化蛋白之包含SEQ ID NO: 1之胺基酸86-111的區域之抗體，其中該抗體包含具有包含一或多個胺基酸取代之CH3域的重鏈，其中該一或多個取代引入在靜電方面不利於同二聚體形成且在靜電方面有利於異二聚體形成的帶電荷胺基酸。在一些實施例中，CH3域中之帶負電荷胺基酸(例如在EU位置D399、E356或E357處)經帶正電荷胺基酸取代。在一些實施例中，EU位置D399、E356及E357處之胺基酸經帶正電荷胺基酸(例如離胺酸)取代。

在替代性實施例中，CH3域中之帶正電荷胺基酸(例如在EU位置K370、K392或K409處)經帶負電荷胺基酸取代。在一些實施例中，如EU位置K370、K392及K409之胺基酸經帶負電荷胺基酸(例如天冬胺酸)取代。

在一些實施例中，異二聚抗體爲抗體、雙特異性抗體、單特異性

單價抗體、雙特異性大抗體、單域抗體、肽體、雙特異性肽體、單價肽體或受體融合蛋白。

亦提供包含編碼本文所述之任何異二聚抗體之核苷酸序列的核酸以及包含核酸之載體及包含核酸(或載體)之宿主細胞。

本發明之另一態樣係關於增加哺乳動物個體中之骨礦物質密度之方法，其包含以有效增加該個體中之骨礦物質密度之量向該個體投與本文所述之異二聚抗體。本發明亦包括使用本文所述之異二聚抗體增加骨礦物質密度之方法。如本文所述之使用方法可或者表徵爲異二聚抗體增加骨礦物質密度之用途。

本發明亦包括包含本文所述之異二聚抗體及醫藥學上可接受之載劑、稀釋劑或佐劑的組合物。在一些實施例中，在約4℃下儲存兩週之後，組合物中小於5%(或小於4%、或小於3%、或小於2%或小於1%或1%以下)之抗體呈聚集體形式。可例如藉由粒徑排阻層析法(SEC)或動態光散射(DLS)測定組合物中之抗體聚集量。

在另一態樣中，本文描述一種包含異二聚抗體或其片段及醫藥學上可接受之載劑、稀釋劑或佐劑的組合物，該異二聚抗體或其片段在以下各域中包含一或多個取代：第一CH_3域、第二CH_3域、CH_1域、C_L域、V_H域及V_L域，其中該一或多個取代引入在靜電方面不利於同二聚體形成且在靜電方面有利於異二聚體形成的帶電荷胺基酸；其中在約4℃下儲存兩週之後，該組合物中小於5%之該抗體或片段呈聚集體形式。

在另一態樣中，本文描述一種包含結合硬化蛋白之包含SEQ ID NO: 1之胺基酸86-111的區域之異二聚抗體及醫藥學上可接受之載劑、稀釋劑或佐劑的組合物，該抗體在以下各域中包含取代：第一CH_3域、第二CH_3域、CH_1域及C_L域，其中該一或多個取代引入在靜電方面不利於同二聚體形成且在靜電方面有利於異二聚體形成的帶電荷胺基

酸；其中在約4℃下儲存兩週之後，該組合物中小於5%之該抗體呈聚集體形式。

本文所用之章節標題僅出於組織目的且不應解釋爲限制所述標的物。本說明書之主體內引用之所有參考文獻皆以全文引用的方式明確併入本文中。

標準技術可用於重組DNA、寡核苷酸合成、組織培養及轉型、蛋白質純化等。可根據製造商說明書或如此項技術中通常所達成或如本文所述來執行酶促反應及純化技術。以下程序及技術可通常根據此項技術中熟知及如本說明書整篇引用及論述之各種一般性及更特定參考文獻中所述之習用方法來執行。參見例如Sambrook等人，2001, Molecular Cloning: A Laboratory Manuel, 第3版, Cold Spring Harbor Laboratory Press, cold Spring Harbor, N.Y.，其出於任何目的以引用的方式併入本文中。除非提供明確定義，否則關聯本文所述之分析化學、有機化學以及醫學及醫藥化學使用之命名法及本文所述之分析化學、有機化學以及醫學及醫藥化學之實驗室程序及技術爲此項技術中熟知且通常使用者。標準技術可用於化學合成、化學分析、醫藥製備、調配及傳遞以及治療患者。

【圖式簡單說明】

圖1說明以下異二聚抗體之活體內研究設計：(1)Ab23-Ab6.147 v2，(2)Ab5-Ab6.37.5 v1，及(3)Ab5-Ab6.147。

圖2比較單特異性Ig(Ab5)、雙特異性DVD(6.147-Ab23)及異二聚抗體(1、2及3)之間的在第3週在小鼠之腰椎及腿中達成的骨物質密度(BMD)增加百分比。

圖3顯示四種硬化蛋白-DKK1異二聚抗體(亦即Ab23-6.37.5 v1、Ab5-6.37.5 v1、Ab5-6.147 v2及Ab23-6.147 v2)之藥物動力學(PK)概況。

圖4：使用不同方法之雙特異性抗體變異體之組態，(a)結合抗原A

之可變區中之一對帶電荷殘基K/D與C_H1/CL中之一對帶電荷殘基D/K組合以增強LC與其同源HC配對；結合抗原B之可變區中之一對帶電荷殘基D/K與C_H1/CL中之一對帶電荷殘基K/D組合以增強LC與其同源HC配對。亦指示C_H3域中之異二聚化電荷殘基。(b)結合抗原A之可變區中之一對帶電荷殘基D/K與C_H1/CL中之兩對帶電荷殘基KK/DD組合以增強LC與其同源HC配對；結合抗原B之可變區中之一對帶電荷殘基K/D與C_H1/CL中之兩對帶電荷殘基DD/KK組合以增強LC與其同源HC配對。亦指示C_H3域中之用於異二聚化之電荷殘基。(c)結合抗原A之可變區中之兩對帶電荷殘基KK/DD與C_H1/CL中之一對帶電荷殘基D/K組合以增強LC與其同源HC配對；結合抗原B之可變區中之兩對帶電荷殘基DD/KK與C_H1/CL中之一對帶電荷殘基K/D組合以增強LC與其同源HC配對。亦指示C_H3域中之用於異二聚化之電荷殘基。(d)結合抗原A之可變區中之兩對帶電荷殘基KK/DD與C_H1/CL中之兩對帶電荷殘基DD/KK組合以增強LC與其同源HC配對；結合抗原B之可變區中之兩對帶電荷殘基DD/KK與C_H1/CL中之兩對帶電荷殘基KK/DD組合以增強LC與其同源HC配對。亦指示C_H3域中之用於異二聚化之電荷殘基。(e)結合抗原A之可變區中之一對帶電荷殘基K/D及一對半胱胺酸殘基與C_H1/CL中之一對帶電荷殘基D/K組合以增強LC與其同源HC配對；結合抗原B之可變區中之一對半胱胺酸殘基及一對帶電荷殘基D/K與C_H1/CL中之一對帶電荷殘基K/D組合以增強LC與其同源HC配對。亦指示C_H3域中之用於異二聚化之電荷殘基。©表示半胱胺酸殘基，在兩個半胱胺酸殘基之間形成之二硫鍵可以正確LC/HC配對使Fab區穩定。(f)結合抗原A之可變區中之一對帶電荷殘基K/D及一對小/大殘基與C_H1/CL中之一對帶電荷殘基D/K組合以增強LC與其同源HC配對；結合抗原B之可變區中之一對帶電荷殘基殘基D/K及一對大/小殘基與C_H1/CL中之一對帶電荷殘基K/D組合以增強LC與其同源HC配對。亦指

示C_H3域中之用於異二聚化之電荷殘基。突出三角表示大殘基；退縮三角表示小殘基。鈕入孔效應可與靜電操縱效應合作起作用以指導及穩定化正確LC/HC配對。

圖5：人類重鏈V區及J區之比對。編號係基於AHo系統。加亮界面殘基。

圖6：人類κ鏈V區及J區之比對。編號係基於AHo系統。加亮界面殘基。

圖7：人類λ鏈V區及J區之比對。編號係基於AHo系統。加亮界面殘基。

圖8爲關聯DKK1 mRNA表現(y軸)與向食蟹獼猴投與之Ab-5之劑量(mg/kg)(x軸)的圖。說明之資料顯示硬化蛋白抗體治療誘導食蟹獼猴之肱骨中段及腰椎中之DKK1 mRNA表現。

圖9爲描述在第1天(IV)、第15天(IV)及第43天(SC)接受25 mg/kg Ab-5、DVD抗體6.147-AbL-Ab23、異二聚抗體Ab23-6.37.5.v.1、異二聚抗體Ab5-6.37.5.v.1及異二聚抗體Ab5-6.147.v.1之食蟹獼猴中絕對血清酒石酸抗性酸性磷酸酶5b(TRACP 5b)濃度(y軸)隨時間(x軸)之變化百分比的圖。

圖10爲描述在第1天(IV)、第15天(IV)及第43天(SC)接受25 mg/kg Ab-5、DVD抗體6.147-AbL-Ab23、異二聚抗體Ab23-6.37.5.v.1、異二聚抗體Ab5-6.37.5.v.1及異二聚抗體Ab5-6.147.v.1之食蟹獼猴中血清骨鈣蛋白(OC)濃度(y軸)隨時間(x軸)之變化百分比的圖。

圖11爲描述在第1天(IV)、第15天(IV)及第43天(SC)接受25 mg/kg Ab-5、DVD抗體6.147-AbL-Ab23、異二聚抗體Ab23-6.37.5.v.1、異二聚抗體Ab5-6.37.5.v.1及異二聚抗體Ab5-6.147.v.1之食蟹獼猴中血清骨鹼性磷酸酶(BAP)濃度(y軸)隨時間(x軸)之變化百分比的圖。

圖12爲描述在第1天(IV)、第15天(IV)及第43天(SC)接受Ab-5、

DVD抗體6.147-AbL-Ab23、異二聚抗體Ab23-6.37.5.v.1、異二聚抗體Ab5-6.37.5.v.1及異二聚抗體Ab5-6.147.v.1之食蟹獼猴中血清C1CP濃度(y軸)隨時間(x軸)之變化百分比的圖。

圖13爲描述在IV及SC注射之後，Ab-5、DVD抗體6.147-AbL-Ab23、異二聚抗體Ab23-6.37.5.v.1、異二聚抗體Ab5-6.37.5.v.1及異二聚抗體Ab5-6.147.v.1之藥物動力學概況(濃度(nM)(y軸)對時間(小時)(x軸))的圖。

圖14爲描述接受異二聚抗體(具有垂直條紋及斜條紋之棒條)、硬化蛋白抗體單藥療法(打點棒條)、DKK1抗體單藥療法(中空棒條)或組合硬化蛋白抗體及DKK1抗體(具有水平條紋之棒條)之小鼠之腰椎中骨物質相較於基線之變化百分比(y軸)的圖。

【實施方式】

本申請案係基於發現可藉由以可在不存在其他污染物質之情況下僅使兩種不同抗體之重鏈及輕鏈裝配至異二聚抗體中的方式工程改造兩種不同抗體之重鏈及輕鏈來產生異二聚IgG。在一個態樣中，藉由工程改造兩個重鏈之CH3區以使其僅形成異二聚體來達成異二聚配對。此外，藉由工程改造輕鏈(LC)與重鏈(HC)之間的界面殘基達成之靜電操縱防止當兩對不同重鏈及輕鏈裝配以形成所要四鏈異二聚抗體時，輕鏈與非同源重鏈錯配。如本文所述，一示範性策略包含在LC1/HC1界面處在第一輕鏈(LC1)中引入一或多個帶負電荷殘基(例如Asp或Glu)且在相伴重鏈(HC1)中引入一或多個帶正電荷殘基(例如Lys、His或Arg)，同時在LC2/HC2界面處在第二輕鏈(LC2)中引入一或多個帶正電荷殘基(例如Lys、His或Arg)且在相伴重鏈(HC2)中引入一或多個帶負電荷殘基(例如Asp或Glu)。靜電操縱效應引導LC1與HC1配對且引導LC2與HC2配對，因爲在界面處之相反帶電荷殘基(極性)吸引，而在界面處之相同類型之帶電荷殘基(極性)產生排斥，從而使非

所要HC/LC配對受抑制。

使選擇用於工程改造之LC/HC界面殘基包埋在VL/VH及CL/CH1界面內且在空間上接近。在不同抗體家族之中，目標殘基充分保守。工程改造輕鏈及重鏈以形成特定異二聚體之其他方式包括用一對半胱胺酸殘基置換VL/VH界面中之一對帶電荷殘基以形成二硫鍵來穩定Fab區，用疏水性殘基(例如麩醯胺酸)置換VL/VH界面中之一或多個親水性殘基(例如甘胺酸)，或工程改造VL/VH界面處之一對大/小殘基以施加鈕入孔(knob-into-hole)效應來容納正確LC/HC配對。本文所述之策略可用於在不使用人工連接子下自兩種先前存在抗體高效產生全長異二聚抗體。所得異二聚抗體穩定且可經受商業製造而無過度聚集或產量損失。因爲此新型異二聚抗體可同時靶向兩種不同抗原或同一抗原上之兩種不同抗原決定基，所以其可具有獨特治療許多疾病之重大潛力。

如本文所用之術語「界面」係指由第一抗體域中之一或多個胺基酸與第二抗體域之一或多個胺基酸相互作用產生的締合表面。示範性界面包括CH1/CL、VH/VL及CH3/CH3。在一些實施例中，界面包括例如形成界面之胺基酸之間的氫鍵、靜電相互作用或鹽橋。

在一個態樣中，本文描述一種在以下各域中包含一或多個取代之異二聚抗體或其片段：第一CH_3域、第二CH_3域、CH_1域、C_L域、V_H域及V_L域，其中該一或多個取代引入在靜電方面不利於同二聚體形成且在靜電方面有利於異二聚體形成的帶電荷胺基酸。

本文所述之異二聚抗體可包含任何恆定區。輕鏈恆定區可爲例如κ或λ型輕鏈恆定區，例如人類κ或λ型輕鏈恆定區。重鏈恆定區可爲例如α、δ、ε、γ或μ型重鏈恆定區，例如人類α、δ、ε、γ或μ型重鏈恆定區。在一個實施例中，輕鏈或重鏈恆定區爲天然存在之恆定區之片段、衍生物、變異體或突變蛋白質。

在一些變化形式中，第一CH3域或第二CH3域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型人類IgG胺基酸序列中在CH3域中之相應位置處之一或多個帶正電荷胺基酸(例如離胺酸、組胺酸及精胺酸)經一或多個帶負電荷胺基酸(例如天冬胺酸及麩胺酸)置換。或者，第一CH3域或第二CH3域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型人類IgG胺基酸序列中在CH3域中之相應位置處之一或多個帶負電荷胺基酸經一或多個帶正電荷胺基酸置換。

在一些變化形式中，CH1域或CL域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型IgG胺基酸序列中之一或多個帶正電荷胺基酸經一或多個帶負電荷胺基酸置換。或者，CH1域或CL域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型IgG胺基酸序列中之一或多個帶負電荷胺基酸經一或多個帶正電荷胺基酸置換。

在一些變化形式中，本文所述之異二聚抗體之VH域或VL域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型IgG胺基酸序列中之一或多個帶正電荷胺基酸經一或多個帶負電荷胺基酸置換。或者，VH域或VL域包含不同於野生型IgG胺基酸序列之胺基酸序列以使野生型IgG胺基酸序列中之一或多個帶負電荷胺基酸經一或多個帶正電荷胺基酸置換。

在另一態樣中，本文描述一種包含重鏈之異二聚抗體或其片段，該重鏈包含(a)在選自由AHo位置42-50組成之群之AHo位置處的在該位置處引入帶電荷胺基酸之第一胺基酸取代，(b)在選自由位置126-213(EU編號)組成之群之位置處的在該位置處引入帶電荷胺基酸之第二胺基酸取代，(c)在選自由位置352-360(EU編號)組成之群之位置處的在該位置處引入帶電荷胺基酸之第三胺基酸取代，及(d)在選自由位置395-403(EU編號)組成之群之位置處的引入帶電荷胺基酸之第四胺基酸取代，其中(a)之該帶電荷胺基酸與(b)之該帶電荷胺基酸具有相

同電荷，且其中(c)及(d)之該等帶電荷胺基酸具有(a)及(b)之該等帶電荷胺基酸之相反電荷。

在本文中，使用AHo編號系統描述可變域之構架區(下述)內之特定胺基酸的位置。因為抗體CDR胺基酸序列長度在抗體與抗體之間不同，所以基於線性序列(假定第一殘基為位置1)對殘基編號會導致在各抗體之間，構架殘基具有不同位置編號。使用Kabat或EU編號流程可避免此衝突且使得能夠在抗體間比較構架位置。然而，結構等效位置可具有不同Kabat或EU編號。類似地，具有相同Kabat編號之殘基可存在於結構上之兩個不同位置處。Annemarie Honegger及Andreas Pluckthun開發在CDR區中引入間隙以使與所比對域之平均結構之偏差最小的結構基編號流程(AHo)。(Honegger, A.及Plückthun, A. (2001). J. Mol. Biol. 309, 657-670) 此導致當比較兩種不同抗體時，結構等效位置具有相同殘基編號。此使得能夠在抗體之間比較可變域構架區中之取代之影響。圖5-7分別提供人類重鏈、κ及λ可變域區域之AHo編號。

如本文所用，術語「構架」或「構架序列」係指可變區減去CDR之區域或序列。因為CDR序列之精確界定可藉由不同系統來確定，所以構架序列之含義易受相應不同解釋。六個CDR(輕鏈之CDR-L1、CDR-L2及CDR-L3以及重鏈之CDR-H1、CDR-H2及CDR-H3)亦將輕鏈及重鏈上之構架區分成各鏈上之四個子區域(FR1、FR2、FR3及FR4)，其中CDR1位於FR1與FR2之間，CDR2位於FR2與FR3之間，且CDR3位於FR3與FR4之間。在不將特定子區域指定為FR1、FR2、FR3或FR4之情況下，構架區代表單一天然存在之免疫球蛋白鏈之可變區內的組合FR。如本文所用，FR代表四個子區域之一，且FRs代表構成構架區之四個子區域之兩者或兩者以上。

「取代」胺基酸或胺基酸「之取代」係指將原始胺基酸殘基取代成一或多個其他胺基酸殘基。

重鏈修飾

為使特定重鏈結合其同源輕鏈之效率最大，重鏈與輕鏈兩者均含有互補胺基酸取代。就「互補胺基酸取代」而言，其意謂對重鏈中之正電荷胺基酸之取代與對輕鏈中之與重鏈殘基締合之胺基酸的帶負電荷胺基酸取代配對。同樣，對重鏈中之負電荷胺基酸之取代與對輕鏈中之與重鏈殘基締合之胺基酸的帶正電荷胺基酸取代配對。

在一些實施例中，工程改造抗體重鏈可變區。圖5為人類重鏈可變域V區及J區之生殖系比對。在一些實施例中，異二聚抗體包含與人類生殖系重鏈可變區至少約70%、至少約71%、至少約72%、至少約73%、至少約74%、至少約75%、至少約76%、至少約77%、至少約78%、至少約79%、至少約80%、至少約81%、至少約82%、至少約83%、至少約84%、至少約85%、至少約86%、至少約87%、至少約88%、至少約89%、至少約90%、至少約91%、至少約92%、至少約93%、至少約94%、至少約95%、至少約96%、至少約97%、至少約98%或至少約99%一致之重鏈可變區。

VH域內之V區界面殘基(亦即介導VH及VL域之裝配之胺基酸殘基)包括AHo位置1(Kabat位置1)、3(Kabat位置3)、42(Kabat位置35)、44(Kabat位置37)、46(Kabat位置39)、50(Kabat位置43)、51(Kabat位置44)、52(Kabat位置45)、53(Kabat位置46)、54(Kabat位置47)、57(Kabat位置50)、70(Kabat位置59)、103(Kabat位置89)、105(Kabat位置91)及107(Kabat位置93)。內部之J區界面殘基包括AHo位置139(Kabat位置103)、140(Kabat位置104)、141(Kabat位置105)及142(Kabat位置106)。在一些實施例中，一或多個界面殘基經帶電荷(帶正電荷或帶負電荷)胺基酸取代。

在一些實施例中，VH域之AHo位置46(Kabat位置39)處之胺基酸經帶正電荷胺基酸置換。在替代性實施例中，VH域之AHo位置46(Kabat

位置39)處之胺基酸經帶負電荷胺基酸置換。

在一些實施例中，VH域之AHo位置51(Kabat位置44)及/或AHo位置141(Kabat位置105)處之胺基酸經帶電荷胺基酸置換。在一些實施例中，AHo位置51處之胺基酸被取代成帶正電荷胺基酸，例如離胺酸。在替代性實施例中，AHo位置51處之胺基酸被取代成帶負電荷胺基酸，例如天冬胺酸。在一些實施例中，AHo位置141處之胺基酸被取代成帶正電荷胺基酸，例如離胺酸。在替代性實施例中，AHo位置141處之胺基酸被取代成帶負電荷胺基酸，例如天冬胺酸。在一些實施例中，AHo位置51及AHo位置141處之胺基酸被取代成帶正電荷胺基酸(例如離胺酸)或帶負電荷胺基酸(例如天冬胺酸)。此等實施例可進一步包含在AHo位置46處取代成帶正電荷或帶負電荷胺基酸。

重鏈之CH1區亦與輕鏈複合，且此區域可經工程改造以增加特定重鏈與其同源輕鏈配對之效率。可藉由以下手段來促進裝配：在或接近界面處將半胱胺酸殘基引入重鏈及輕鏈中以允許形成二硫鍵，改變胺基酸以產生鈕入孔效應，及與本文對於可變區所述之靜電工程改造類似之靜電工程改造。

在一些實施例中，異二聚抗體包含與人類生殖系重鏈CH1區至少約70%、至少約71%、至少約72%、至少約73%、至少約74%、至少約75%、至少約76%、至少約77%、至少約78%、至少約79%、至少約80%、至少約81%、至少約82%、至少約83%、至少約84%、至少約85%、至少約86%、至少約87%、至少約88%、至少約89%、至少約90%、至少約91%、至少約92%、至少約93%、至少約94%、至少約95%、至少約96%、至少約97%、至少約98%或至少約99%一致之重鏈CH1區。

在一些實施例中，異二聚抗體之CH1域中之在選自由F126、P127、L128、A141、L145、K147、D148、H168、F170、P171、V173、Q175、S176、S183、V185及K213組成之群之EU位置處的一或多個胺基酸經

帶電荷胺基酸置換。就此而言，供用帶負電荷或帶正電荷胺基酸取代之一特別較佳殘基爲S183(EU編號系統)。在一些實施例中，S183經帶正電荷胺基酸取代。在替代性實施例中，S183經帶負電荷胺基酸取代。

本文所述之異二聚抗體視情況進一步包含兩個CH3域，其中至少一者含有將非天然帶電荷胺基酸引入域中之一或多個取代。在一些實施例中，各CH3域在CH3域中包含一或多個胺基酸取代以不利於同二聚化，且更佳地，有利於與相應CH3域之異二聚化。國際公開案第WO 2009/089004號(以全文引用的方式併入本文中)描述用於工程改造CH3域界面以在兩個含有CH3域之分子之間降低同二聚化且增加異二聚化之組合物及方法。在一些實施例中，CH3域之一或多個選自由399、356及357(EU編號系統)組成之群之位置處的胺基酸經帶負電荷胺基酸置換。在一些實施例中，一或多個選自由370、392及409(EU編號系統)組成之群之位置處的胺基酸經帶正電荷胺基酸置換。在替代性實施例中，CH3域之一或多個選自由399、356及357(EU編號系統)組成之群之位置處的胺基酸經帶正電荷胺基酸置換。在其他實施例中，一或多個選自370、392及409(EU編號系統)之群之位置處的胺基酸經帶負電荷胺基酸置換。在一些實施例中，異二聚抗體包含在位置399及356處包含帶正電荷胺基酸(例如D399K及E356K)之第一重鏈、及在位置392及409處包含帶負電荷胺基酸(例如K392D及K409D)之第二重鏈。

在一個態樣中，本文所述之異二聚抗體包含(a)在選自由AHo位置42-50組成之群之AHo位置處的在該位置處引入帶電荷胺基酸之第一胺基酸取代，(b)在選自由EU位置126-213組成之群之EU位置處的在該位置處引入帶電荷胺基酸之第二胺基酸取代，(c)在選自由EU位置352-360組成之群之EU位置處的在該位置處引入帶電荷胺基酸之第三胺基酸取代，及(d)在選自由EU位置395-403組成之群之EU位置處的引入帶電荷胺基酸之第四胺基酸取代，其中(a)之該帶電荷胺基酸與(b)

之該帶電荷胺基酸具有相同電荷，且其中(c)及(d)之該等帶電荷胺基酸具有(a)及(b)之該等帶電荷胺基酸之相反電荷。舉例而言，在一些實施例中，(a)及(b)之帶電荷胺基酸具有正電荷且(c)及(d)之帶電荷胺基酸具有負電荷。在替代性實施例中，(a)及(b)之帶電荷胺基酸具有負電荷且(c)及(d)之帶電荷胺基酸具有正電荷。在一些實施例中，第一胺基酸取代在AHo位置46處，第二胺基酸取代在EU位置183處，第三胺基酸取代在EU位置356處且第四胺基酸取代在EU位置399處。

在另一態樣中，本文所述之異二聚抗體包含重鏈，該重鏈包含(a)在選自由AHo位置42-50組成之群之AHo位置處的在該位置處引入帶電荷胺基酸之第一胺基酸取代，(b)在選自由EU位置126-213組成之群之EU位置處的在該位置處引入帶電荷胺基酸之第二胺基酸取代，(c)在選自由EU位置388-397組成之群之EU位置處的在該位置處引入帶電荷胺基酸之第三胺基酸取代，及(d)在選自由EU位置404-413組成之群之EU位置處的引入帶電荷胺基酸之第四胺基酸取代，其中(a)之該帶電荷胺基酸與(b)之該帶電荷胺基酸具有相同電荷，且其中(c)及(d)之該等帶電荷胺基酸具有(a)及(b)之該等帶電荷胺基酸之相反電荷。舉例而言，在一些實施例中，(a)及(b)之帶電荷胺基酸具有正電荷且(c)及(d)之帶電荷胺基酸具有負電荷。在替代性實施例中，(a)及(b)之帶電荷胺基酸具有負電荷且(c)及(d)之帶電荷胺基酸具有正電荷。在一些實施例中，第一胺基酸取代在AHo位置46處，第二胺基酸取代在EU位置183處，第三胺基酸取代在EU位置392處且第四胺基酸取代在EU位置409處。

本文亦提供一種包含第一重鏈及第二重鏈以及第一輕鏈及第二輕鏈之異二聚抗體，其中該第一重鏈在位置46(AHo，Kabat 39)、183(EU)、356(EU)及399(EU)處包含胺基酸取代，其中該第二重鏈在位置46(AHo)、183(EU)、392(EU)及409(EU)處包含胺基酸取代，且其中

該第一輕鏈及該第二輕鏈在位置46(AHo，Kabat 38)及176(EU)處包含胺基酸取代，其中該等胺基酸取代在該等位置處引入帶電荷胺基酸。在一些實施例中，第一重鏈之AHo位置46(Kabat 39)處之麩醯胺酸經麩胺酸置換，第二重鏈之AHo位置46(Kabat 39)處之麩醯胺酸經離胺酸置換，第一輕鏈之AHo位置46(Kabat 38)處之麩醯胺酸經離胺酸置換，第二輕鏈之AHo位置46(Kabat 38)處之麩醯胺酸經麩胺酸置換，第一重鏈之位置183(EU)處之絲胺酸經麩胺酸置換，第一重鏈之位置356(EU)處之麩胺酸經離胺酸置換，第一重鏈之位置399(EU)處之麩胺酸經離胺酸置換，第二重鏈之位置183(EU)處之絲胺酸經離胺酸置換，第二重鏈之位置392(EU)處之離胺酸經天冬胺酸置換，及/或第二重鏈之位置409(EU)處之離胺酸經天冬胺酸置換。

在另一態樣中，本文描述一種結合硬化蛋白之包含SEQ ID NO: 1之胺基酸86-111的區域之抗體，其中該抗體包含具有包含一或多個胺基酸取代之CH3域的重鏈，其中該一或多個取代引入在靜電方面不利於同二聚體形成且在靜電方面有利於異二聚體形成的帶電荷胺基酸。在一些實施例中，CH3域中之帶負電荷胺基酸(例如在EU位置D399、E356或E357處)經帶正電荷胺基酸取代。在一些實施例中，EU位置D399、E356及E357處之胺基酸經帶正電荷胺基酸(例如離胺酸)取代。國際公開案第WO 2009/089004號(以全文引用的方式併入本文中)描述用於工程改造CH3域界面以在兩個含有CH3域之分子之間降低同二聚化且增加異二聚化之組合物及方法。

輕鏈修飾

如上所論述，爲使特定重鏈與其同源輕鏈之結合最大，重鏈與輕鏈兩者均較佳含有互補胺基酸取代以靜電操縱鏈裝配。因此，在各種實施例中，輕鏈包含一或多個互補於以上論述之重鏈取代之胺基酸取代。

在一些實施例中，輕鏈爲κ輕鏈。圖6爲人類κ輕鏈可變域V區及J區之生殖系比對。在一些實施例中，異二聚抗體包含與人類生殖系κ鏈可變區至少約70%、至少約71%、至少約72%、至少約73%、至少約74%、至少約75%、至少約76%、至少約77%、至少約78%、至少約79%、至少約80%、至少約81%、至少約82%、至少約83%、至少約84%、至少約85%、至少約86%、至少約87%、至少約88%、至少約89%、至少約90%、至少約91%、至少約92%、至少約93%、至少約94%、至少約95%、至少約96%、至少約97%、至少約98%或至少約99%一致之κ鏈可變區。

VL域內之V區界面殘基(亦即介導VH及VL域之裝配之胺基酸殘基)包括AHo位置40(Kabat 32)、42(Kabat 34)、43(Kabat 35)、44(Kabat 36)、46(Kabat 38)、49(Kabat 41)、50(Kabat 42)、51(Kabat 43)、52(Kabat 44)、53(Kabat 45)、54(Kabat 46)、56(Kabat 48)、57(Kabat 49)、58(Kabat 50)、67(Kabat 51)、69(Kabat 53)、70(Kabat 54)、71(Kabat 55)、72(Kabat 56)、73(Kabat 57)、74(Kabat 58)、103(Kabat 85)、105(Kabat 87)、107(Kabat 89)、108(Kabat 90)及109(Kabat 91)。J區殘基包括AHo位置116、117及118。在一些實施例中，VL域中之一或多個界面殘基經較佳與引入同源重鏈可變域(亦即VH域)中之帶電荷胺基酸具有相反電荷之帶電荷胺基酸取代。在一些實施例中，VL域之AHo位置46(Kabat 38)處之胺基酸經帶正電荷胺基酸置換。在一些實施例中，諸如當VH域中之AHo位置46(Kabat 39)處之胺基酸經帶正電荷胺基酸取代時，VL域之AHo位置46(Kabat 38)處之胺基酸經帶負電荷胺基酸置換。

在一些實施例中，AHo位置51(Kabat 43)及/或AHo位置141(Kabat 100)處之胺基酸被取代成帶正電荷或帶負電荷胺基酸。此等實施例可進一步包括使AHo位置46處之胺基酸被取代成帶正電荷或帶負電荷胺基酸。在一些實施例中，AHo位置51處之胺基酸被取代成帶正電荷胺

基酸，例如離胺酸。在替代性實施例中，AHo位置51處之胺基酸被取代成帶負電荷胺基酸，例如天冬胺酸。在一些實施例中，AHo位置141處之胺基酸被取代成帶正電荷胺基酸，例如離胺酸。在替代性實施例中，AHo位置141處之胺基酸被取代成帶負電荷胺基酸，例如天冬胺酸。在一些實施例中，AHo位置51及AHo位置141處之胺基酸被取代成帶正電荷胺基酸(例如離胺酸)或帶負電荷胺基酸(例如天冬胺酸)。此等實施例可進一步包含在AHo位置46(Kabat 38)處取代成帶正電荷或帶負電荷胺基酸。

輕鏈之恆定區(亦即CL域)亦與重鏈複合，且此區域可經工程改造以增加特定輕鏈與其同源重鏈配對之效率。可藉由以下手段來促進裝配：在或接近界面處將半胱胺酸殘基引入重鏈及輕鏈中以允許形成二硫鍵，改變胺基酸以產生鈕入孔效應，及與本文對於可變區所述之靜電工程改造類似之靜電工程改造。

在輕鏈爲κ輕鏈之實施例中，異二聚抗體之CL域中之在選自由F116、F118、S121、D122、E123、Q124、S131、V133、L135、N137、N138、Q160、S162、T164、S174及S176組成之群之位置(kappa輕鏈中之EU及Kabat編號)處的一或多個胺基酸經帶電荷胺基酸置換。在一些實施例中，供用帶負電荷或帶正電荷胺基酸取代之一示範性殘基爲CL域之位置176(EU及Kabat編號系統)處之胺基酸。在一些實施例中，CL域之位置176處之胺基酸經帶正電荷胺基酸置換。在替代性實施例中，CL域之位置176處之胺基酸經帶負電荷胺基酸，例如天冬胺酸置換。

在一些實施例中，輕鏈爲λ輕鏈。在一些實施例中，異二聚抗體之CL域中之在選自由T116、F118、S121、E123、E124、K129、T131、V133、L135、S137、E160、T162、S165、Q167、A174、S176及Y178組成之群之位置(λ鏈中之Kabat編號)處的一或多個胺基酸經帶電荷胺基酸置換。在一些實施例中，供用帶負電荷或帶正電荷胺基酸取代之

一示範性殘基爲CL域之位置176(EU及Kabat編號系統)處之胺基酸。在一些實施例中，CL域之位置176處之胺基酸經帶正電荷胺基酸置換。在替代性實施例中，CL域之位置176處之胺基酸經帶負電荷胺基酸，例如天冬胺酸置換。

圖7爲人類λ輕鏈可變域V及J區之生殖系比對。在一些實施例中，抗原結合蛋白或抗體包含與人類生殖系λ鏈可變區至少約70%、至少約71%、至少約72%、至少約73%、至少約74%、至少約75%、至少約76%、至少約77%、至少約78%、至少約79%、至少約80%、至少約81%、至少約82%、至少約83%、至少約84%、至少約85%、至少約86%、至少約87%、至少約88%、至少約89%、至少約90%、至少約91%、至少約92%、至少約93%、至少約94%、至少約95%、至少約96%、至少約97%、至少約98%或至少約99%一致之輕鏈可變區。

CL域中之人類生殖系λ鏈可變區之V區界面殘基包括AHo位置40(Kabat 32)、42(Kabat 34)、43(Kabat 35)、44(Kabat 36)、46(Kabat 38)、49(Kabat 41)、50(Kabat 42)、51(Kabat 43)、52(Kabat 44)、53(Kabat 45)、54(Kabat 46)、56(Kabat 48)、57(Kabat 49)、58(Kabat 50)、67(Kabat 51)、69(Kabat 53)、70(Kabat 54)、71(Kabat 55)、72(Kabat 56)、73(Kabat 57)、74(Kabat 58)、103(Kabat 85)、105(Kabat 87)、107(Kabat 89)、108(Kabat 90)及109(Kabat 91)。J區殘基包括AHo位置139及140。涵蓋用帶電荷胺基酸取代在此等位置處之一或多個胺基酸。在較佳實施例中，一或多個胺基酸經電荷與引入同源重鏈可變域中之帶電荷胺基酸相反之帶正電荷或帶負電荷胺基酸取代。

在一些實施例中，λ可變區之AHo位置51(Kabat 43)及/或AHo位置141(Kabat 100)處之胺基酸被取代成帶正電荷或帶負電荷胺基酸。此等實施例可進一步包括使AHo位置46處之胺基酸被取代成帶正電荷或帶負電荷胺基酸。在一些實施例中，AHo位置51處之胺基酸被取代成帶

正電荷胺基酸，例如離胺酸。在替代性實施例中，AHo位置51處之胺基酸被取代成帶負電荷胺基酸，例如天冬胺酸。在一些實施例中，AHo位置141處之胺基酸被取代成帶正電荷胺基酸，例如離胺酸。在替代性實施例中，AHo位置141處之胺基酸被取代成帶負電荷胺基酸，例如天冬胺酸。在一些實施例中，AHo位置51及AHo位置141處之胺基酸被取代成帶正電荷胺基酸(例如離胺酸)或帶負電荷胺基酸(例如天冬胺酸)。此等實施例可進一步包含在AHo位置46處取代成帶正電荷或帶負電荷胺基酸。

視情況選用之其他修飾

本文所述之異二聚抗體之重鏈可進一步包含一或多個影響含有重鏈之抗體結合一或多種Fc受體之突變。抗體之Fc部分之一個功能在於當抗體結合其目標時與免疫系統通訊。此通常稱爲「效應物功能」。通訊會產生抗體依賴性細胞毒性(ADCC)、抗體依賴性細胞吞噬(ADCP)及/或補體依賴性細胞毒性(CDC)。ADCC及ADCP係經由Fc與免疫系統之細胞之表面上的Fc受體結合來介導。CDC係經由Fc與補體系統之蛋白質(例如C1q)結合來介導。

IgG子類介導效應物功能之能力不同。舉例而言，IgG1在介導ADCC及CDC方面優於IgG2及IgG4。可藉由將一或多個突變引入Fc中來增加或降低抗體之效應物功能。本發明之實施例包括具有經工程改造以增加效應物功能之Fc的異二聚抗體(U.S. 7,317,091及Strohl, Curr. Opin. Biotech., 20:685-691, 2009；兩者均以全文引用的方式併入本文中)。效應物功能增加之示範性IgG1 Fc分子包括具有一或多個以下取代者[編號基於EU編號流程]：

S239D/I332E

S239D/A330S/I332E

S239D/A330L/I332E

S298A/D333A/K334A

P247I/A339D

P247I/A339Q

D280H/K290S

D280H/K290S/S298D

D280H/K290S/S298V

F243L/R292P/Y300L

F243L/R292P/Y300L/P396L

F243L/R292P/Y300L/V305I/P396L

G236A/S239D/I332E

K326A/E333A

K326W/E333S

K290E/S298G/T299A

K290N/S298G/T299A

K290E/S298G/T299A/K326E

K290N/S298G/T299A/K326E

K334V

L235S+S239D+K334V

Q311M+K334V

S239D+K334V

F243V+K334V

E294L+K334V

S298T+K334V

E233L+Q311M+K334V

L234I+Q311M+K334V

S298T+K334V

A330M+K334V

A330F+K334V

Q311M+A330M+K334V

Q311M+A330F+K334V

S298T+A330M+K334V

S298T+A330F+K334V

S239D+A330M+K334V

S239D+S298T+K334V

L234Y+K290Y+Y296W

L234Y+F243V+Y296W

L234Y+E294L+Y296W

L234Y+Y296W

K290Y+Y296W

本發明之其他實施例包括具有經工程改造以降低效應物功能之Fc的異二聚抗體。效應物功能降低之示範性Fc分子包括具有一或多個以下取代者[編號基於EU編號流程]：

N297A(IgG1)

L234A/L235A(IgG1)

V234A/G237A(IgG2)

L235A/G237A/E318A(IgG4)

H268Q/V309L/A330S/A331S(IgG2)

C220S/C226S/C229S/P238S(IgG1)

C226S/C229S/E233P/L234V/L235A(IgG1)

L234F/L235E/P331S(IgG1)

S267E/L328F(IgG1)

增加含有IgG Fc之蛋白質之效應物功能的另一方法係藉由降低Fc

之海藻糖基化。自連接於Fc之雙觸角複合型寡醣移除核心海藻糖極大增加ADCC效應物功能而不改變抗原結合或CDC效應物功能。已知用於降低或消除含有Fc之分子(例如抗體)之海藻糖基化的若干方法。此等方法包括在某些哺乳動物細胞株中進行重組表現，該等細胞株包括FUT8基因剔除細胞株、變異CHO株系Lec13、大鼠融合瘤細胞株YB2/0、包含特異性針對FUT8基因之小干擾RNA之細胞株、及共表現β-1,4-N-乙醯基葡萄糖胺基轉移酶III及高爾基體β-甘露糖苷酶II之細胞株。或者，含有Fc之分子可在非哺乳動物細胞，諸如植物細胞、酵母或原核細胞(例如大腸桿菌(E. coli))中表現。因此，在某些實施例中，組合物包含海藻糖基化降低或完全缺乏海藻糖基化之抗體。

意欲基本上任何抗體可變域皆可併入本文所述之異二聚抗體形式中。示範性抗體可變域(及其特異性結合之抗原)包括但不限於以下中所述者：美國專利第7947809號及美國專利申請公開案第20090041784號(升糖素(glucagon)受體)、美國專利第7939070號、美國專利第7833527號、美國專利第7767206號及美國專利第7786284號(IL-17受體A)、美國專利第7872106號及美國專利第7592429號(硬化蛋白)、美國專利第7871611號、美國專利第7815907號、美國專利第7037498號、美國專利第7700742號及美國專利申請公開案第20100255538號(IGF-1受體)、美國專利第7868140號(B7RP1)、美國專利第7807159號及美國專利申請公開案第20110091455號(肌抑素(myostatin))、美國專利第7736644號、美國專利第7628986號、美國專利第7524496號及美國專利申請公開案第20100111979號(表皮生長因子受體之缺失突變體)、美國專利第7728110號(SARS冠狀病毒)、美國專利第7718776號及美國專利申請公開案第20100209435號(OPGL)、美國專利第7658924號及美國專利第7521053號(促血管生成素-2(Angiopoietin-2))、美國專利第7601818號、美國專利第7795413號、

美國專利申請公開案第20090155274號、美國專利申請公開案第20110040076號(NGF)、美國專利第7579186號(TGF-β II型受體)、美國專利第7541438號(結締組織生長因子)、美國專利第7438910號(IL1-R1)、美國專利第7423128號(備解素(properdin))、美國專利第7411057號、美國專利第7824679號、美國專利第7109003號、美國專利第6682736號、美國專利第7132281號及美國專利第7807797號(CTLA-4)、美國專利第7084257號、美國專利第7790859號、美國專利第7335743號、美國專利第7084257號及美國專利申請公開案第20110045537號(干擾素-γ)、美國專利第7932372號(MAdCAM)、美國專利第7906625號、美國專利申請公開案第20080292639號及美國專利申請公開案第20110044986號(澱粉狀蛋白(amyloid))、美國專利第7815907號及美國專利第7700742號(胰島素樣生長因子)、美國專利第7566772號及美國專利第7964193號(介白素-1β(interleukin-1β))、美國專利第7563442號、美國專利第7288251號、美國專利第7338660號、美國專利第7626012號、美國專利第7618633號及美國專利申請公開案第20100098694號(CD40)、美國專利第7498420號(c-Met)、美國專利第7326414號、美國專利第7592430號及美國專利第7728113號(M-CSF)、美國專利第6924360號、美國專利第7067131號及美國專利第7090844號(MUC18)、美國專利第6235883號、美國專利第7807798號及美國專利申請公開案第20100305307號(表皮生長因子受體)、美國專利第6716587號、美國專利第7872113號、美國專利第7465450號、美國專利第7186809號、美國專利第7317090號及美國專利第7638606號(介白素-4受體)、美國專利申請公開案第20110135657號(β-KLOTHO)、美國專利第7887799號及美國專利第7879323號(纖維母細胞生長因子樣多肽)、美國專利第7867494號(IgE)、美國專利申請公開案第20100254975號(α-4 β-7)、美國專利申請公開案第20100197005號及美國專利第

7537762號(活化素(ACTIVIN)受體樣激酶-1)、美國專利第7585500號及美國專利申請公開案第20100047253號(IL-13)、美國專利申請公開案第20090263383號及美國專利第7449555號(CD148)、美國專利申請公開案第20090234106號(活化素A)、美國專利申請公開案第20090226447號(促血管生成素-1及促血管生成素-2)、美國專利申請公開案第20090191212號(促血管生成素-2)、美國專利申請公開案第20090155164號(C-FMS)、美國專利第7537762號(活化素受體樣激酶-1)、美國專利第7371381號(甘丙肽(galanin))、美國專利申請公開案第20070196376號(胰島素樣生長因子)、美國專利第7267960號及美國專利第7741115號(LDCAM)、US7265212(CD45RB)、美國專利第7709611號、美國專利申請公開案第20060127393號及美國專利申請公開案第20100040619號(DKK1)、美國專利第7807795號、美國專利申請公開案第20030103978號及美國專利第7923008號(骨保護素(osteoprotegerin))、美國專利申請公開案第20090208489號(OV064)、美國專利申請公開案第20080286284號(PSMA)、美國專利第7888482號、美國專利申請公開案第20110165171號及美國專利申請公開案第20110059063號(PAR2)、美國專利申請公開案第20110150888號(鐵調素(HEPCIDIN))、美國專利第7939640號(B7L-1)、美國專利第7915391號(c-Kit)、美國專利第7807796號、美國專利第7193058號及美國專利第7427669號(ULBP)、美國專利第7786271號、美國專利第7304144號及美國專利申請公開案第20090238823號(TSLP)、美國專利第7767793號(SIGIRR)、美國專利第7705130號(HER-3)、美國專利第7704501號(共濟失調蛋白(ataxin)-1樣多肽)、美國專利第7695948號及美國專利第7199224號(TNF-α轉化酶)、美國專利申請公開案第20090234106號(活化素A)、美國專利申請公開案第20090214559號及美國專利第7438910號(IL1-R1)、美國專利第7579186號(TGF-β II型受體)、美國專利第

7569387號(TNF受體樣分子)、美國專利第7541438號(結締組織生長因子)、美國專利第7521048號(TRAIL受體-2)、美國專利第6319499號、美國專利第7081523號及美國專利申請公開案第20080182976號(紅血球生成素(erythropoietin)受體)、美國專利申請公開案第20080166352號及美國專利第7435796號(B7RP1)、美國專利第7423128號(備解素)、美國專利第7422742號及美國專利第7141653號(介白素-5)、美國專利第6740522號及美國專利第7411050號(RANKL)、美國專利第7378091號(碳酸酐酶IX(CA IX)腫瘤抗原)、美國專利第7318925號及美國專利第7288253號(副甲狀腺激素(parathyroid hormone))、美國專利第7285269號(TNF)、美國專利第6692740號及美國專利第7270817號(ACPL)、美國專利第7202343號(單核細胞化學吸引蛋白質-1)、美國專利第7144731號(SCF)、美國專利第6355779號及美國專利第7138500號(4-1BB)、美國專利第7135174號(PDGFD)、美國專利第6630143號及美國專利第7045128號(Flt-3配體)、美國專利第6849450號(金屬蛋白酶抑制劑)、美國專利第6596852號(LERK-5)、美國專利第6232447號(LERK-6)、美國專利第6500429號(腦源性神經滋養因子)、美國專利第6184359號(上皮源性T細胞因子)、美國專利第6143874號(神經滋養因子NNT-1)、美國專利申請公開案第20110027287號(原蛋白轉化酶枯草桿菌蛋白酶克欣蛋白酶9型(PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9，PCSK9))、美國專利申請公開案第20110014201號(IL-18受體)及美國專利申請公開案第20090155164號(C-FMS)。以上專利及公開之專利申請案就其揭露可變域多肽、可變域編碼核酸、宿主細胞、載體、製備編碼該等可變域之多肽之方法、醫藥組合物、及治療與含有可變域之抗原結合蛋白或抗體之各別目標相關的疾病之方法而言以全文引用的方式併入本文中。

抗體及其片段

在一些實施例中，本文所述之異二聚抗體包含如本文所述之抗硬化蛋白及抗DKK1抗體及其片段(例如包含介導與硬化蛋白之結合之重鏈及輕鏈及介導與DKK1之結合之重鏈及輕鏈的異二聚抗體)。術語「抗體」係指完整抗體或其結合片段。抗體可包含完全抗體(免疫球蛋白)分子(包括具有全長重鏈及/或輕鏈之多株、單株、嵌合、人類化及/或人類形式)，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，且可併入單域抗體(例如奈米抗體)、單鏈抗體、大抗體、微抗體、內抗體、微型雙功能抗體、微型三功能抗體、微型四功能抗體、v-NAR及雙scFv（參見例如Hollinger及Hudson, *Nature Biotechnology, 23*(9):1126-1136 (2005))。抗體多肽，包括纖維結合蛋白多肽單域抗體，亦揭露於美國專利第6,703,199號中。其他抗體多肽揭露於美國專利公開案第20050238646號中。

抗體片段可爲合成或遺傳工程改造蛋白質。舉例而言，抗體片段包括由輕鏈可變區組成之經分離片段、由重鏈及輕鏈可變區組成之「Fv」片段、以及輕鏈可變區與重鏈可變區藉由肽連接子連接之重組單鏈多肽分子(scFv蛋白質)。

抗體片段之另一形式爲包含抗體之一或多個互補決定區(CDR)的肽。如本文所用，術語「CDR」係指抗體可變序列內之補充決定區。在重鏈及輕鏈之各可變區中存在三個CDR，其被指定爲各可變區之CDR1、CDR2及CDR3。如本文所用之術語「CDR組」係指存在於單一可變區中之能夠結合抗原的一組三個CDR。此等CDR之精確邊界已根據不同系統加以不同界定。由Kabat(Kabat等人, Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987)及(1991))所述之系統不僅提供可適用於抗體之任何可變區之明確殘基編號系統，而且亦提供界定三個CDR之準確殘基邊界。此等CDR可稱爲Kabat CDR。Chothia及同事(Chothia及Lesk, J. Mol. Biol.

196:901-917 (1987)及Chothia等人, Nature 342:877-883 (1989))發現儘管在胺基酸序列之層面上具有巨大多樣性，但Kabat CDR內之某些子部分採用幾乎相同之肽骨架構形。此等子部分指定爲L1、L2及L3或H1、H2及H3，其中「L」及「H」分別指定輕鏈及重鏈區域。此等區域可稱爲Chothia CDR，其具有與Kabat CDR重疊之邊界。界定與Kabat CDR重疊之CDR之其他邊界已由Padlan(FASEB J. 9:133-139 (1995))及MacCallum (J Mol Biol 262(5):73245 (1996))描述。其他CDR邊界定義可不嚴格遵循一種以上系統，但將仍然與Kabat CDR重疊，儘管鑒於特定殘基或殘基組或甚至整個CDR不顯著影響抗原結合之預測或實驗研究結果，其可能縮短或延長。本文所用之方法可利用根據任何此等系統確定之CDR，但較佳實施例使用Kabat或Chothia確定之CDR。

CDR(亦稱爲「最小識別單位」或「高變區」)係藉由例如構築編碼相關CDR之聚核苷酸獲得。此等聚核苷酸例如藉由使用利用抗體產生細胞之mRNA作爲模板之聚合酶鏈反應以合成可變區來製備(參見例如Larrick等人, *Methods: A Companion to Methods in Enzymology,* *2*:106 (1991)；Courtenay-Luck, 「Genetic Manipulation of Monoclonal Antibodies」, *Monoclonal Antibodies Production, Engineering and Clinical Application*, Ritter等人 (編), 第166頁, Cambridge University Press (1995)；及Ward等人, 「Genetic Manipulation and Expression of Antibodies」, *Monoclonal Antibodies: Principles and Applications*, Birch等人, (編), 第137頁, Wiley-Liss公司 (1995))。

本文所述之方法及抗體鏈適用於產生異二聚抗體。如本文所用之「特異性結合」意謂抗原結合蛋白結合抗原優先於結合其他蛋白質。在一些實施例中,「特異性結合」意謂抗原結合蛋白對抗原之親和力高於對其他蛋白質之親和力。特異性結合抗原之抗原結合蛋白對抗原之結合親和力可小於或等於1×10^{-7} M、小於或等於2×10^{-7} M、小於或

等於3×10^{-7} M、小於或等於4×10^{-7} M、小於或等於5×10^{-7} M、小於或等於6×10^{-7} M、小於或等於7×10^{-7} M、小於或等於8×10^{-7} M、小於或等於9×10^{-7} M、小於或等於1×10^{-8} M、小於或等於2×10^{-8} M、小於或等於3×10^{-8} M、小於或等於4×10^{-8} M、小於或等於5×10^{-8} M、小於或等於6×10^{-8} M、小於或等於7×10^{-8} M、小於或等於8×10^{-8} M、小於或等於9×10^{-8} M、小於或等於1×10^{-9} M、小於或等於2×10^{-9} M、小於或等於3×10^{-9} M、小於或等於4×10^{-9} M、小於或等於5×10^{-9} M、小於或等於6×10^{-9} M、小於或等於7×10^{-9} M、小於或等於8×10^{-9} M、小於或等於9×10^{-9} M、小於或等於1×10^{-10} M、小於或等於2×10^{-10} M、小於或等於3×10^{-10} M、小於或等於4×10^{-10} M、小於或等於5×10^{-10} M、小於或等於6×10^{-10} M、小於或等於7×10^{-10} M、小於或等於8×10^{-10} M、小於或等於9×10^{-10} M、小於或等於1×10^{-11} M、小於或等於2×10^{-11} M、小於或等於3×10^{-11} M、小於或等於4×10^{-11} M、小於或等於5×10^{-11} M、小於或等於6×10^{-11} M、小於或等於7×10^{-11} M、小於或等於8×10^{-11} M、小於或等於9×10^{-11} M、小於或等於1×10^{-12} M、小於或等於2×10^{-12} M、小於或等於3×10^{-12} M、小於或等於4×10^{-12} M、小於或等於5×10^{-12} M、小於或等於6×10^{-12} M、小於或等於7×10^{-12} M、小於或等於8×10^{-12} M或小於或等於9×10^{-12} M。

抗硬化蛋白抗體

在一些實施例中，，本文所述之異二聚抗體包含含有抗硬化蛋白抗體之硬化蛋白結合部分。「抗硬化蛋白抗體」結合硬化蛋白或其部分以阻斷或損害人類硬化蛋白結合一或多種配體。硬化蛋白，SOST基因之產物，不存在於硬化性骨化病中，硬化性骨化病爲一種特徵在於骨過度生長及強密質骨的骨骼疾病(Brunkow等人，Am. J. Hum. Genet., 68:577-589 (2001)；Balemans等人，Hum. Mol. Genet., 10:537-543 (2001))。人類硬化蛋白之胺基酸序列由Brunkow等人報導且在美國專

利公開案第20070110747號中揭露爲SEQ ID NO: 1(該專利公開案就其描述硬化蛋白結合劑及序列表而言全文併入本文中)。重組人類硬化蛋白/SOST可購自R&D Systems(Minneapolis, Minn., USA; 2006 目錄號1406-ST-025)。另外，重組小鼠硬化蛋白/SOST可購自R&D Systems(Minneapolis, Minn., USA; 2006 目錄號1589-ST-025)。研究級硬化蛋白結合單株抗體可購自R&D Systems(Minneapolis, Minn., 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號以及美國專利公開案第2004/0009535號及第2005/0106683號大體上涉及抗硬化蛋白抗體。適用於本發明之情形下之硬化蛋白結合劑的實例亦描述於美國專利公開案第2007/0110747號及第2007/0072797號中，該等專利公開案據此以引用的方式併入本文中。關於產生硬化蛋白結合劑之材料及方法的其他資訊可見於美國專利公開案第20040158045號(據此以引用的方式併入)。

抗硬化蛋白抗體或其片段結合具有SEQ ID NO: 1之硬化蛋白或其天然存在之變異體的親和力(Kd)可小於或等於1×10^{-7} M、小於或等於1×10^{-8} M、小於或等於1×10^{-9} M、小於或等於1×10^{-10} M、小於或等於1×10^{-11} M或小於或等於1×10^{-12} M。使用多種技術測定親和力，該等技術之一實例爲親和力ELISA分析。在各種實施例中，藉由BIAcore分析測定親和力。在各種實施例中，藉由動力學方法測定親和力。在各種實施例中，藉由平衡/溶解方法測定親和力。美國專利公開案第2007/0110747號含有對適於決定抗體對硬化蛋白之親和力(Kd)之親和力分析的其他描述。

在一些或任何實施例中，抗硬化蛋白抗體或抗體片段結合包含SEQ ID NO: 1中所述之胺基酸序列之硬化蛋白多肽且結合硬化蛋白之包含序列SEQ ID NO: 6(CGPARLLPNAIGRGKWWRPSGPDFRC；對應

於SEQ ID NO: 1之胺基酸86-111)之區域。此區域在本文中亦稱爲硬化蛋白之「環2」區域。硬化蛋白之在環2區域外部之區域在本文中定義爲「非環2區域」。或者或此外，抗硬化蛋白抗體結合包含SEQ ID NO: 1之胺基酸57-146之硬化蛋白多肽。或者或此外，抗硬化蛋白抗體結合包含SEQ ID NO: 1之胺基酸89-103及/或SEQ ID NO: 1之胺基酸137-151之硬化蛋白多肽。或者或此外，抗硬化蛋白抗體結合包含SEQ ID NO: 1中所述之胺基酸序列的硬化蛋白多肽且結合SEQ ID NO: 1內之以下中之至少一者的序列：SEQ ID NO: 2 (DVSEYSCRELHFTR；對應於SEQ ID NO: 1之胺基酸51-64)、SEQ ID NO: 3 (SAKPVTELVCSGQCGPAR；對應於SEQ ID NO: 1之胺基酸73-90)、SEQ ID NO: 4 (WWRPSGPDFRCIPDRYR；對應於SEQ ID NO: 1之胺基酸101-117)、SEQ ID NO: 5 (LVASCKCKRLTR；對應於SEQ ID NO: 1之胺基酸138-149)、SEQ ID NO: 70 (SAKPVTELVCSGQC；對應於SEQ ID NO: 1之胺基酸73-86)、SEQ ID NO: 71 (LVASCKC；對應於SEQ ID NO: 1之胺基酸138-144)、SEQ ID NO: 72 (C1RELHFTR；對應於SEQ ID NO: 1之胺基酸57-64)、或SEQ ID NO: 73 (CIPDRYR；對應於SEQ ID NO: 1之胺基酸111-117)。舉例而言，在一個態樣中，抗硬化蛋白抗體結合具有SEQ ID NO: 1之硬化蛋白之包含SEQ ID NO: 2-5(及/或SEQ ID NO: 70-73)的子區域，視情況呈其天然三維構形。視情況，抗硬化蛋白抗體結合由SEQ ID NO: 2、SEQ ID NO: 3、SEQ ID NO: 4、SEQ ID NO: 5、SEQ ID NO: 6、SEQ ID NO: 70、SEQ ID NO: 71、SEQ ID NO: 72或SEQ ID NO: 73之一或多者組成之肽(例如由SEQ ID NO: 2、SEQ ID NO: 3、SEQ ID NO: 4及SEQ ID NO: 5組成之肽或由SEQ ID NO: 70、SEQ ID NO: 71、SEQ ID NO: 72及SEQ ID NO: 73組成之肽)。

在一些或任何實施例中，抗硬化蛋白抗體結合包含SEQ ID NO: 1之胺基酸89-103及137-151之硬化蛋白多肽。

在一些或任何實施例中，抗硬化蛋白抗體結合具有胺基酸序列SEQ ID NO:2、SEQ ID NO:3、SEQ ID NO:4及SEQ ID NO:5之硬化蛋白多肽，其中SEQ ID NO: 2與SEQ ID NO: 4在參考SEQ ID NO:1之胺基酸位置57及111處藉由二硫鍵接合，且SEQ ID NO: 3與SEQ ID NO: 5藉由以下至少一者接合：(a)在參考SEQ ID NO:1之胺基酸位置82及142處之二硫鍵，及(b)在參考SEQ ID NO:1之胺基酸位置86及144處之二硫鍵；該多肽可保留具有SEQ ID NO:1之人類硬化蛋白之相應多肽區域的三級結構。或者或此外，抗硬化蛋白抗體結合具有胺基酸序列SEQ ID NO: 70、SEQ ID NO: 71、SEQ ID NO: 72及SEQ ID NO: 73之多肽，其中SEQ ID NO: 72與SEQ ID NO: 73在參考SEQ ID NO: 1之胺基酸位置57及111處藉由二硫鍵接合，且SEQ ID NO: 70與SEQ ID NO: 71藉由以下至少一者接合：(a)在參考SEQ ID NO: 1之胺基酸位置82及142處之二硫鍵，及(b)在參考SEQ ID NO: 1之胺基酸位置86及144處之二硫鍵。

視情況，抗硬化蛋白抗體結合基本上由胺基酸序列SEQ ID NO: 2、SEQ ID NO: 3、SEQ ID NO: 4及SEQ ID NO: 5組成之肽，其中SEQ ID NO: 2與SEQ ID NO: 4在參考SEQ ID NO:1之胺基酸位置57及111處藉由二硫鍵接合，且SEQ ID NO: 3與SEQ ID NO: 5藉由以下至少一者接合：(a)在參考SEQ ID NO:1之胺基酸位置82及142處之二硫鍵，及(b)在參考SEQ ID NO:1之胺基酸位置86及144處之二硫鍵。

視情況，抗硬化蛋白抗體結合基本上由SEQ ID NO: 1之多截短人類硬化蛋白蛋白質組成之多肽，其中(a)該多肽無SEQ ID NO: 1之胺基酸1-50、65-72、91-100、118-137及150-190，或(b)該多肽無SEQ ID NO: 1之胺基酸1-56、65-72、87-110、118-137及145-190。

在一些或任何實施例中，抗硬化蛋白抗體結合具有胺基酸序列SEQ ID NO: 70、SEQ ID NO: 71、SEQ ID NO: 72及SEQ ID NO: 73之多肽，其中SEQ ID NO: 72與SEQ ID NO: 73在參考SEQ ID NO:1之胺基

酸位置57及111處藉由二硫鍵接合，且SEQ ID NO: 70與SEQ ID NO: 71藉由以下至少一者接合：(a)在參考SEQ ID NO:1之胺基酸位置82及142處之二硫鍵，及(b)在參考SEQ ID NO:1之胺基酸位置86及144處之二硫鍵。

在一些或任何實施例中，硬化蛋白多肽保留具有SEQ ID NO: 1之人類硬化蛋白之相應多肽區域的三級結構。

在一些或任何實施例中，抗硬化蛋白抗體結合(i)人類硬化蛋白之包含SEQ ID NO: 1之胺基酸51-64、73-90、101-117及138-149的部分，其中該部分具有以下至少一者、至少兩者或全部三者：(a)胺基酸57與111之間的二硫鍵；(b)胺基酸82與142之間的二硫鍵；及(c)胺基酸86與144之間的二硫鍵；或(ii)人類硬化蛋白之包含SEQ ID NO: 1之胺基酸57-64、73-86、111-117及138-144的部分，其中該部分具有以下至少一者、至少兩者或全部三者：(a)胺基酸57與111之間的二硫鍵；(b)胺基酸82與142之間的二硫鍵；及(c)胺基酸86與144之間的二硫鍵。

在一些或任何實施例中，抗硬化蛋白抗體亦結合具有SEQ ID NO: 6之抗原決定基。

用於產生本文所述之異二聚抗體之抗硬化蛋白抗體較佳在美國專利公開案第2007/0110747號中所述之細胞基分析及/或美國專利公開案第20070110747號中所述之活體內分析中調節硬化蛋白功能及/或結合美國專利公開案第2007/0110747號中所述之一或多種抗原決定基及/或交叉阻斷美國專利公開案第2007/0110747號中所述之一種抗體之結合及/或由美國專利公開案第2007/0110747號(以全文引用的方式且就其描述用於表徵抗硬化蛋白抗體之分析而言併入本文中)中所述之一種抗體交叉阻斷結合硬化蛋白。

在各種態樣中，當相較於每孔之硬化蛋白莫耳數，每孔存在小於6倍過量莫耳數之硬化蛋白結合位點時，抗硬化蛋白抗體亦能夠在

MC3T3細胞基礦化分析中中和人類硬化蛋白。藉由培養物中之骨母細胞譜系細胞(初級細胞或細胞株)達成之礦化用作活體外骨形成模型。示範性細胞基礦化分析描述於美國專利公開案第20070110747號中例如實例8處(據此以引用的方式併入)。MC3T3-E1細胞(Sudo等人, J. Cell Biol., 96:191-198 (1983))及原始細胞株之次純系可在分化劑存在下生長後在培養物中形成礦物質。此等次純系包括MC3T3-E1-BF (Smith等人, J. Biol. Chem., 275:19992-20001 (2000))。對於MC3T3-E1-BF次純系以及原始MC3T3-E1細胞兩者，硬化蛋白可抑制導致且包括礦物質沈積之一系列事件之一或多者(亦即硬化蛋白抑制礦化)。能夠中和硬化蛋白之抑制活性之抗硬化蛋白抗體允許培養物在硬化蛋白存在下礦化，以使相較於在僅有硬化蛋白(亦即無抗體)治療組中量測之鈣量，例如磷酸鈣(量測爲鈣)沈積存在統計顯著增加。

當以確定特定抗硬化蛋白抗體(或其他硬化蛋白抑制劑)是否可中和硬化蛋白爲目標進行分析時，分析中所用之硬化蛋白之量合乎需要地爲相較於在無硬化蛋白組中量測之鈣量，在僅有硬化蛋白組中導致磷酸鈣(量測爲鈣)沈積統計顯著降低至少70%之硬化蛋白的最小量。抗硬化蛋白中和抗體定義爲相較於在僅有硬化蛋白(亦即無抗體)治療組中量測之鈣量，導致磷酸鈣(量測爲鈣)沈積統計顯著增加之抗體。爲確定抗硬化蛋白抗體是否具有中和性，分析中使用之抗硬化蛋白抗體之量需要使相較於每孔之硬化蛋白莫耳數，每孔存在過量莫耳數之硬化蛋白結合位點。視抗體之效能而定，可能需要之過量倍數可爲24、18、12、6、3或1.5，且熟習此項技術者熟悉測試一個以上濃度之結合劑(抗體)的常規規範。舉例而言，當相較於每孔之硬化蛋白莫耳數，每孔存在小於6倍過量莫耳數之硬化蛋白結合位點時，極強力抗硬化蛋白中和抗體將中和硬化蛋白。次強力抗硬化蛋白中和抗體將僅在12、18或24倍過量下中和硬化蛋白。

在細胞基分析，諸如骨特異性鹼性磷酸酶分析，例如國際專利公開案第WO 2008/115732號及美國專利第7,744,874號(就其描述細胞基分析及抗硬化蛋白抗體而言以全文引用的方式併入本文中)中所述之骨特異性鹼性磷酸酶分析中，抗硬化蛋白抗體中和人類硬化蛋白之IC50視情況爲100 nM或100 nM以下、或75 nM或75 nM以下、或50 nM或50 nM以下、或25 nM或25 nM以下。骨特異性鹼性磷酸酶分析基於硬化蛋白降低多潛力鼠類細胞株C2C12中BMP-4及Wnt3a刺激之鹼性磷酸酶含量的能力。根據WO 2008/115732，中和抗硬化蛋白抗體在此分析中介導鹼性磷酸酶活性之劑量依賴性增加。

或者或此外，在HEK293細胞株中，在細胞基Wnt信號傳導分析，諸如描述於例如國際專利公開案第WO 2009/047356號(就其論述抗硬化蛋白抗體及細胞基分析而言以引用的方式併入本文中)中之涉及Wnt1介導之STF報導體基因誘導的Wnt分析中，抗硬化蛋白抗體中和人類硬化蛋白之IC50爲100 nM或100 nM以下(例如75 nM或75 nM以下、或50 nM或50 nM以下)。或者或此外，在MC3T3細胞中，在BMP2誘導之礦化分析，諸如描述於例如國際專利公開案第WO 2009/047356號中之礦化分析中，抗硬化蛋白抗體中和人類硬化蛋白之IC50爲500 nM或500 nM以下(例如250 nM或250 nM以下、150 nM或150 nM以下、100 nM或100 nM以下、或50 nM或50 nM以下)。

適用於本發明之情形下之抗硬化蛋白抗體的實例描述於國際專利公開案第2007/0110747號及第2007/0072797號中，該等公開案據此以引用的方式併入本文中。在一些實施例中，抗硬化蛋白抗體交叉阻斷以下至少一者結合硬化蛋白：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(其全部描述於美國專利公開案第

20070110747號中)。或者或此外，抗硬化蛋白抗體由以下至少一者交叉阻斷結合硬化蛋白：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 (其全部描述於美國專利公開案第20070110747號中)。術語「交叉阻斷(cross-block/cross-blocked/cross-blocking)」在本文中可互換使用以意謂抗體干擾其他抗體結合硬化蛋白之能力。抗體能夠干擾另一抗體結合硬化蛋白之程度且因此是否可稱其交叉阻斷可使用競爭結合分析來確定。在本發明之一些態樣中，交叉阻斷抗體或其片段使參考抗體之硬化蛋白結合降低在約40%與約100%，諸如約60%與約100%之間、詳言之在70%與100%之間、且更詳言之在80%與100%之間。偵測交叉阻斷之一特別適合定量分析使用利用表面電漿子共振技術量測相互作用程度之Biacore機器。另一適合定量交叉阻斷分析使用ELISA基方法來量測抗體之間就其結合硬化蛋白而言之競爭。

在一些實施例中，抗硬化蛋白抗體交叉阻斷包含全長重鏈及輕鏈之免疫球蛋白結合具有SEQ ID NO: 1之硬化蛋白及/或由包含全長重鏈及輕鏈之免疫球蛋白交叉阻斷結合具有SEQ ID NO: 1之硬化蛋白，其中包含全長重鏈及輕鏈之該免疫球蛋白包含本文揭露之CDR序列，諸如以下三組CDR序列之一：a)CDR-L1 SEQ ID NO: 284、CDR-L2 SEQ ID NO: 285、CDR-L3 SEQ ID NO: 286、CDR-H1 SEQ ID NO: 296、CDR-H2 SEQ ID NO: 297及CDR-H3 SEQ ID NO: 298；b) CDR-L1 SEQ ID NO: 48、CDR-L2 SEQ ID NO: 49、CDR-L3 SEQ ID NO: 50、CDR-H1 SEQ ID NO: 45、CDR-H2 SEQ ID NO: 46及CDR-H3 SEQ ID NO: 47；或c) CDR-L1 SEQ ID NO: 42、CDR-L2 SEQ ID NO: 43、CDR-L3 SEQ ID NO: 44、CDR-H1 SEQ ID NO: 39、CDR-H2 SEQ ID NO: 40及CDR-H3 SEQ ID NO: 41。或者或此外，抗硬化蛋白抗體交叉阻斷包含全長重鏈

及輕鏈之免疫球蛋白結合具有SEQ ID NO: 1之硬化蛋白及/或由包含全長重鏈及輕鏈之免疫球蛋白交叉阻斷結合具有SEQ ID NO: 1之硬化蛋白，其中包含全長重鏈及輕鏈之該免疫球蛋白包含以下CDR：CDR-H1 SEQ ID NO: 245、CDR-H2 SEQ ID NO: 246、CDR-H3 SEQ ID NO: 247、CDR-L1 SEQ ID NO: 78、CDR-L2 SEQ ID NO: 79及CDR-L3 SEQ ID NO: 80。

或者或此外，抗硬化蛋白抗體交叉阻斷包含全長重鏈及輕鏈之免疫球蛋白結合具有SEQ ID NO: 1之硬化蛋白及/或由包含全長重鏈及輕鏈之免疫球蛋白交叉阻斷結合具有SEQ ID NO: 1之硬化蛋白，其中包含全長重鏈及輕鏈之該免疫球蛋白包含以下CDR：CDR-H1 SEQ ID NO: 269、CDR-H2 SEQ ID NO: 270、CDR-H3 SEQ ID NO: 271、CDR-L1 SEQ ID NO: 239、CDR-L2 SEQ ID NO: 240及CDR-L3 SEQ ID NO: 241。

適合抗硬化蛋白抗體及其片段之實例包括具有以下一或多者之抗體及抗體片段：本文明確揭露且美國專利公開案第2007/0110747號中揭露之CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3。CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3之區域之至少一者可具有至少一個胺基酸取代，其限制條件爲抗體保留非經取代之CDR之結合特異性。示範性抗硬化蛋白抗體包括但不限於美國專利公開案第2007/0110747號之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。其他示範性抗硬化蛋白抗體包括但不限於27H6、19D11及20C3。

此外，抗硬化蛋白抗體可包含至少一個與選自以下之CDR具有至少75%一致性(例如100%一致性)的CDR序列：提供於序列表中且揭露於美國專利公開案第20070110747號中之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。此外，抗硬化蛋白抗體可包含至少一個與選自以下之CDR具有至少75%一致性(例如100%一致性)的CDR序列：提供於序列表中之SEQ ID NO: 417-422、425-430及433-438。抗硬化蛋白抗體較佳包含至少一個與選自以下之CDR具有至少75%一致性的CDR序列：全部提供於序列表中且描述於美國專利公開案第20070110747號中之SEQ ID NO: 245、246、247、78、79、80、269、270、271、239、240及241。如美國專利公開案第2007/0110747號中所述，抗硬化蛋白抗體可包含：a)CDR序列SEQ ID NO: 54、55及56及CDR序列SEQ ID NO: 51、52及53；b)CDR序列SEQ ID NO: 60、61及62及CDR序列SEQ ID NO: 57、58及59；c)CDR序列SEQ ID NO: 48、49及50及CDR序列SEQ ID NO: 45、46及47；d)CDR序列SEQ ID NO: 42、43及44及CDR序列SEQ ID NO: 39、40及41；e)CDR序列SEQ ID NO: 275、276及277及CDR序列SEQ ID NO: 287、288及289；f)CDR序列SEQ ID NO: 278、279及280及CDR序列SEQ ID NO: 290、291及292；g)CDR序列SEQ ID NO: 78、79及80及CDR序列SEQ ID NO: 245、246及247；h)CDR序列SEQ ID NO: 81、99及100及CDR序列SEQ ID NO: 248、249及250；i)CDR序列SEQ ID NO: 101、102及103及CDR序列SEQ ID NO: 251、252及253；j)CDR序列SEQ ID NO: 104、105及106及CDR

序列SEQ ID NO: 254、255及256；k)CDR序列SEQ ID NO: 107、108及109及CDR序列SEQ ID NO: 257、258及259；l)CDR序列SEQ ID NO: 110、111及112及CDR序列SEQ ID NO: 260、261及262；m)CDR序列SEQ ID NO: 281、282及283及CDR序列SEQ ID NO: 293、294及295；n)CDR序列SEQ ID NO: 113、114及115及CDR序列SEQ ID NO: 263、264及265；o)CDR序列SEQ ID NO: 284、285及286及CDR序列SEQ ID NO: 296、297及298；p)CDR序列SEQ ID NO: 116、237及238及CDR序列SEQ ID NO: 266、267及268；q)CDR序列SEQ ID NO: 239、240及241及CDR序列SEQ ID NO: 269、270及271)CDR序列SEQ ID NO: 242、243及244及CDR序列SEQ ID NO: 272、273及274；或s)CDR序列SEQ ID NO: 351、352及353及CDR序列SEQ ID NO: 358、359及360。

抗硬化蛋白抗體可包含至少一個與選自以下之CDR具有至少75%一致性(例如100%一致性)的CDR序列：CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3，其中CDR-H1具有SEQ ID NO: 245中給出之序列，CDR-H2具有SEQ ID NO: 246中給出之序列，CDR-H3具有SEQ ID NO: 247中給出之序列，CDR-L1具有SEQ ID NO: 78中給出之序列，CDR-L2具有SEQ ID NO: 79中給出之序列，且CDR-L3具有SEQ ID NO: 80中給出之序列，其全部提供於序列表中且描述於美國專利公開案第20070110747號中。在各種態樣中，抗硬化蛋白抗體包含兩個CDR或六個CDR。視情況，抗硬化蛋白抗體包含含有SEQ ID NO: 378之重鏈(例如兩個重鏈)之全部或一部分及含有SEQ ID NO: 376之輕鏈(例如兩個輕鏈)之全部或一部分。

抗硬化蛋白抗體可包含至少一個與選自以下之CDR具有至少75%一致性(例如100%一致性)的CDR序列：CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3，其中CDR-H1具有SEQ ID NO: 269中給出之序列，CDR-H2具有SEQ ID NO: 270中給出之序列，CDR-H3具有

SEQ ID NO: 271中給出之序列，CDR-L1具有SEQ ID NO: 239中給出之序列，CDR-L2具有SEQ ID NO: 240中給出之序列，且CDR-L3具有SEQ ID NO: 241中給出之序列，其全部提供於序列表中且描述於美國專利公開案第20070110747號中。在各種態樣中，抗硬化蛋白抗體包含至少兩個CDR或六個CDR。視情況，抗硬化蛋白抗體包含含有SEQ ID NO: 366之重鏈(例如兩個重鏈)之全部或一部分及含有SEQ ID NO: 364之輕鏈(例如兩個輕鏈)之全部或一部分。

或者，抗硬化蛋白抗體可具有重鏈，該重鏈包含CDR之H1、H2及H3且包含具有SEQ ID NO: 137、145或392中提供之序列之多肽或其變異體，其中CDR分別與SEQ ID NO: 245、246及247至少75%一致(例如100%一致)；及輕鏈，該輕鏈包含CDR之L1、L2及L3且包含具有SEQ ID NO: 133或141中提供之序列之多肽或其變異體，其中CDR分別與SEQ ID NO: 78、79及80至少75%一致(例如100%一致)(如美國專利公開案第2007/0110747號中所述)。

抗硬化蛋白抗體可具有重鏈，該重鏈包含CDR之H1、H2及H3且包含具有SEQ ID NO: 335、331、345或396中提供之序列之多肽或任何上述者之變異體，其中CDR分別與SEQ ID NO: 269、270及271至少75%一致(例如100%一致)；及輕鏈，該輕鏈包含CDR之L1、L2及L3且包含具有SEQ ID NO: 334或341中提供之序列之多肽或任何上述者之變異體，其中CDR分別與SEQ ID NO: 239、240及241至少75%一致(例如100%一致)(如美國專利公開案第20070110747號中所述)。涵蓋重鏈及輕鏈序列之所有組合(例如包含SEQ ID NO: 335之重鏈及包含SEQ ID NO: 334之輕鏈；包含SEQ ID NO: 331之重鏈及包含SEQ ID NO: 334之輕鏈；及包含SEQ ID NO: 345或396之重鏈及包含SEQ ID NO: 341之輕鏈)。

或者，抗硬化蛋白抗體具有包含具有SEQ ID NO: 137中提供之序

列之多肽的重鏈、及包含具有SEQ ID NO: 133中提供之序列之多肽的輕鏈；包含具有SEQ ID NO: 145或392中提供之序列之多肽的重鏈、及包含具有SEQ ID NO: 141中提供之序列之多肽的輕鏈；包含具有SEQ ID NO: 335中提供之序列之多肽的重鏈、及包含具有SEQ ID NO: 334中提供之序列之多肽的輕鏈；包含具有SEQ ID NO: 331中提供之序列之多肽的重鏈、及包含具有SEQ ID NO: 341中提供之序列之多肽的輕鏈；或包含具有SEQ ID NO: 345或396中提供之序列之多肽的重鏈、及包含具有SEQ ID NO: 341中提供之序列之多肽的輕鏈(如美國專利公開案第2007/0110747號中所述)。或者，抗硬化蛋白抗體交叉阻斷針對硬化蛋白之任何以上提及之抗體(或由針對硬化蛋白之任何以上提及之抗體交叉阻斷)。

在一些實施例中，抗硬化蛋白抗體包含含有選自由SEQ ID NO: 1038、SEQ ID NO: 1046、SEQ ID NO: 1040及SEQ ID NO: 1048組成之群之胺基酸序列的重鏈；視情況進一步包含選自由SEQ ID NO: 1039、SEQ ID NO: 1047、SEQ ID NO: 1041及SEQ ID NO: 1049組成之群之輕鏈胺基酸序列。

抗硬化蛋白抗體之實例亦包括但不限於國際專利公開案第WO 2008/092894號、第WO 2008/115732號、第WO 2009/056634號、第WO 2009/047356號、第WO 2010/100200號、第WO 2010/100179號、第WO 2010/115932號及第WO 2010/130830號(其各自以全文引用的方式併入本文中)中揭露之抗硬化蛋白抗體，諸如國際專利公開案第WO 2008/115732號之包含CDR SEQ ID NO: 20-25(在本文中爲SEQ ID NO: 416-421)之抗硬化蛋白抗體、國際專利公開案第WO 2008/115732號之包含CDR SEQ ID NO: 26-31(在本文中爲SEQ ID NO: 422-427)之抗硬化蛋白抗體、國際專利公開案第WO 2008/115732號之包含CDR SEQ ID NO: 32-37(在本文中爲SEQ ID NO: 428-433)之抗硬化蛋白抗體、國際

專利公開案第WO 2009/047356號之包含CDR SEQ ID NO: 4、15、26、37、48及59(在本文中分別爲SEQ ID NO: 443、454、465、476、487及498)之抗硬化蛋白抗體、或國際專利公開案第WO 2010/130830號之包含胺基酸序列SEQ ID NO: 135-143、153-161或171-179(在本文中分別爲SEQ ID NO: 745-753、763-771、781-789)之至少一者的抗硬化蛋白抗體。

抗DKK1抗體

在一些實施例中，本文所述之異二聚抗體包含含有抗DKK1抗體之DKK1結合部分。「抗DKK1抗體」結合DKK1或其部分以阻斷或損害人類DKK1結合一或多種配體。人類DKK1聚核苷酸及胺基酸序列分別闡述於SEQ ID NO: 810及811中。小鼠及大鼠DKK1之聚核苷酸及胺基酸序列闡述於SEQ ID NO: 812及813(小鼠)及SEQ ID NO: 814及815(大鼠)中。適用於本發明之情形下之抗DKK1抗體的實例描述於國際公開案第WO 2012/118903號中，該公開案之揭露內容以引用的方式併入本文中。在一些實施例中，抗DKK1抗體交叉阻斷以下至少一者結合DKK1或與以下至少一者競爭結合DKK1：抗體11H10Hu、11H10Rat、2.4.1、2.20.1、2.37.1、2.40.1、2.41.1、2.47.1、5.17.1、5.23.1、5.25.1、5.31.1、5.32.1、5.40.1、5.65.1、5.76.1、5.77.1、5.78.1、5.80.1、5.85.1、6.37.5、6.116.6、6.139.5及6.147.4(其全部描述於國際公開案第WO 2012/118903號中)。或者或此外，抗DKK1抗體由以下至少一者交叉阻斷結合DKK1：抗體11H10Hu、11H10Rat、2.4.1、2.20.1、2.37.1、2.40.1、2.41.1、2.47.1、5.17.1、5.23.1、5.25.1、5.31.1、5.32.1、5.40.1、5.65.1、5.76.1、5.77.1、5.78.1、5.80.1、5.85.1、6.37.5、6.116.6、6.139.5及6.147.4。術語「交叉阻斷(cross-block/cross-blocked/cross-blocking)」在本文中可互換使用以意謂抗體干擾其他抗體結合DKK1之能力。抗體能夠干擾另一抗體結合DKK1之程度且因此是否可稱其交叉阻斷可使用競爭結

合分析來確定。在一些態樣中，交叉阻斷抗體或其片段使參考抗體之DKK1結合降低在約40%與約100%，諸如約60%與約100%之間、或在70%與100%之間、或在80%與100%之間。偵測交叉阻斷之一特別適合定量分析使用利用表面電漿子共振技術量測相互作用程度之Biacore機器。另一適合定量交叉阻斷分析使用ELISA基方法來量測抗體之間就其結合DKK1而言之競爭。

在一些實施例中，抗DKK1抗體交叉阻斷包含全長重鏈及輕鏈之免疫球蛋白結合具有SEQ ID NO: 811之DKK1及/或由包含全長重鏈及輕鏈之免疫球蛋白交叉阻斷結合具有SEQ ID NO: 811之DKK1，其中包含全長重鏈及輕鏈之該免疫球蛋白包含本文揭露之CDR序列，諸如以下三組CDR序列之一：SEQ ID NO: 820-822、828-830、836-838、844-846、852-854、860-862、868-869、876-878、884-886、892-894、900-902、908-910、916-918、925-927、932-934、940-942、948-950、956-958、964-966、972-974、980-982、988-990、996-998、1004-1006、823-825、831-833、839-841、847-849、855-857、863-865、871-873、879-881、887-889、897-897、903-905、911-913、919-921、927-929、935-937、943-945、951-953、959-961、967-969、975-977、983-985、991-993、999-1001及1007-1009。

適合抗DKK1抗體及其片段之實例包括具有以下一或多者之抗體及抗體片段：本文明確揭露且國際公開案第WO 2012/118903號中揭露之CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3，該公開案以全文引用的方式併入本文中。在一些實施例中，CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3之區域之至少一者可具有至少一個胺基酸取代，其限制條件爲抗體保留非經取代之CDR之結合特異性。示範性抗DKK1抗體包括但不限於抗體11H10Hu、11H10Rat、2.4.1、2.20.1、2.37.1、2.40.1、2.41.1、2.47.1、5.17.1、5.23.1、

5.25.1、5.31.1、5.32.1、5.40.1、5.65.1、5.76.1、5.77.1、5.78.1、5.80.1、5.85.1、6.37.5、6.116.6、6.139.5及6.147.4(其全部描述於國際公開案第WO 2012/118903號中)。

在一些實施例中，抗DKK1抗體包含至少一個與選自由以下組成之群之CDR具有至少75%一致性(例如至少80%、或至少85%、或至少90%、或至少95%、或至少100%一致性)的CDR：820-822(Ab 11H10Hu之CDRL1-L3)、828-830(Ab 11H10Rat之CDRL1-CDRL3)、836-838(Ab 2.4.1 之 CDRL1-CDRL3)、844-846(Ab 2.20.1 之 CDRL1-CDRL3)、852-854(Ab 2.37.1 之 CDRL1-CDRL3)、860-862(Ab 2.40.1 之 CDRL1-CDRL3)、868-869(Ab 2.41.1 之 CDRL1-CDRL3)、876-878(Ab2.47.1 之 CDRL1-CDRL3)、884-886(Ab 5.17.1 之 CDRL1-CDRL3)、892-894(Ab 5.23.1之CDRL1-CDRL3)、900-902(Ab 5.25.1 之 CDRL1-CDRL3)、908-910(Ab5.31.1 之 CDRL1-CDRL3)、916-918(Ab 5.32.1 之 CDRL1-CDRL3)、925-927(Ab 5.40.1 之 CDRL1-CDRL3)、932-934(Ab 5.65.1之CDRL1-CDRL3)、940-942(Ab 5.76.1 之 CDRL1-CDRL3)、948-950(Ab5.77.1 之 CDRL1-CDRL3)、956-958(Ab 5.78.1 之 CDRL1-CDRL3)、964-966(Ab 5.80.1 之 CDRL1-CDRL3)、972-974(Ab 5.85.1之CDRL1-CDRL3)、980-982(Ab 6.37.5 之 CDRL1-CDRL3)、988-990(Ab 6.116.6 之 CDRL1-CDRL3)、996-998(Ab 6.139.5 之 CDRL1-CDRL3)、1004-1006(Ab 6.147.4 之 CDRL1-CDRL3)、823-825(Ab 11H10Hu之CDRH1-CDRH3)、831-833(Ab 11H10Rat之CDRH1-CDRH3)、839-841(Ab 2.4.1之CDRH1-CDRH3)、847-849 (Ab 2.20.1 之 CDRH1-CDRH3)、855-857(Ab 2.37.1 之 CDRH1-CDRH3)、863-865(Ab 2.40.1之CDRH1-CDRH3)、871-873(Ab 2.41.1 之 CDRH1-CDRH3)、879-881(Ab 2.47.1 之 CDRH1-CDRH3)、887-889 (Ab 5.17.1 之 CDRH1-CDRH3)、895-897(Ab 5.23.1 之

CDRH1-CDRH3)、903-905(Ab 5.25.1之CDRH1-CDRH3)、911-913(Ab 531.1 之 CDRH1-CDRH3)、919-921(Ab 5.32.1 之 CDRH1-CDRH3)、927-929(Ab 5.40.1 之 CDRH1-CDRH3)、935-937(Ab 5.65.1 之 CDRH1-CDRH3)、943-945 (Ab 5.76.1之CDRH1-CDRH3)、951-953(Ab 5.77.1 之 CDRH1-CDRH3)、959-961(Ab 5.78.1 之 CDRH1-CDRH3)、967-969(Ab 5.80.1 之 CDRH1-CDRH3)、975-977(Ab5.85.1 之 CDRH1-CDRH3)、983-985(Ab 6.37.5之CDRH1-CDRH3)、991-993(Ab 6.116.6之CDRH1-CDRH3)、999-1001(Ab 6.139.5之CDRH1-CDRH3)及1007-1009(Ab 6.147.4之CDRH1-CDRH3)。

在一些實施例中，抗DKK1抗體包含與選自由以下組成之群之抗DKK1重鏈可變域胺基酸序列具有至少75%一致性(例如至少80%、或至少85%、或至少90%、或至少95%、或至少100%一致性)的重鏈可變域胺基酸序列：SEQ ID NO: 819、827、835、843、851、859、867、875、883、891、899、907、915、923、931、939、947、955、963、971、979、987、995及1003。在一些實施例中，抗DKK1抗體包含與選自由以下組成之群之抗DKK1輕鏈可變域胺基酸序列具有至少75%一致性(例如至少80%、或至少85%、或至少90%、或至少95%、或至少100%一致性)的輕鏈可變域胺基酸序列：SEQ ID NO: 818、826、834、842、850、866、874、882、890、898、906、814、822、830、938、946、954、962、970、978、988、994及1002。

在一些實施例中，異二聚抗體之DKK1結合組分包含於各SEQ ID NO:中闡述之以下CDR之一者、兩者、三者、四者、五者或六者：820-822(Ab 11H10Hu 之 CDRL1-L3)、828-830(Ab 11H10Rat 之 CDRL1-CDRL3)、836-838(Ab 2.4.1 之 CDRL1-CDRL3)、844-846(Ab 2.20.1 之 CDRL1-CDRL3)、852-854(Ab 2.37.1 之 CDRL1-CDRL3)、860-862(Ab 2.40.1 之 CDRL1-CDRL3)、868-869(Ab 2.41.1 之

CDRL1-CDRL3)、876-878(Ab2.47.1之CDRL1-CDRL3)、884-886(Ab 5.17.1之CDRL1-CDRL3)、892-894(Ab 5.23.1之CDRL1-CDRL3)、900-902(Ab 5.25.1之CDRL1-CDRL3)、908-910(Ab5.31.1之CDRL1-CDRL3)、916-918(Ab 5.32.1之CDRL1-CDRL3)、925-927(Ab 5.40.1之CDRL1-CDRL3)、932-934(Ab 5.65.1之CDRL1-CDRL3)、940-942(Ab 5.76.1之CDRL1-CDRL3)、948-950(Ab5.77.1之CDRL1-CDRL3)、956-958(Ab 5.78.1之CDRL1-CDRL3)、964-966(Ab 5.80.1之CDRL1-CDRL3)、972-974(Ab 5.85.1之CDRL1-CDRL3)、980-982(Ab 6.37.5之CDRL1-CDRL3)、988-990(Ab 6.116.6之CDRL1-CDRL3)、996-998(Ab 6.139.5之CDRL1-CDRL3)、1004-1006(Ab 6.147.4之CDRL1-CDRL3)、823-825(Ab 11H10Hu之CDRH1-CDRH3)、831-833(Ab 11H10Rat之CDRH1-CDRH3)、839-841(Ab 2.4.1之CDRH1-CDRH3)、847-849 (Ab 2.20.1之CDRH1-CDRH3)、855-857(Ab 2.37.1之CDRH1-CDRH3)、863-865(Ab 2.40.1之CDRH1-CDRH3)、871-873(Ab 2.41.1之CDRH1-CDRH3)、879-881(Ab 2.47.1之CDRH1-CDRH3)、887-889 (Ab 5.17.1之CDRH1-CDRH3)、895-897(Ab 5.23.1之CDRH1-CDRH3)、903-905(Ab 5.25.1之CDRH1-CDRH3)、911-913(Ab 531.1之CDRH1-CDRH3)、919-921(Ab 5.32.1之CDRH1-CDRH3)、927-929(Ab 5.40.1之CDRH1-CDRH3)、935-937(Ab 5.65.1之CDRH1-CDRH3)、943-945 (Ab 5.76.1之CDRH1-CDRH3)、951-953(Ab 5.77.1之CDRH1-CDRH3)、959-961(Ab 5.78.1之CDRH1-CDRH3)、967-969(Ab 5.80.1之CDRH1-CDRH3)、975-977(Ab5.85.1之CDRH1-CDRH3)、983-985(Ab 6.37.5之CDRH1-CDRH3)、991-993(Ab 6.116.6之CDRH1-CDRH3)、999-1001(Ab 6.139.5之CDRH1-CDRH3)及1007-1009(Ab 6.147.4之CDRH1-CDRH3)。意欲異二聚抗體可包括來自單一抗體之兩個或兩個

以上CDR、或來自本文所述之DKK1抗體之任何組合的兩個或兩個以上CDR。一些DKK1結合組分包括輕鏈CDR3與重鏈CDR3兩者。某些DKK1結合組分具有SEQ ID NO: 820-822、828-830、836-838、844-846、852-854、860-862、868-869、876-878、884-886、892-894、900-902、908-910、916-918、925-927、932-934、940-942、948-950、956-958、964-966、972-974、980-982、988-990、996-998、1004-1006、823-825、831-833、839-841、847-849、855-857、863-865、871-873、879-881、887-889、897-897、903-905、911-913、919-921、927-929、935-937、943-945、951-953、959-961、967-969、975-977、983-985、991-993、999-1001及1007-1009中闡述之CDR之變異形式，其中一或多個(亦即2、3、4、5或6個)CDR各自與SEQ ID NO: 820-822、828-830、836-838、844-846、852-854、860-862、868-869、876-878、884-886、892-894、900-902、908-910、916-918、925-927、932-934、940-942、948-950、956-958、964-966、972-974、980-982、988-990、996-998、1004-1006、823-825、831-833、839-841、847-849、855-857、863-865、871-873、879-881、887-889、897-897、903-905、911-913、919-921、927-929、935-937、943-945、951-953、959-961、967-969、975-977、983-985、991-993、999-1001及1007-1009中闡述之CDR序列具有至少80%、85%、90%或95%序列一致性。舉例而言，異二聚抗體之DKK1結合組分可包括輕鏈CDR3與重鏈CDR3兩者，其各自與選自由SEQ ID NO: 822、830、838、846、854、862、870、878、886、894、902、910、918、926、934、942、950、958、966、974、982、990、998及1006組成之群之輕鏈CDR3序列具有至少80%、85%、90%或95%序列一致性；且與選自由SEQ ID NO: 825、833、841、849、857、865、873、881、889、897、905、913、921、929、937、945、953、961、969、977、985、993、1001及1009組成之群之重鏈CDR3序列具有至少80%、

85%、90%或95%序列一致性。

提供之一些DKK1結合組分之CDR序列亦可不同於SEQ ID NO: 820-822、828-830、836-838、844-846、852-854、860-862、868-869、876-878、884-886、892-894、900-902、908-910、916-918、925-927、932-934、940-942、948-950、956-958、964-966、972-974、980-982、988-990、996-998、1004-1006、823-825、831-833、839-841、847-849、855-857、863-865、871-873、879-881、887-889、897-897、903-905、911-913、919-921、927-929、935-937、943-945、951-953、959-961、967-969、975-977、983-985、991-993、999-1001及1007-1009中闡述之CDR序列以使任何既定CDR之胺基酸序列有至多1、2、3、4或5個胺基酸殘基不同。與所列序列之差異通常爲但不限於保守性取代。

在一些實施例中，抗DKK1抗體包含含有選自由SEQ ID NO: 1034、SEQ ID NO: 1042、SEQ ID NO: 1036及SEQ ID NO: 1044組成之群之胺基酸序列的重鏈；視情況進一步包含選自由SEQ ID NO: 1035、SEQ ID NO: 1043、SEQ ID NO: 1037及SEQ ID NO: 1045組成之群之輕鏈胺基酸序列。

在其他實施例中，異二聚分子之結合DKK1之部分係選自美國專利第7,709,611號、美國專利公開案第2008/0193449號、美國專利第7,642,238號、美國專利第7,700,101號及WO 2007/084344中揭露之彼等DKK1結合分子，該等專利之揭露內容皆以全文引用的方式併入本文中。

編碼工程改造重鏈或輕鏈之聚核苷酸

本發明內涵蓋編碼本文所述之重鏈及/或輕鏈恆定域及/或可變域之核酸。本發明之核酸分子包括呈單股形式與雙股形式兩者之DNA及RNA以及相應互補序列。DNA包括例如cDNA、基因組DNA、化學合成DNA、藉由PCR擴增之DNA及其組合。本發明之核酸分子包括全長

基因或cDNA分子以及其片段之組合。本發明之核酸優先源於人類來源，但本發明亦包括源於非人類物種者。

在自天然存在之來源分離核酸之情況下，「經分離核酸」爲已與自其分離核酸之生物體之基因組中存在之鄰近遺傳序列分離的核酸。在自模板酶促合成或化學合成核酸(諸如PCR產物、cDNA分子或例如寡核苷酸)之情況下，應瞭解由此等方法產生之核酸爲經分離核酸。經分離核酸分子係指呈各別片段形式或呈較大核酸構築體之組分形式之核酸分子。在一個較佳實施例中，核酸實質上不含污染性內源物質。核酸分子已較佳源於至少分離一次之呈實質上純淨形式且量或濃度使得能夠藉由標準生物化學方法(諸如Sambrook等人, Molecular Cloning: A Laboratory Manual, 第2版, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989)中所概述者)鑒別、操作及回收其組成核苷酸序列之DNA或RNA。較佳以不由通常存在於真核基因中之內部非轉譯序列或內含子中斷之開放閱讀框形式提供及/或構築此等序列。非轉譯DNA之序列可存在於開放閱讀框之5'或3'，在5'或3'處，該等序列不干擾編碼區之操作或表現。

本發明亦包括在中等嚴格條件且更佳高度嚴格條件下雜交於編碼如本文所述之多肽之核酸的核酸。影響雜交條件之選擇之基本參數及對設計適合條件之指導由Sambrook、Fritsch及Maniatis(1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 第9及11章；及Current Protocols in Molecular Biology, 1995, Ausubel等人編, John Wiley & Sons公司, 第2.10及6.3-6.4章節)所闡述，且可易於由一般技藝人士基於例如DNA之長度及/或鹼基組成加以確定。一種達成中等嚴格條件之方法涉及使用含有5×SSC、0.5% SDS、1.0 mM EDTA(pH 8.0)之預洗滌溶液；具有約50%甲醯胺、6×SSC之雜交緩衝液；及雜交溫度約55℃(或

其他類似雜交溶液，諸如含有約50%甲醯胺之雜交溶液，其中雜交溫度爲約42℃)，以及於0.5×SSC、0.1% SDS中進行約60℃之洗滌條件。通常，高度嚴格條件定義爲如上雜交條件，但在約68℃下於0.2×SSC、0.1% SDS中進行洗滌。在雜交及洗滌緩衝液中，SSPE(1×SSPE爲0.15 M NaCl、10 mM NaH_2PO_4及1.25 mM EDTA，pH 7.4)可被替換成SSC(1×SSC爲0.15 M NaCl及15 mM檸檬酸鈉)；在雜交完成之後進行洗滌15分鐘。應瞭解必要時可藉由應用如熟習此項技術者已知且以下進一步所述之支配雜交反應及雙鏈體穩定性之基本原則調整洗滌溫度及洗滌鹽濃度以達成所要嚴格程度(參見例如Sambrook等人, 1989)。當使核酸雜交於序列未知之目標核酸時，雜交物長度假定爲雜交核酸之長度。當雜交序列已知之核酸時，雜交物長度可藉由比對核酸序列及鑒別具有最佳序列互補性之一或多個區域來確定。預期長度小於50個鹼基對之雜交物之雜交溫度應比雜交物之熔融溫度(Tm)小5至10℃，其中Tm係根據以下等式確定。對於長度小於18個鹼基對之雜交物，Tm(℃)=2(A+T鹼基數)+4(G+C鹼基數)。對於長度大於18個鹼基對之雜交物，Tm(℃)=81.5+16.6(log10 [Na+])+0.41(G+C%)-(600/N)，其中N爲雜交物中之鹼基數，且([Na+]爲雜交緩衝液中之鈉離子濃度(1×SSC之[Na+]=0.165 M)。較佳地，各此雜交核酸之長度爲至少15個核苷酸(或更佳至少18個核苷酸、或至少20個核苷酸、或至少25個核苷酸、或至少30個核苷酸、或至少40個核苷酸、或最佳至少50個核苷酸)，或爲其與之雜交之本發明核酸的長度之至少25%(更佳至少50%、或至少60%、或至少70%，且最佳至少80%)，且與其與之雜交之本發明核酸的序列一致性爲至少60%(更佳至少70%、至少75%、至少80%、至少81%、至少82%、至少83%、至少84%、至少85%、至少86%、至少87%、至少88%、至少89%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%或至少99%，且最

佳至少99.5%)，其中序列一致性係藉由在對準以使重疊及一致性最大，同時使如上更詳細所述之序列間隙最小時比較雜交核酸之序列來確定。

變異體通常藉由以下方式來製備：使用卡匣或PCR突變誘發或此項技術中熟知之DNA其他技術，使編碼多肽之DNA中之核苷酸經受位點特異性突變誘發以產生編碼變異體之DNA，及此後在如本文概述之細胞培養物中表現重組DNA。然而，可藉由使用確定技術進行活體外合成來製備包含變異CDR之具有多達約100-150個殘基之抗體或抗體片段。變異體通常展現與天然存在之類似物相同之定性生物活性，例如結合抗原，但亦可選擇具有改進特徵之變異體，如本文中將更充分概述。

如此項技術者將瞭解，歸因於遺傳密碼之簡併性，可製備極大數目之皆編碼本發明之CDR(及本文所述之異二聚抗體之重鏈及輕鏈或其他組分)的核酸。因此，在已鑒別特定胺基酸序列時，熟習此項技術者可藉由以不改變編碼蛋白質之胺基酸序列之方式，僅修改一或多個密碼子之序列來製備許多不同核酸。

本發明亦提供呈質體、表現載體、轉錄或表現卡匣形式之包含至少一種如上聚核苷酸之表現系統及構築體。此外，本發明提供包含此等表現系統或構築體之宿主細胞。

通常，用於宿主細胞中之表現載體將含有用於質體維持及外源性核苷酸序列之選殖及表現之序列。在某些實施例中總稱爲「側接序列」之此等序列將通常包括以下核苷酸序列之一或多者：啓動子、一或多種增強子序列、複製起點、轉錄終止序列、含有供體及接受體拼接位點之完全內含子序列、編碼用於多肽分泌之前導序列之序列、核糖體結合位點、聚腺苷酸化序列、用於插入欲表現之編碼多肽之核酸的多連接子區域、及可選擇標記物元件。以下論述此等序列之各者。

視情況，載體可含有「標籤」編碼序列，亦即位於多肽編碼序列之5'或3'末端之寡核苷酸分子；寡核苷酸序列編碼多聚His(諸如六His)或市售抗體存在之另一「標籤」，諸如FLAG、HA(血球凝集素流感病毒(hemaglutinin influenza virus))或myc。此標籤通常在多肽表現後融合於多肽，且可充當一種自宿主細胞親和純化或偵測多肽之手段。親和純化可例如藉由使用針對標籤之抗體作爲親和基質進行管柱層析來達成。視情況，可隨後藉由各種手段，諸如使用用於裂解之某些肽酶自純化多肽移除標籤。

側接序列可爲同源的(亦即來自與宿主細胞相同之物種及/或品系)、異源的(亦即來自除宿主細胞物種或品系以外之物種)、雜交的(亦即來自一種以上來源之側接序列之組合)、合成的或天然的。因此，側接序列之來源可爲任何原核或真核生物體、任何脊椎動物或無脊椎動物生物體、或任何植物，其限制條件爲側接序列在宿主細胞機構中具有功能性且可藉由宿主細胞機構活化。

適用於本發明之載體中之側接序列可藉由此項技術中熟知之若干方法之任一者獲得。通常，適用於本文中之側接序列將已先前藉由圖譜分析及/或藉由限制核酸內切酶消化鑒別且因此可使用適當限制核酸內切酶自適當組織來源分離 在一些情況下，側接序列之完整核苷酸序列可爲已知的。在本文中，可使用本文對於核酸合成或選殖所述之方法合成側接序列。

無論已知全部或僅一部分側接序列，其可使用聚合酶鏈反應(PCR)及/或藉由用適合探針，諸如來自相同或另一物種之寡核苷酸及/或側接序列片段篩檢基因組文庫來獲得。當側接序列未知時，含有側接序列之DNA片段可自一段可含有例如編碼序列或甚至另外一或多種基因之較大DNA分離。分離可藉由以下方式達成：限制核酸內切酶消化以產生適當DNA片段，隨後使用瓊脂糖凝膠純化Qiagen®管柱層析

(Chatsworth, CA)或熟練技術人員已知之其他方法進行分離。對用以達成此目的之適合酶之選擇將易於爲一般技藝人士所顯而易知。

複製起點通常爲彼等商購原核表現載體之一部分，且起點有助於在宿主細胞中擴增載體。若所選載體不含有複製起點位點，則可基於已知序列化學合成複製起點位點，且連接至載體中。舉例而言，來自質體pBR322(New England Biolabs, Beverly, MA)之複製起點適於大多數革蘭氏陰性細菌，且各種病毒起點(例如SV40、多瘤、腺病毒、水泡性口炎病毒(VSV)或諸如HPV或BPV之乳頭狀瘤病毒)適用於哺乳動物細胞中之選殖載體。通常，複製起點組分不爲哺乳動物表現載體所需(例如僅因爲SV40起點亦含有病毒早期啓動子而常加以使用)。

轉錄終止序列通常位於多肽編碼區之末端之3'且用於終止轉錄。通常，原核細胞中之轉錄終止序列爲G-C富集片段，繼之以多聚T序列。儘管序列易於自文庫選殖或甚至作爲載體之一部分商購，但其亦可易於使用用於核酸合成之方法(諸如本文所述者)合成。

可選擇標記基因編碼爲在選擇性培養基中生長之宿主細胞之存活及生長所必需的蛋白質。典型選擇標記基因編碼(a)賦予原核宿主細胞對抗生素或其他毒素，例如胺苄青黴素(ampicillin)、四環素(tetracycline)或康黴素(kanamycin)之抗性；(b)彌補細胞之營養缺陷不足；或(c)供應不可自複合或成分確定培養基獲得之關鍵養分之蛋白質。特定可選擇標記物爲康黴素抗性基因、胺苄青黴素抗性基因及四環素抗性基因。有利的是新黴素(neomycin)抗性基因亦可用於在原核宿主細胞與真核宿主細胞兩者中進行選擇。

其他可選擇基因可用於擴增將表現之基因。擴增爲產生對生長或細胞存活關鍵之蛋白質所需之基因在連續多代重組細胞之染色體內串聯重複的過程。適於哺乳動物細胞之可選擇標記物之實例包括二氫葉酸還原酶(DHFR)及無啓動子胸苷激酶基因。將哺乳動物細胞轉型體置

於選擇壓力下，其中僅轉型體藉助於載體中存在之可選擇基因而唯一適應於存活。選擇壓力係藉由在以下條件下培養經轉型細胞來施加：連續增加培養基中之選擇劑之濃度，藉此導致擴增可選擇基因與編碼另一基因(諸如抗體輕鏈或重鏈)之DNA兩者。因此，自擴增之DNA合成增加量之多肽。

核糖體結合位點通常爲rnRNA之轉譯啓始所必需且特徵在於具有Shine-Dalgarno序列(原核生物)或Kozak序列(真核生物)。該元件通常位於啓動子之3'及欲表現之多肽之編碼序列的5'。在某些實施例中，一或多個編碼區可可操作地連接於內部核糖體結合位點(IRES)，從而允許自單一RNA轉錄物轉譯兩個開放閱讀框。

在一些情況下，諸如當在真核宿主細胞表現系統中需要糖基化時，可操作各種前序列或原序列以改良糖基化或產率。舉例而言，可改變特定信號肽之肽酶裂解位點，或添加原序列，此亦可影響糖基化。最終蛋白質產物可在-1位置(相對於成熟蛋白質之第一個胺基酸)具有一或多個與表現相伴之可能尚未完全移除之額外胺基酸。舉例而言，最終蛋白質產物可具有一或兩個見於肽酶裂解位點中之連接於胺基末端之胺基酸殘基。或者，若酶在成熟多肽內之此區域處切割，則使用一些酶裂解位點可產生所要多肽之略微截短形式。

本發明之表現及選殖載體將通常含有由宿主生物體識別且可操作地連接於編碼多肽之分子之啓動子。啓動子爲位於結構基因(通常在約100至1000 bp內)之起始密碼子上游(亦即5')之未轉錄序列，其控制結構基因之轉錄。啓動子依照慣例分組至以下兩個類別之一：誘導性啓動子及組成性啓動子。誘導性啓動子可反應於培養條件之某一變化(諸如存在或不存在某一養分或溫度變化)來引發在其控制下自DNA之轉錄程度增加。另一方面，組成性啓動子均一轉錄其所可操作地連接之基因，亦即少許控制或不控制基因表現。許多由多種潛在宿主細胞識

別之啓動子爲熟知的。藉由限制酶消化自來源DNA移除啓動子及將所要啓動子序列插入載體中來使適合啓動子可操作地連接於編碼例如重鏈或輕鏈的DNA。

適合與酵母宿主一起使用之啓動子亦在此項技術中爲熟知的。酵母增強子有利地與酵母啓動子一起使用。適合與哺乳動物宿主細胞一起使用之啓動子爲熟知的且包括但不限於自病毒之基因組獲得者，該等病毒諸如多瘤病毒、禽痘病毒、腺病毒(諸如腺病毒2)、牛乳頭狀瘤病毒、禽肉瘤病毒、巨細胞病毒、逆轉錄病毒、B型肝炎病毒及最佳猿猴病毒40(SV40)。其他適合哺乳動物啓動子包括異源哺乳動物啓動子，例如熱休克啓動子及肌動蛋白(actin)啓動子。

可爲相關之其他啓動子包括但不限於：SV40早期啓動子(Benoist及Chambon, 1981, Nature 290:304-310)；CMV啓動子(Thornsen等人, 1984, Proc. Natl. Acad. U.S.A. 81:659-663)；勞斯肉瘤病毒(Rous sarcoma virus)之3'長末端重複序列中含有之啓動子(Yamamoto等人, 1980, Cell 22:787-797)；皰疹胸苷激酶啓動子(Wagner等人, 1981, Proc. Natl. Acad. Sci. U.S.A. 78:1444-1445)；金屬硫蛋白(metallothionine)基因之啓動子及調控序列(Prinster等人, 1982, Nature 296:39-42)；及原核啓動子，諸如β-內醯胺酶啓動子(Villa-Kamaroff等人, 1978, Proc. Natl. Acad. Sci. U.S.A. 75:3727-3731)；或tac啓動子(DeBoer等人, 1983, Proc. Natl. Acad. Sci. U.S.A. 80:21-25)。亦相關的是展現組織特異性且已用於轉殖基因動物中之以下動物轉錄控制區：在胰腺腺泡細胞中具有活性之彈性蛋白酶(elastase)I基因控制區(Swift等人, 1984, Cell 38:639-646；Ornitz等人, 1986, Cold Spring Harbor Symp. Quant. Biol. 50:399-409；MacDonald, 1987, Hepatology 7:425-515)；在胰腺β細胞中具有活性之胰島素基因控制區(Hanahan, 1985, Nature 315:115-122)；在淋巴樣細胞中具有活性之免疫球蛋白基因控制區(Grosschedl等人,

1984, Cell 38:647-658；Adames等人，1985, Nature 318:533-538；Alexander等人, 1987, Mol. Cell. Biol. 7:1436-1444)；在睾丸、乳房、淋巴樣及肥大細胞中具有活性之小鼠乳腺腫瘤病毒控制區(Leder等人, 1986, Cell 45:485-495)；在肝中具有活性之白蛋白(albumin)基因控制區(Pinkert等人, 1987, Genes and Devel. 1 :268-276)；在肝中具有活性之α-胎蛋白(alpha-feto-protein)基因控制區(Krumlauf等人, 1985, Mol. Cell. Biol. 5:1639-1648；Hammer等人, 1987, Science 253:53-58)；在肝中具有活性之α1-抗胰蛋白酶基因控制區(Kelsey等人, 1987, Genes and Devel. 1:161-171)；在骨髓細胞中具有活性之β-球蛋白基因控制區(Mogram等人, 1985, Nature 315:338-340；Kollias等人, 1986, Cell 46:89-94)；在腦中之寡樹突細胞中具有活性之髓磷脂(myelin)鹼性蛋白基因控制區(Readhead等人, 1987, Cell 48:703-712)；在骨骼肌中具有活性之肌球蛋白(myosin)輕鏈-2基因控制區(Sani, 1985, Nature 314:283-286)；及在下視丘中具有活性之促性腺釋放激素基因控制區(Mason等人, 1986, Science 234:1372-1378)。

增強子序列可插入載體中以增加由高等真核生物轉錄編碼本發明之輕鏈或重鏈的DNA。增強子爲DNA之順式作用元件，長度通常約10-300 bp，其作用於啓動子以增加轉錄。增強子具有相對定向及位置非依賴性，其已見於轉錄單元之5'位置與3'位置兩者處。可自哺乳動物基因獲得之若干增強子序列爲已知的(例如球蛋白、彈性蛋白酶、白蛋白、α-胎蛋白及胰島素)。然而，通常使用來自病毒之增強子。此項技術中已知之SV40增強子、巨細胞病毒早期啓動子增強子、多瘤增強子及腺病毒增強子爲用於活化真核啓動子之示範性增強元件。儘管增強子可在載體中位於編碼序列之5'或3'，但其通常位於啓動子之5'位點處。編碼適當天然或異源信號序列(前導序列或信號肽)之序列可併入表現載體中以促進抗體之細胞外分泌。對信號肽或前導物之選擇取決

於欲在其中產生抗體之宿主細胞之類型，且異源信號序列可替換天然信號序列。在哺乳動物宿主細胞中具有功能性之信號肽之實例包括以下：美國專利第4,965,195號中所述之介白素(interleukin)-7(IL-7)之信號序列；Cosman等人,1984, Nature 312:768中所述之介白素-2受體之信號序列；EP專利第0367 566號中所述之介白素-4受體信號肽；美國專利第4,968,607號中所述之I型介白素-1受體信號肽；EP專利第0 460 846號中所述之II型介白素-1受體信號肽。

載體可含有一或多種當使載體整合入宿主細胞基因組中時有助於表現之元件。實例包括EASE元件(Aldrich等人 2003 Biotechnol Prog. 19:1433-38)及基質連接區(MAR)。MAR介導染色質之結構組構且可使整合載體與「位置」效應隔離。因此，當載體用於產生穩定轉染子時，MAR特別適用。許多天然及合成含MAR核酸在此項技術中爲已知的，例如美國專利第6,239,328號；第7,326,567號；第6,177,612號；第6,388,066號；第6,245,974號；第7,259,010號；第6,037,525號；第7,422,874號；第7,129,062號。

本發明之表現載體可自諸如市售載體之起始載體構築。此等載體可或可不含有全部所要側接序列。當本文所述之一或多種側接序列未已存在於載體中時，其可個別地加以獲得且連接至載體中。用於獲得各側接序列之方法爲熟習此項技術者所熟知。

在已構築載體且編碼輕鏈、重鏈、或輕鏈及重鏈序列之核酸分子已插入載體之適當位點中之後，所完成之載體可插入適合宿主細胞中以達成擴增及/或多肽表現。將表現載體轉型至所選宿主細胞中可藉由熟知方法來達成，該等方法包括轉染、感染、磷酸鈣共沈澱、電穿孔、顯微注射、脂質體轉染、DEAE-葡聚糖介導之轉染或其他已知技術。所選方法將部分地隨欲使用之宿主細胞之類型而變。此等方法及其他適合方法爲熟練技術人員所熟知，且例如闡述於Sambrook等人,

2001(上文)中。

當在適當條件下培養時，宿主細胞合成異二聚抗體，其可隨後自培養基收集(若宿主細胞將其分泌至培養基中)或直接自產生其之宿主細胞收集(若其未經分泌)。對適當宿主細胞之選擇將取決於各種因素，諸如所要表現量、合乎活性需要或爲活性所必需之多肽修飾(諸如糖基化或磷酸化)及折疊成生物活性分子之容易性。宿主細胞可爲真核或原核細胞。

可用作表現宿主之哺乳動物細胞株在此項技術中爲熟知的且包括但不限於可自美國菌種中心(ATCC)獲得之永生化細胞株且用於此項技術中已知之表現系統中之任何細胞株皆可用於製備本發明之重組多肽。一般而言，用包含編碼所要異二聚抗體之DNA之重組表現載體轉型宿主細胞。可採用之宿主細胞尤其爲原核生物、酵母或高等真核細胞。原核生物包括革蘭氏陰性或革蘭氏陽性生物體，例如大腸桿菌或桿菌。高等真核細胞包括昆蟲細胞及哺乳動物來源之確定細胞株。適合哺乳動物宿主細胞株之實例包括猴腎細胞之COS-7株系(ATCC CRL 1651)(Gluzman等人, 1981, Cell 23:175)、L細胞、293細胞、C127細胞、3T3細胞(ATCC CCL 163)、中國倉鼠卵巢(CHO)細胞或其衍生物(諸如Veggie CHO及在無血清培養基中生長之相關細胞株(Rasmussen等人, 1998, Cytotechnology 28: 31))、HeLa細胞、BHK(ATCC CRL 10)細胞株、及如藉由McMahan等人, 1991, EMBO J. 10: 2821所述之源於非洲綠猴腎細胞株CVI之CVI/EBNA細胞株(ATCC CCL 70)、人類胚腎細胞(諸如293、293 EBNA或MSR 293)、人類表皮A431細胞、人類Colo205細胞、其他經轉型靈長類動物細胞株、正常二倍體細胞、源於活體外培養原生組織、原生外植體之細胞株、HL-60、U937、HaK或Jurkat細胞。視情況，當需要在各種信號轉導或報導體分析中使用多肽時，例如哺乳動物細胞株(諸如HepG2/3B、KB、NIH 3T3或S49)可用於

表現多肽。或者，有可能在諸如酵母之低等真核生物中或在諸如細菌之原核生物中產生多肽。適合酵母包括釀酒酵母(Saccharomyces cerevisiae)、粟酒裂殖酵母(Schizosaccharomyces pombe)、克魯維酵母菌株(Kluyveromyces strain)、念珠菌屬(Candida)或能夠表現異源多肽之任何酵母菌株。適合細菌菌株包括大腸桿菌(Escherichia coli)、枯草芽孢桿菌(Bacillus subtilis)、鼠傷寒沙氏桿菌(Salmonella typhimurium)或能夠表現異源多肽之任何細菌菌株。

若在酵母或細菌中製備抗體或片段，則可合乎需要的是例如藉由使適當位點磷酸化或糖基化來修飾其中產生之產物以獲得功能性產物。此等共價連接可使用已知化學或酶促方法達成。亦可藉由使本發明之經分離核酸可操作地連接於一或多種昆蟲表現載體中之適合控制序列及採用昆蟲表現系統來產生多肽。用於桿狀病毒/昆蟲細胞表現系統之材料及方法可以套組形式自例如Invitrogen, San Diego, Calif., U.S.A.(MaxBac®套組)購得，且此等方法在此項技術中爲熟知的，如Summers及Smith, Texas Agricultural Experiment Station Bulletin 第1555期 (1987)、以及Luckow及Summers, Bio/Technology 6:47 (1988)中所述。無細胞轉譯系統亦可用於使用源於本文揭露之核酸構築體之RNA產生多肽，諸如抗體或片段。供與細菌、真菌、酵母及哺乳動物細胞宿主一起使用之適當選殖及表現載體由Pouwels等人(Cloning Vectors: A Laboratory Manual, Elsevier, New York, 1985)加以描述。包含較佳可操作地連接於至少一種表現控制序列之本發明之經分離核酸的宿主細胞爲「重組宿主細胞」。

在某些實施例中，可經由確定哪些細胞株具有高表現量且組成性產生具有所要結合性質之抗原結合蛋白來選擇細胞株。在另一實施例中，可選擇來自B細胞譜系之不產生其自身抗體，但能夠製備且分泌異源抗體之細胞株。

治療方法

本文所述之異二聚抗體分子適用於治療或預防骨相關病症，諸如與骨母細胞或破骨細胞活性異常相關之骨相關病症。在一些實施例中，向罹患選自由以下組成之群之骨相關病症的個體投與異二聚抗體：軟骨發育不全、鎖骨顱骨發育不全、軟骨發育不良、纖維性發育不良、高雪氏病(Gaucher's Disease)、低磷酸鹽血性佝僂病、馬方氏症候群(Marfan's syndrome)、多發性遺傳性外生骨疣、神經纖維瘤病、骨發生不全、骨硬化病、脆弱性骨硬化、硬化性病變、假關節(pseudoarthrosis)、化膿性骨髓炎、牙周病、抗癲癇藥物誘發之骨損失、原發性及繼發性副甲狀腺機能亢進、家族性副甲狀腺機能亢進症候群、失重誘發之骨損失、男性骨質疏鬆、絕經後骨損失、骨關節炎、腎性骨營養不良、滲透性骨病症、口腔骨損失、顎骨壞死、青少年佩吉特氏病(juvenile Paget's disease)、肢骨紋狀肥大(melorheostosis)、代謝性骨病、肥大細胞增多症、鐮狀細胞貧血/疾病、器官移植相關之骨損失、腎移植相關之骨損失、全身性紅斑狼瘡、關節黏連性脊椎炎、癲癇症、青少年關節炎、地中海貧血(thalassemia)、黏多醣貯積症、法布里病(Fabry Disease)、特納症候群(Turner Syndrome)、唐症候群(Down Syndrome)、克蘭費爾特症候群(Klinefelter Syndrome)、麻瘋、佩爾特氏病(Perthe's Disease)、青少年特發性疹柱側凸、嬰兒發作性多系統發炎性疾病、溫徹斯特症候群(Winchester Syndrome)、蒙克斯病(Menkes Disease)、威爾遜氏病(Wilson's Disease)、缺血性骨病(諸如萊格-卡夫-佩爾特斯病(Legg-Calve-Perthes disease)及區域性遷移性骨質疏鬆)、貧血狀態、由類固醇引起之病狀、糖皮質素誘發之骨損失、肝素誘發之骨損失、骨髓病症、壞血病、營養不良、鈣缺乏症、骨質疏鬆、骨量減少、酒精中毒、慢性肝病、絕經後狀態、慢性發炎性病狀、類風濕性關節炎、發炎性腸病、潰瘍性結腸炎、發炎性結腸炎、克羅恩氏病

(Crohn's disease)、月經過少、停經、妊娠相關之骨損失、糖尿病、甲狀腺機能亢進、甲狀腺病症、副甲狀腺病症、庫興氏病(Cushing's disease)、肢端肥大症、性腺低能症(hypogonadism)、不動或廢用(immobilization or disuse)、反射性交感神經營養不良症候群、區域性骨質疏鬆、骨軟化、與關節置換相關之骨損失、HIV相關之骨損失、與生長激素損失相關之骨損失、與囊性纖維化相關之骨損失、化學療法相關之骨損失、腫瘤誘發之骨損失、癌症相關之骨損失、激素消除性骨損失、多發性骨髓瘤、藥物誘發之骨損失、神經性厭食、疾病相關之面骨損失、疾病相關之顱骨損失、疾病相關之顎骨損失、疾病相關之頭骨損失、與老化相關之骨損失、與老化相關之面骨損失、與老化相關之顱骨損失、與老化相關之顎骨損失、與老化相關之頭骨損失及與太空旅行相關之骨損失。

在一些實施例中，本文所述之異二聚抗體適用於改良矯形程序、牙科程序、植入手術、關節置換、骨移植、骨整容手術及骨修復(諸如骨折癒合、骨不連接癒合、連接延遲癒合及面部重建)中之結果。包含一或多種異二聚抗體或片段之組合物可在程序、置換、移植、手術或修復之前、期間及/或之後投與。

異二聚抗體無需治癒患有病症之個體或完全防止骨相關病症之發作以達成有益生物反應。異二聚抗體可防治性地加以使用，意謂完全或部分防止骨相關病症或其症狀。異二聚抗體亦可治療性用於完全或部分改善骨相關病症或其症狀，或完全或部分防止骨相關病症或其症狀進一步進展。實際上，本發明之材料及方法特別適用於增加骨礦物質密度且歷經一段時期維持增加之骨礦物質密度。

在一些實施例中，歷經例如以下治療時期來進行本文所述之異二聚抗體之一或多次投與：約1週至約18個月(例如約1個月至約12個月、約1個月至約9個月或約1個月至約6個月或約1個月至約3個月)。在一些

實施例中，歷經例如以下治療時期向個體投與一或多劑本文所述之異二聚抗體：約1個月至約12個月(52週)(例如約2個月、約3個月、約4個月、約5個月、約6個月、約7個月、約8個月、約9個月、約10個月或約11個月)。在一些實施例中，向個體投與一或多劑異二聚抗體以維持骨礦物質密度。如本文所用之術語「維持骨礦物質密度」意謂由初始劑量之異二聚抗體所致之骨礦物質密度增加歷經約6個月、約9個月、約1年、約18個月、約2年之時程或歷經患者一生不降低超過約1%至約5%。應瞭解患者可需要交替治療階段以增加骨密度及維持骨密度。

此外，可爲有利的是視選擇用於特定個體之治療方案而定，投與多劑異二聚抗體或分開投與各劑量。在一些實施例中，歷經1年(12個月，52週)或1年以下(例如9個月或9個月以下、6個月或6個月以下、或3個月或3個月以下)之時期定期投與異二聚抗體或其片段。就此而言，每約3天、或約7天、或2週、或3週、或4週、或5週、或6週、或7週、或8週、或9週、或10週、或11週、或12週、或13週、或14週、或15週、或16週、或17週、或18週、或19週、或20週、或21週、或22週、或23週、或6個月、或12個月一次向人類投與異二聚抗體或其片段。

在一些實施例中，以有效治療與骨礦物質密度降低相關之骨病症之量且持續有效治療與骨礦物質密度降低相關之骨病症之時間投與一或多劑異二聚抗體或其片段。在各種實施例中，每週向個體(例如人類個體)投與一或多個包含約50毫克至約1,000毫克異二聚抗體之劑量。舉例而言，一劑異二聚抗體可包含至少約5 mg、15 mg、25 mg、50 mg、約60 mg、約70 mg、約80 mg、約90 mg、約100 mg、約120 mg、約150 mg、約200 mg、約240 mg、約250 mg、約280 mg、約300 mg、約350 mg、約400 mg、約420 mg、約450 mg、約500 mg、約550 mg、約600 mg、約650 mg、約700 mg、約750 mg、約800 mg、約850 mg、約900 mg、約950 mg或多達約1,000 mg異二聚抗體。亦涵蓋介於任何及所有此等

終點之間的範圍，例如約50 mg至約80 mg、約70 mg至約140 mg、約70 mg至約270 mg、約75 mg至約100 mg、約100 mg至約150 mg、約140 mg至約210 mg、或約150 mg至約200 mg、或約180 mg至約270 mg、或約280至約410 mg。在任何間隔下投與劑量，諸如一週多次(例如每週兩或三次)、一週一次、每兩週一次、每三週一次或每四週一次。在一些或任何實施例中，一週兩次投與劑量在約120 mg至約210 mg之範圍內之異二聚抗體。在一些或任何實施例中，一週兩次投與約140 mg劑量之異二聚抗體。

在一些實施例中，一或多劑異二聚抗體可包含每公斤體重約0.1至約50毫克(例如約5與約50毫克之間)或約1至約100毫克之間的異二聚抗體(mg/kg)。舉例而言，異二聚抗體之劑量可包含至少約0.1 mg/kg、0.5 mg/kg、1 mg/kg、約2 mg/kg、約3 mg/kg、約4 mg/kg、約5 mg/kg、約6 mg/kg、約7 mg/kg、約8 mg/kg、約9 mg/kg、約10 mg/kg、約20 mg/kg、約25 mg/kg、約26 mg/kg、約27 mg/kg、約28 mg/kg、約29 mg/kg、約30 mg/kg、約31 mg/kg、約32 mg/kg、約33 mg/kg、約34 mg/kg、約35 mg/kg、約36 mg/kg、約37 mg/kg、約38 mg/kg、約39 mg/kg、約40 mg/kg、約41 mg/kg、約42 mg/kg、約43 mg/kg、約44 mg/kg、約45 mg/kg、約46 mg/kg、約47 mg/kg、約48 mg/kg、或約49 mg/kg、或約50 mg/kg、約55 mg/kg、約60 mg/kg、約65 mg/kg、約70 mg/kg、約75 mg/kg、約80 mg/kg、約85 mg/kg、約90 mg/kg、約95 mg/kg或多達約100 mg/kg。亦涵蓋介於任何及所有此等終點之間的範圍，例如約1 mg/kg至約3 mg/kg、約1 mg/kg至約5 mg/kg、約1 mg/kg至約8 mg/kg、約3 mg/kg至約8 mg/kg、約1 mg/kg至約10 mg/kg、約1 mg/kg至約20 mg/kg、約1 mg/kg至約40 mg/kg、約5 mg/kg至約30 mg/kg、或約5 mg/kg至約20 mg/kg。

監測療法

可使用單一及雙重能量X射線吸光測定法、超音波、電腦斷層攝影術、放射線攝影術及磁共振成像來量測異二聚抗體介導之骨礦物質含量或骨密度增加。骨物質之量亦可由體重或藉由使用其他方法(參見Guinness-Hey, Metab. Bone Dis. Relat. Res., 5:177-181 (1984))加以計算。動物模型在此項技術中用於測試醫藥組合物及方法對例如以下模擬人類疾病(諸如骨質疏鬆及骨量減少)狀況之參數之影響：骨損失、骨再吸收、骨形成、骨強度或骨礦化。此類模型之實例包括切除卵巢的大鼠模型(Kalu, Bone and Mineral, 15:175-192 (1991)；Frost及Jee, Bone and Mineral, 18:227-236 (1992)；及Jee及Yao, J. Musculoskel. Neuron. Interact., 1:193-207 (2001))。量測本文所述之異二聚抗體活性之方法亦可用於測定其他硬化蛋白抑制劑之功效。

在人類中，在臨床上可使用例如髖及脊柱之雙重x射線吸光測定法(DXA)來測定骨礦物質密度。其他技術包括定量電腦斷層攝影術(QCT)、超音波檢查術、單一能量x射線吸光測定法(SXA)及放射線攝影吸光測定法。通常用於量測之中心骨骼部位包括脊柱及髖；周邊部位包括前臂、手指、腕及踵。除超音波檢查術以外，美國醫藥協會指示BMD技術通常涉及使用x射線且基於輻射衰減取決於輻射路徑中組織之厚度及組成的原理。所有技術皆涉及使結果與標準資料庫進行比較。

或者，可藉由監測骨標記物含量來計量對一或多種硬化蛋白結合劑之生理反應。骨標記物為骨重塑過程期間產生之產物且由骨、骨母細胞及/或破骨細胞釋放。骨再吸收及/或骨形成「標記物」含量之波動暗示骨重塑/塑造之變化。國際骨質疏鬆基金會(IOF)推薦使用骨標記物來監測骨密度療法 (參見例如Delmas等人，Osteoporos Int.，增刊6:S2-17 (2000)，以引用的方式併入本文中)。指示骨再吸收(或破骨細胞活性)之標記物包括例如C-端肽(例如1型膠原蛋白之C末端端肽

(CTX)或血清交聯C-端肽)、N-端肽(1型膠原蛋白之N末端端肽(NTX))、去氧吡啶啉(DPD)、吡啶啉、尿羥脯胺酸、半乳糖羥離胺酸、及酒石酸抗性酸性磷酸酶(例如血清酒石酸抗性酸性磷酸酶同功異型物5b)。骨形成/礦化標記物包括但不限於骨特異性鹼性磷酸酶(BSAP)、自I型原膠原之N末端及C末端延伸部分釋放之肽(P1NP、PICP)、及骨鈣蛋白(osteocalcin，OstCa)。若干套組可商購以偵測且定量諸如尿及血液之臨床樣品中之標記物。

組合療法

相對於單獨使用治療相關劑量之各藥劑，藉由組合兩種或兩種以上靶向相同病原體或生物化學路徑或生物過程之藥劑來治療病變有時會使功效更大且副作用減少。在一些情況下，藥物組合之功效爲累加性的(組合之功效約等於各單獨藥物之效應之總和)，但在其他情況下，效應爲協同性的(組合之功效大於各單獨既定藥物之效應之總和)。如本文所用，術語「組合療法」意謂以同時方式(例如併行)傳遞兩種或兩種以上藥劑，或其中首先投與一種藥劑，隨後例如連續投與第二藥劑。

在一些實施例中，連同用於治療骨礦物質密度降低之照護標準治療劑一起投與異二聚抗體(亦即異二聚抗體及照護標準治療劑爲相同治療計劃之一部分)。如本文所用，術語「照護標準」係指通常爲臨床醫師接受之用於診斷有一種類型之疾病的某一類型之患者之治療劑。在一些實施例中，連同適用於治療骨礦物質密度降低或骨缺陷之第二骨增強劑一起投與異二聚抗體。在一些實施例中，骨增強劑係選自由以下組成之群：抗再吸收劑、骨形成劑(亦即合成代謝劑)、雌激素受體調節劑(包括但不限於雷洛昔芬(raloxifene)、巴多昔芬(bazedoxifene)及拉索昔芬(lasofoxifene))及對破骨細胞具有抑制效應之藥物。在一些實施例中，第二骨增強劑係選自由以下組成之群：雙膦酸鹽(包括但不

限於阿侖膦酸鈉(alendronate sodium)(FOSAMAX®)、利塞膦酸鹽(risedronate)、伊班膦酸鈉(ibandronate sodium)(BONIVA®)及唑來膦酸(zoledronic acid)(RECLAST®))；雌激素或雌激素類似物；抗RANK配體(RANKL)抑制劑，諸如抗RANKL抗體(例如PROLIA®)；維生素D或維生素D衍生物或其模擬物；鈣源、組織蛋白酶-K(cathepsin-K，cat-K)抑制劑(例如奧丹昔布(odanacatib))、替勃龍(Tibolone)、降血鈣素(calcitonin)或鈣三醇(calcitriol)；及激素補充療法。在一些實施例中，第二骨增強劑包括但不限於副甲狀腺激素(PTH)或其肽片段、PTH相關蛋白質(PTHrp)、骨形態發生蛋白質、成骨素(osteogenin)、NaF、PGE2促效劑、士他汀(statin)、雷尼酸鍶(strontium ranelate)、硬化蛋白抑制劑(例如描述於例如美國專利第7,592,429號或第7,872,106號中之抗硬化蛋白抗體)及抗DKK1抗體或抑制劑。在一些實施例中，第二骨增強劑爲Forteo®(特立帕肽(Teriparatide))、Preotact®或Protelos®。

在一些實施例中，採用本文所述之異二聚抗體之組合療法可在投與其他治療劑(例如第二骨增強劑)之前或之後間隔數分鐘至數週至數月範圍。舉例而言，各別用藥程式在彼此之約24小時內，例如在彼此之約6-12小時內或在彼此之約1-2小時內或在彼此之約10-30分鐘內投與。在一些情形下，可合乎需要的是顯著延長治療時期，其中不同用藥程式之各別投與之間間隔數天(2、3、4、5、6或7天)至數週(1、2、3、4、5、6、7或8週)。明確涵蓋用組合療法之一種或兩種藥劑/療法重複治療。

維持治療方案

亦涵蓋在維持方案中使用第二骨增強劑及/或本文所述之異二聚抗體來例如預防或減緩骨礦物質密度損失。就此而言，本文所述之方法或用途視情況包含在用異二聚抗體進行之治療時期已結束之後，持續約1週至約5年之維持時期投與有效維持骨礦物質密度之一或多個量

之第二骨增強劑。舉例而言，在一些實施例中，本文所述之方法或用途包含持續約至少約1週、2週、3週、4週、5週、6週、7週、8週、9週、10週、11週、12週、3個月、13週、14週、15週、16週、4個月、17週、18週、19週、20週、5個月、21週、22週、23週、24週、6個月、25週、26週、27週、28週、7個月、29週、30週、31週或更長時間(例如8個月、9個月、10個月、11個月、1年、15個月、18個月、2年、3年、4年、5年或5年以上(例如歷經個體一生)之維持時期向個體投與第二骨增強劑。在一些實施例中，維持時期爲約6-12週。在一些實施例中，維持時期爲約4-12週或約1-3個月。在一些實施例中，維持時期爲約12-20週或約3-5個月。在一些實施例中，維持時期爲約20-32週或約5-8個月。在一些實施例中，維持時期爲約24-36週或約6-9個月。在一些實施例中，維持時期爲約1年、約2年、約3年、約4年、約5年或5年以上。「維持」骨礦物質密度包括使接受異二聚抗體治療之個體中經歷之骨礦物質密度參數維持在類似程度下。

類似地，本文所述之方法或用途視情況包含在治療時期已結束之後，隨後持續至少約1週、2週、3週、4週、5週、6週、7週、8週、9週、10週、11週、12週、3個月、13週、14週、15週、16週、4個月、17週、18週、19週、20週、5個月、21週、22週、23週、24週、6個月、1年、2年、3年、4年、5年或5年以上(例如歷經個體一生)之維持時期投與有效維持骨礦物質密度之一或多個量之異二聚抗體。在一些實施例中，維持時期爲約6-12週。在一些實施例中，維持時期爲約4-12週或約1-3個月。在一些實施例中，維持時期爲約12-20週或約3-5個月。在一些實施例中，維持時期爲約20-32週或約5-8個月。在一些實施例中，維持時期爲約24-36週或約6-9個月。在一些實施例中，維持時期爲約1年、約2年、約3年、約4年、約5年或更長時間。

醫藥組合物

在一些實施例中，本發明提供一種包含治療有效量之一種或複數種本發明之抗原結合蛋白以及醫藥有效稀釋劑、載劑、增溶劑、乳化劑、防腐劑及/或佐劑的醫藥組合物。本發明之醫藥組合物包括但不限於液體、冷凍及凍乾組合物。

較佳地，調配物質在所用劑量及濃度下對接受者無毒。在特定實施例中，提供包含治療有效量之異二聚抗體或片段的醫藥組合物。

在一些實施例中，醫藥組合物可含有用於調節、維持或保持例如組合物之pH值、容積莫耳滲透濃度、黏度、澄清度、顏色、等張性、氣味、無菌性、穩定性、溶解或釋放速率、吸收或滲透之調配物質。在此等實施例中，適合調配物質包括但不限於胺基酸(諸如甘胺酸、麩醯胺酸、天冬醯胺、精胺酸、脯胺酸或離胺酸)；抗微生物劑；抗氧化劑(諸如抗壞血酸(ascorbic acid)、亞硫酸鈉或亞硫酸氫鈉)；緩衝劑(諸如硼酸鹽、碳酸氫鹽、Tris-HCl、檸檬酸鹽、磷酸鹽或其他有機酸)；增積劑(諸如甘露糖醇或甘胺酸)；螯合劑(諸如乙二胺四乙酸(EDTA))；錯合劑(諸如咖啡鹼(caffeine)、聚乙烯吡咯啶酮、β-環糊精或羥丙基-β-環糊精)；填充劑；單醣；雙醣；及其他碳水化合物(諸如葡萄糖、甘露糖或糊精)；蛋白質(諸如血清白蛋白、明膠或免疫球蛋白)；著色劑、調味劑及稀釋劑；乳化劑；親水性聚合物(諸如聚乙烯吡咯啶酮)；低分子量多肽；成鹽相對離子(諸如鈉)；防腐劑(諸如氯化苯甲烴銨、苯甲酸、水楊酸、硫柳汞(thimerosal)、苯乙醇、對羥基苯甲酸甲酯、對羥基苯甲酸丙酯、氯己定(chlorhexidine)、山梨酸(sorbic acid)或過氧化氫)；溶劑(諸如甘油、丙二醇或聚乙二醇)；糖醇(諸如甘露糖醇或山梨糖醇)；懸浮劑；界面活性劑或濕潤劑(諸如普洛尼克(pluronic)、PEG、脫水山梨醇酯、聚山梨醇酯(諸如聚山梨醇酯20、聚山梨醇酯)、曲通(triton)、緩血酸胺(tromethamine)、卵磷脂(lecithin)、膽固醇、泰洛沙泊(tyloxapal))；穩定性增強劑(諸如蔗糖或山梨糖醇)；

張力增強劑(諸如鹼金屬鹵化物(較佳氯化鈉或氯化鉀)、甘露糖醇山梨糖醇)；傳遞媒劑；稀釋劑；賦形劑及/或醫藥佐劑。參見REMINGTON'S PHARMACEUTICAL SCIENCES, 第18版, (A.R. Genrmo編), 1990, Mack出版公司。

在一些實施例中，最佳醫藥組合物將由熟習此項技術者視例如預定投藥途徑、傳遞形式及所要劑量而確定。參見例如REMINGTON'S PHARMACEUTICAL SCIENCES(上文)。在某些實施例中，此等組合物可影響異二聚抗體或片段之物理狀態、穩定性、活體內釋放速率及活體內清除速率。在某些實施例中，醫藥組合物中之主要媒劑或載劑在性質方面可爲水性或非水性。舉例而言，適合媒劑或載劑可爲注射用水、生理鹽水溶液或人工腦脊髓液，可能補充有用於非經腸投藥之組合物中常見之其他物質。與血清白蛋白混合之中性緩衝生理食鹽水或生理食鹽水爲其他示範性媒劑。在特定實施例中，醫藥組合物包含pH值約7.0-8.5之Tris緩衝液或pH值約4.0-5.5之乙酸鹽緩衝液，且可進一步包括山梨糖醇或其適合替代物。在本發明之某些實施例中，可藉由混合具有所要純度之所選組合物與視情況選用之調配劑(REMINGTON'S PHARMACEUTICAL SCIENCES(上文))來以凍乾餅或水溶液形式製備組合物以供儲存。此外，在一些實施例中，可使用諸如蔗糖之適當賦形劑將異二聚抗體或片段調配成凍乾物。

可選擇本發明之醫藥組合物以用於非經腸傳遞。或者，可選擇組合物以用於吸入或經由消化道傳遞，諸如經口傳遞。製備此等醫藥學上可接受之組合物屬於此項技術之技能。調配組分較佳以可爲投藥部位接受之濃度存在。在某些實施例中，緩衝劑用於維持組合物在生理pH值或略微較低pH值下，通常在約5至約8之pH值範圍內。

當意欲非經腸投藥時，用於本發明中之治療組合物可以於醫藥學上可接受之媒劑中包含所要異二聚抗體或片段之無熱原、非經腸可接

受之水溶液形式提供。特別適於非經腸注射之媒劑爲異二聚抗體或片段於其中調配成經適當防腐之無菌等張溶液之無菌蒸餾水。在某些實施例中，製備涉及調配所要分子與可提供可經由儲槽注射傳遞之產品之控制或持續釋放的試劑，諸如可注射微球、生物可腐蝕粒子、聚合化合物(諸如聚乳酸或聚乙醇酸)、珠粒或脂質體。在某些實施例中，亦可使用具有提升在循環中之持續時間之作用的透明質酸。在某些實施例中，可植入藥物傳遞裝置可用於引入所要異二聚抗體或片段。

可調配用於吸入之本發明之醫藥組合物。在此等實施例中，異二聚抗體或片段有利地調配成乾燥可吸入散劑。在特定實施例中，異二聚抗體或片段吸入溶液亦可與推進劑一起調配以用於氣霧劑傳遞。在某些實施例中，溶液可經霧化。經肺投藥及因此調配方法進一步描述於國際專利申請案第PCT/US94/001875號中，該申請案以引用的方式併入本文中且描述經肺傳遞化學修飾蛋白質。

亦意欲調配物可經口投與。以此方式投與之異二聚抗體或片段可與或不與慣常用於混配諸如錠劑及膠囊之固體劑型之載劑一起調配。在某些實施例中，膠囊可經設計以在於胃腸道中時釋放調配物之活性部分，此時生物可用性最大且全身前降解最小。可包括其他試劑以促進異二聚抗體或片段吸收。亦可採用稀釋劑、調味劑、低熔點蠟、植物油、潤滑劑、懸浮劑、錠劑崩解劑及黏合劑。

其他醫藥組合物將爲熟習此項技術者所顯而易知，包括涉及呈持續或控制傳遞調配物形式之抗原結合蛋白之調配物。調配多種其他持續或控制傳遞機構，諸如脂質體載劑、生物可腐蝕微粒或多孔珠粒及儲槽注射液之技術亦爲熟習此項技術者所知。參見例如國際專利申請案第PCT/US93/00829號，其以引用的方式併入本文中且描述多孔聚合微粒之控制釋放以傳遞醫藥組合物。持續釋放製劑可包括呈定形物品，例如薄膜或微膠囊形式之半透性聚合物基質。持續釋放基質可包

括聚酯、水凝膠、聚交酯(如美國專利第3773919號及歐洲專利申請公開案第EP058481號中所揭露，其各自以引用的方式併入本文中)、L-麩胺酸與L-麩胺酸γ乙酯之共聚物(Sidman等人，1983，Biopolymers 2:547-556)、聚(甲基丙烯酸2-羥乙酯)(Langer等人，1981，J. Biomed. Mater. Res. 15:167-277及Langer, 1982, Chem. Tech. 12:98-105)、乙烯乙酸乙烯酯(Langer等人, 1981(上文))或聚D(-)-3-羥丁酸(歐洲專利申請公開案第EP133988號)。持續釋放組合物亦可包括可藉由此項技術中已知之若干方法之任一者製備的脂質體。參見例如Eppstein等人，1985, Proc. Natl. Acad. Sci. U.S.A. 82:3688-3692；歐洲專利申請公開案第EP036676號；第EP088046號及第EP143949號，該等文獻及專利以引用的方式併入本文中。

通常以無菌製劑形式提供用於活體內投藥之醫藥組合物。滅菌可藉由經無菌過濾膜過濾達成。當凍乾組合物時，使用此方法進行之滅菌可在凍乾及復原之前或之後進行。用於非經腸投藥之組合物可以凍乾形式或以溶液形式儲存。非經腸組合物通常置放入具有無菌入口之容器，例如具有可由皮下注射針刺穿之塞之靜脈內溶液袋或小瓶中。

本發明之態樣包括可用作醫藥組合物之自緩衝異二聚抗體或片段調配物，如以全文引用的方式併入本文中之國際專利申請案WO 2006/138181A2(PCT/US2006/022599)中所述。

如上所論述，某些實施例提供除異二聚抗體或片段之外亦包含一或多種賦形劑(諸如此章節中及本文其他地方以說明方式所述者)之異二聚抗體或片段組合物，特定言之醫藥異二聚抗體或片段組合物。就此而言，賦形劑可在本發明中用於廣泛多種目的，諸如調整調配物之物理、化學或生物性質(諸如調整黏度)及/或本發明之製程以改良有效性及/或使此等調配物及製程穩定以對抗歸因於例如在製造、運送、儲存、使用前製備、投與期間及此後產生之應激的降解及腐敗。

關於蛋白質穩定化及調配物質及就此而言適用之方法，有多個闡述可用，諸如Arakawa等人，「Solvent interactions in pharmaceutical formulations,」 Pharm Res. 8(3): 285-91 (1991)；Kendrick等人，「Physical stabilization of proteins in aqueous solution,」RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS: THEORY AND PRACTICE, Carpenter及Manning編 Pharmaceutical Biotechnology. 13: 61-84 (2002)；及Randolph等人，「Surfactant-protein interactions,」Pharm Biotechnol. 13: 159-75 (2002)，其各自以全文引用的方式併入本文中，特定言之關於該等文獻之用於本發明之自緩衝蛋白質調配物之賦形劑及方法的部分，尤其關於用於獸醫學及/或人類醫學用途之蛋白質醫藥產品及方法。

可根據本發明之某些實施例使用鹽以例如調整調配物之離子強度及/或等張性及/或改良本發明之組合物之蛋白質或其他成分之溶解性及/或物理穩定性。

如所熟知，離子可藉由結合於蛋白質之表面上之帶電荷殘基及藉由遮蔽蛋白質中之帶電荷及極性基團且降低其靜電相互作用、吸引及排斥相互作用之強度來使蛋白質之天然狀態穩定。離子亦可藉由結合於特定言之蛋白質之變性肽鍵(--CONH)來使蛋白質之變性狀態穩定。此外，與蛋白質中之帶電荷及極性基團之離子相互作用亦可降低分子間靜電相互作用，且藉此防止或降低蛋白質聚集及不溶。

離子物質在其對蛋白質之影響方面顯著不同。已建立對離子及其對蛋白質之影響之許多種類分級，其可用於調配本發明之醫藥組合物。一個實例爲郝夫麥士特序列(Hofmeister series)，其根據離子及極性非離子溶質對溶液中之蛋白質之構形穩定性的影響來將其分級。穩定性溶質稱爲「低離液序列(kosmotropic)」溶質。去穩性溶質稱爲「高離液序列(chaotropic)」溶質。低離液序列物通常在高濃度(例如>1莫耳

硫酸銨)下用於使蛋白質自溶液沈澱(「鹽析」)。高離液序列物通常用於使蛋白質變性及/或溶解(「鹽溶」)。離子「鹽溶」及「鹽析」之相對有效性劃定其在郝夫麥士特序列中之位置。

游離胺基酸可在根據本發明之各種實施例之異二聚抗體或片段調配物中用作增積劑、穩定劑及抗氧化劑以及用於其他標準用途。離胺酸、脯胺酸、絲胺酸及丙胺酸可用於使調配物中之蛋白質穩定。甘胺酸適用於凍乾中以確保恰當餅結構及性質。精胺酸可適用於在液體調配物與凍乾調配物兩者中抑制蛋白質聚集。甲硫胺酸適用作抗氧化劑。

多元醇包括糖，例如甘露糖醇、蔗糖及山梨糖醇；及多羥基醇，諸如甘油及丙二醇，及出於本文論述之目的，包括聚乙二醇(PEG)及相關物質。多元醇爲低離液序列的。其爲液體調配物與凍乾調配物兩者中之適用於保護蛋白質免遭物理及化學降解過程之穩定劑。多元醇亦適用於調整調配物之張力。

適用於本發明之所選實施例中之多元醇尤其爲通常用於確保凍乾調配物中之餅之結構穩定性的甘露糖醇。其確保餅之結構穩定性。其通常與例如蔗糖之凍乾保護劑一起使用。山梨糖醇及蔗糖爲用於調整張力且作爲在運輸期間或在製造過程期間製備大塊期間防止凍融應激之穩定劑的較佳試劑。諸如葡萄糖及乳糖之還原糖(其含有游離醛或酮基團)可使表面離胺酸及精胺酸殘基糖化。因此，其通常不爲供根據本發明使用之較佳多元醇。此外，形成此等反應性物質之糖，諸如在酸性條件下水解成果糖及葡萄糖，且因此導致糖化之蔗糖，亦就此而言不爲本發明之較佳多元醇。PEG適用於使蛋白質穩定並適用作低溫保護劑且就此而言可用於本發明中。

異二聚抗體或片段調配物之實施例進一步包含界面活性劑。蛋白質分子可易吸附於表面上且易變性及隨後在空氣-液體、固體-液體及

液體-液體界面處聚集。此等效應通常與蛋白質濃度成反比。此等有害相互作用通常與蛋白質濃度成反比且通常藉由物理攪動，諸如在產品之運送及處理期間產生之物理攪動加劇。

界面活性劑常規用於防止、最小化或降低表面吸附。就此而言，適用於本發明中之界面活性劑包括聚山梨醇酯20、聚山梨醇酯80、脫水山梨醇聚乙氧基化物之其他脂肪酸酯及泊洛沙姆188(poloxamer 188)。

界面活性劑亦通常用於控制蛋白質構形穩定性。就此而言，界面活性劑之使用具有蛋白質特異性，因爲任何既定界面活性劑通常皆將使一些蛋白質穩定且使其他蛋白質去穩。

聚山梨醇酯易經受氧化降解且如所供應，常含有會導致蛋白質殘基側鏈，尤其甲硫胺酸氧化之足量過氧化物。因此，聚山梨醇酯應小心使用，且當使用時，應在其最低有效濃度下採用。就此而言，聚山梨醇酯示範賦形劑應以其最低有效濃度使用之一般性準則。

異二聚抗體或片段調配物之實施例進一步包含一或多種抗氧化劑。在某種程度上，蛋白質之有害氧化可藉由維持適當環境氧及溫度程度及藉由避免暴露於光而在醫藥調配物中加以防止。抗氧化劑賦形劑亦可用於防止蛋白質之氧化降解。就此而言，適用抗氧化劑尤其爲還原劑、氧/自由基清除劑及螯合劑。用於本發明之治療蛋白質調配物中之抗氧化劑較佳爲水溶性的且在產品之整個保存期限期間維持其活性。就此而言，EDTA爲本發明之一種較佳抗氧化劑。

本發明之調配物可包括作爲蛋白質輔因子且爲形成蛋白質配位複合物所必需之金屬離子，諸如爲形成某些胰島素懸浮液所必需之鋅。金屬離子亦可抑制一些使蛋白質降解之過程。然而，金屬離子亦催化使蛋白質降解之物理及化學過程。

鎂離子(10-120 mM)可用於抑制天冬胺酸異構化成異天冬胺酸。

Ca^{+2}離子(多達100 mM)可增加人類去氧核糖核酸酶之穩定性。然而，Mg^{+2}、Mn^{+2}及Zn^{+2}可使rhDNa酶去穩。類似地，Ca^{+2}及Sr^{+2}可使因子VIII穩定，因子VIII可由Mg^{+2}、Mn^{+2}及Zn^{+2}、Cu^{+2}及Fe^{+2}去穩，且其聚集可由Al+3離子增加。

異二聚抗體或片段調配物之實施例進一步包含一或多種防腐劑。當開發涉及自同一容器抽取一次以上之多劑量非經腸調配物時，防腐劑爲必需的。其主要功能在於在藥物產品之整個保存期限或使用條款期間抑制微生物生長且確保產品無菌。通常使用之防腐劑包括苯甲醇、苯酚及間甲酚。儘管防腐劑具有與小分子非經腸劑一起使用之悠久歷史，但開發包括防腐劑之蛋白質調配物可具有挑戰性。防腐劑對蛋白質幾乎始終具有去穩效應(聚集)，且此已變爲限制其在多劑量蛋白質調配物中使用之主要因素。迄今爲止，大多數蛋白質藥物已調配僅供單次使用。然而，當多劑量調配物爲可能時，其具有使得患者能夠得到方便及使得可銷售性能夠增加的累加優勢。一良好實例爲人類生長激素(hGH)之多劑量調配物，其中開發防腐調配物已導致更方便之多次使用注射筆呈現物商業化。至少四種含有hGH防腐調配物之此等筆裝置當前可在市場上獲得。諾德托平(Norditropin)(液體，Novo Nordisk)、魯托平水溶液(Nutropin AQ)(液體，Genentech)及增若托平(Genotropin)(凍乾--雙室藥筒，Pharmacia & Upjohn)含有苯酚，而索瑪托普(Somatrope)(Eli Lilly)係與間甲酚一起調配。

在調配及開發防腐劑型期間需要考慮若干態樣。必須使藥物產品中之有效防腐劑濃度最佳化。此需要以賦予抗微生物有效性而不損害蛋白質穩定性之一定濃度範圍測試劑型中之既定防腐劑。

正如所預期，開發含有防腐劑之液體調配物比凍乾調配物更具挑戰。冷凍乾燥產品可在無防腐劑下凍乾且在使用時用含有防腐劑之稀釋劑復原。此舉縮短防腐劑與蛋白質接觸之時間，從而使相關穩定性

風險顯著最小。就液體調配物而言，防腐劑有效性及穩定性應歷經整個產品保存期限(約18至24個月)加以維持。一個需注意之要點爲防腐劑有效性應在含有活性藥物及所有賦形劑組分之最終調配物中進行證明。

異二聚抗體或片段調配物通常將針對特定投藥途徑及方法、特定投藥劑量及投藥頻率、對特定疾病之特定治療以及尤其生物可用性及持久性之範圍加以設計。因此，可根據本發明設計用於藉由任何適合途徑傳遞之調配物，該途徑包括但不限於經口、經耳、經眼、經直腸及經陰道、及藉由非經腸途徑，包括靜脈內及動脈內注射、肌肉內注射及皮下注射。

一旦醫藥組合物已經調配，其可以溶液、懸浮液、凝膠劑、乳液、固體、晶體形式或以脫水或凍乾散劑形式儲存在無菌小瓶中。此等調配物可以備用形式或以在投與之前復原之形式(例如凍乾形式)儲存。本發明亦提供用於產生單次劑量投藥單位之套組。本發明之套組可各自含有具有乾燥蛋白質之第一容器與具有水性調配物之第二容器兩者。在本發明之某些實施例中，提供含有單室及多室預填充注射器(例如液體注射器及冷凍注射器)之套組。

欲採用之含有抗原結合蛋白之醫藥組合物的治療有效量將例如取決於治療情形及目標。熟習此項技術者將瞭解適用於治療之劑量將部分地視傳遞之分子、使用抗原結合蛋白所針對之適應症、投藥途徑及患者之尺寸(體重、身體表面或器官尺寸)及/或狀況(年齡及總體健康狀況)而變化。在某些實施例中，臨床醫師可滴定劑量且改變投藥途徑以獲得最佳治療效應。

穩定性

如本文在包含異二聚抗體(或其抗原結合片段)之組合物之情形下所用之術語「穩定性」及「穩定」係指組合物中之異二聚抗體(或其抗

原結合片段)在既定製造、製備、運輸及/或儲存條件下對聚集、降解或片段化具有抗性。包含高度穩定性之抗體調配物顯示可靠性及安全性增強且因此有利於臨床使用。

視情況藉由隨時間檢查組合物中之抗體之所要參數(例如重鏈及/或輕鏈之聚集、降解、化學修飾等)來評估組合物中之抗體穩定性。就此而言，通常在初始時間點(T0)及評估時間點(T1)，視情況當使抗體或其片段暴露於許多環境條件之任一者時檢查參數且進行比較。初始時間點可爲例如最初以組合物形式調配抗體或其片段或最初檢查品質(亦即檢查以確定抗體組合物是否滿足關於聚集或降解之管理或製造規範)的時間。初始時間點亦可爲以組合物形式再調配抗體或抗體片段(例如相較於初始製劑，在更高或更低濃度下再調配)所處之時間。在各種實施例中，評估時間點爲在初始時間點之後約1週(或約2週、或約3週、或約4週、或約5週、或約6週、或約7週、或約8週、或約10週、或約3個月、或約6個月或約1年)。可在多種儲存條件下評估組合物中之抗體或其片段之所要參數(例如聚集或降解)，該等儲存條件諸如溫度-30℃、4℃、20℃或40℃；振盪；pH值；在不同容器材料(例如玻璃小瓶、預填充注射器等)中儲存及其類似儲存條件。

測定包含異二聚抗體之組合物中存在之聚集體的聚集度及/或類型及/或尺寸之示範性方法包括但不限於粒徑排阻層析(SEC)、高效粒徑排阻層析(HPSEC)、靜態光散射(SLS)、傅立葉轉換紅外光譜術(FTIR)、圓二色性(CD)、脲誘導之蛋白質展開技術、內在色胺酸螢光、示差掃描熱析法及1-苯胺基-8-萘磺酸(ANS)蛋白質結合技術。可藉由使分子經裝填有適當樹脂之管柱穿過來進行粒徑排阻層析(SEC)以基於分子尺寸分離分子，較大分子(例如聚集體)將在較小分子(例如單體)之前溶離。通常藉由280 nm下之UV吸光度偵測分子且可收集以供進一步表徵。高壓液體層析管柱常用於SEC分析(HP-SEC)。或者，可利用

分析型超速離心(AUC)。AUC爲一種測定液體樣品中之巨分子之沈降係數(以斯維德伯格(Svedberg)S加以報導)的正交技術。如同SEC一樣，AUC能夠使抗體片段/聚集體與單體分離並對其進行偵測且進一步能夠提供關於分子質量之資訊。組合物中之抗體或抗體片段聚集亦可藉由使用庫爾特計數器(coulter counter)進行粒子計數器分析或藉由使用濁度計進行濁度量測來表徵。混濁爲溶液中之粒子使光散射之量之量度，且因此可用作蛋白質聚集之一般性指標。此外，非還原性聚丙烯醯胺凝膠電泳(PAGE)或毛細管凝膠電泳(CGE)可用於表徵組合物中之抗體或抗體片段之聚集及/或片段化狀態。

測定抗體降解之示範性方法包括但不限於粒徑排阻層析(SEC)、十二烷基硫酸鈉-聚丙烯醯胺凝膠電泳(SDS-PAGE)及連同SDS一起之毛細管電泳(CE-SDS)以及伴有線上MS探測之逆相HPLC。

在各種實施例中，在相關條件下，組合物中小於5%之本文所述之異二聚抗體或抗體片段呈聚集體形式。舉例而言，在-30℃、4℃、20℃或40℃下儲存約1週(或約2週、或約3週、或約4週、或約5週、或約6週、或約7週、或約8週、或約10週、或約3個月、或約6個月或約1年)之時期之後，組合物中小於4%、或小於3%、或小於2%、或小於1%之異二聚抗體或其片段呈聚集體形式。在一些實施例中，在約4℃下儲存兩週之後，組合物中小於5%(或小於4%或小於3%或小於2%或小於1%或1%以下)之本文所述之異二聚抗體或抗體片段呈聚集體形式。

舉例而言，在-30℃、4℃、20℃或40℃下儲存約1週(或約2週、或約3週、或約4週、或約5週、或約6週、或約7週、或約8週、或約10週、或約3個月、或約6個月或約1年)之時期之後，組合物中至少85%(或至少90%、或至少91%、或至少92%、或至少93%、或至少94%、或至少95%、或至少96%、或至少97%、或至少98%、或至少99%)之抗體或其片段視情況以非聚集體(亦即單體)形式存在。在一些實施例中，在約

4℃下儲存兩週之後，至少85%(或至少90%、或至少91%、或至少92%、或至少93%、或至少94%、或至少95%、或至少96%、或至少97%、或至少98%、或至少99%或99%以上)之抗體或其片段以非聚集體形式存在於組合物中。在一些實施例中，在約4℃下儲存兩週之後，至少99%之抗體以非聚集體形式存在於組合物中，及/或在40℃下儲存兩週之後至少95%之抗體以非聚集體形式存在於組合物中。

在各種實施例中，組合物中小於5%之本文所述之異二聚抗體或抗體片段降解。舉例而言，在相關條件下，組合物中小於4%、或小於3%、或小於2%、或小於1%或1%以下之異二聚抗體或其片段降解。舉例而言，在約-30℃、約4℃、約20℃或約40℃下儲存約1週(或約2週、或約3週、或約4週、或約5週、或約6週、或約7週、或約8週、或約10週、或約3個月、或約6個月或約1年)之時期之組合物中的視情況至少85%(或至少90%、或至少91%、或至少92%、或至少93%、或至少94%、或至少95%、或至少96%、或至少97%、或至少98%、或至少99%)之抗體或片段爲完整的(亦即未降解)。在一些態樣中，在以組合物形式在約4℃下儲存兩週之時期之後，至少85%(或至少90%、或至少91%、或至少92%、或至少93%、或至少94%、或至少95%、或至少96%、或至少97%、或至少98%、或至少99%或99%以上)之抗體或其片段爲完整的(亦即非降解)。在一些實施例中，當以組合物形式在約4℃下儲存兩週時，至少99%之抗體或片段保持完整，及/或當以組合物形式在約40℃下儲存兩週時至少95%保持完整。

本文亦涵蓋組合物中之異二聚抗體(或其抗原結合片段)之功能或活性穩定性。偵測及/或定量例如結合目標之抗體、硬化蛋白中和及DKK-1中和之分析在此項技術中爲已知的且在本文中描述於實例4-6中。視情況，相較於抗體或其片段在初始時間點時之活性，抗體或其片段在相關條件下顯示約50-100%活性。舉例而言，相較於初始時間

點之活性，抗體或其片段保留之活性程度在約60-90%或70-80%之間。因此，相較於在初始時間點時之活性，抗體或其片段之功能穩定性包括保留至少約50%、55%、60%、65%、70%、75%、80%、85%、90%、95%或100%之活性且可包括大於100%(諸如105%、110%、115%、120%、125%或150%或150%以上)之活性量測結果。

黏度

在一些實施例中，測定包含一或多種本文所述之異二聚抗體之組合物的黏度。如本文所用之術語「黏度」係指「絕對黏度」。絕對黏度，有時稱爲動態或簡單黏度，爲運動黏度與流體密度之乘積(絕對黏度=運動黏度×密度)。運動黏度之量綱爲L^2/T，其中L爲長度且T爲時間。通常，運動黏度用厘史(centistoke，cSt)表示。運動黏度之SI單位爲mm^2/s，其爲1 cSt。絕對黏度用厘泊(cP)單位表示。絕對黏度之SI單位爲毫帕-秒(mPa-s)，其中1 cP = 1 mPa-s。

可在向組合物中添加抗體之後數小時(例如1-23小時)、數天(例如1-10天)、數週(例如1-5週)、數月(例如1-12個月)或數年(例如1-2年、1-3年)量測組合物之黏度。可在儲存或投藥溫度，例如2-8℃或25℃(室溫)下進行黏度量測。在一些實施例中，液體或復原液體組合物在儲存及/或投藥溫度下之絕對黏度爲15 cP或15 cP以下、或14、13、12、11、10、9、8、7、6、5或4 cP或4 cP以下。在一些實施例中，液體或復原液體組合物之絕對黏度爲6 cP或6 cP以下。

在一些實施例中，在添加異二聚抗體之前及之後量測抗體組合物之黏度。量測黏度之方法在此項技術中爲熟知的且包括例如使用毛細管黏度計或錐板流變儀。任何方法皆可使用，其限制條件爲相同方法用於比較測試調配物與參考調配物。

套組

包含一或多種本文所述之異二聚抗體之醫藥組合物可連同提供

關於此等醫藥組合物之使用之說明書的包裝材料一起置放在容器(例如小瓶或注射器)內。通常，此等說明書將包括描述異二聚抗體濃度以及在某些實施例內可爲復原醫藥組合物所必需之賦形劑成分或稀釋劑(例如水、生理食鹽水或PBS)之相對量的明確表述。

其他實施例

亦涵蓋以下編號段落中提供之以下實施例：

1. 一種經分離抗體重鏈可變區，其在構架區內在AHo位置51或141處包含胺基酸取代，其中該取代在該位置處將帶正電荷胺基酸或帶負電荷胺基酸引入該重鏈可變區構架中。

2. 如段落1之經分離抗體重鏈可變區，其中AHo位置51或AHo位置141被取代成帶正電荷胺基酸。

3. 如段落2之經分離抗體重鏈可變區，其進一步包含在AHo位置46處被帶正電荷胺基酸取代。

4. 如段落2或段落3之經分離抗體重鏈可變區，其中AHo位置51被取代成帶正電荷胺基酸。

5. 如段落1、2或3之經分離抗體重鏈可變區，其中AHo位置141被取代成正電荷胺基酸。

6. 如段落3之經分離抗體重鏈可變區，其中AHo位置46及AHo位置141被取代成帶正電荷胺基酸。

7. 如段落2-6中任一者之經分離抗體重鏈，其中該帶正電荷胺基酸爲離胺酸。

8. 如段落1之經分離抗體重鏈可變區，其中AHo位置51或AHo位置141被取代成帶負電荷胺基酸。

9. 如段落8之經分離抗體重鏈可變區，其進一步包含在AHo位置46處被帶負電荷胺基酸取代。

10. 如段落8或段落9之經分離抗體重鏈可變區，其中AHo位置51

被取代成帶負電荷胺基酸。

11. 如段落8、9或10之經分離抗體重鏈可變區，其中AHo位置141被取代成帶負電荷胺基酸。

12. 如段落9之經分離抗體重鏈可變區，其中AHo位置46及AHo位置141被取代成帶負電荷胺基酸。

13. 如段落8-12中任一者之經分離抗體重鏈，其中該帶負電荷胺基酸爲天冬胺酸。

14. 如段落1-13中任一者之經分離抗體重鏈可變區，其進一步包含重鏈CH1區。

15. 如段落14之經分離抗體重鏈可變區，其中該CH1區包含一或多個胺基酸添加、缺失或取代。

16. 如段落15之經分離抗體重鏈可變區，其中取代某一胺基酸以將帶正電荷或帶負電荷胺基酸引入該CH1區中。

17. 如段落16之經分離抗體重鏈可變區，其中在EU位置S183處引入該帶正電荷或帶負電荷胺基酸。

18. 如段落17之經分離抗體重鏈可變區，其中EU位置S183被取代成帶正電荷胺基酸。

19. 如段落18之經分離抗體重鏈可變區，其中該取代爲S183K。

20. 如段落17之經分離抗體重鏈可變區，其中EU位置S183被取代成帶負電荷胺基酸。

21. 如段落20之經分離抗體重鏈可變區，其中該取代爲S183D。

22. 一種抗體重鏈，其包含如段落1-21中任一者之經分離抗體重鏈可變區。

23. 如段落22之抗體重鏈，其中該重鏈包含含有一或多個不利於同二聚化之胺基酸取代之CH3區。

24. 如段落23之抗體重鏈，其中該CH3區中之帶負電荷胺基酸經

帶正電荷胺基酸取代。

25. 如段落24之抗體重鏈，其中該帶負電荷胺基酸爲EU位置D399、E356或E357。

26. 如段落25之抗體重鏈，其中該帶正電荷胺基酸爲離胺酸。

27. 如段落26之抗體重鏈，其中該CH3區包含D399K及E356K取代。

28. 如段落23之抗體重鏈，其中該CH3區中之帶正電荷胺基酸經帶負電荷胺基酸取代。

29. 如段落28之抗體重鏈，其中該帶正電荷胺基酸爲EU位置K370、K392或K409。

30. 如段落29之抗體重鏈，其中該帶負電荷胺基酸爲天冬胺酸。

31. 如段落30之抗體重鏈，其中該CH3區包含K392D及K409D取代。

32. 一種抗體，其包含如段落24-27中任一者之抗體重鏈及如段落28-31中任一者之抗體重鏈。

33. 如段落22-31中任一者之抗體重鏈，其中該重鏈包含含有一或多個改變Fc效應物功能之胺基酸取代之CH2區。

34. 一種抗體κ輕鏈可變區，其在構架區內在AHo位置51或141處包含胺基酸取代，其中該取代在該位置處將帶正電荷或帶負電荷胺基酸引入該κ輕鏈可變區構架中。

35. 如段落34之抗體κ輕鏈可變區，其中AHo位置51或AHo位置141被取代成帶正電荷胺基酸。

36. 如段落35之抗體κ輕鏈可變區，其進一步包含在AHo位置46處被帶正電荷胺基酸取代。

37. 如段落35或36之抗體κ輕鏈可變區，其中AHo位置51被取代成帶正電荷胺基酸。

38. 如段落35、36或37之抗體κ輕鏈可變區，其中AHo位置141被取代成帶正電荷胺基酸。

39. 如段落35-38中任一者之抗體輕鏈，其中該帶正電荷胺基酸爲離胺酸。

40. 如段落34之抗體κ輕鏈可變區，其中AHo位置51或AHo位置141被取代成帶負電荷胺基酸。

41. 如段落40之抗體κ輕鏈可變區，其進一步包含在AHo位置46處被帶負電荷胺基酸取代。

42. 如段落40或41之抗體κ輕鏈可變區，其中AHo位置51被取代成帶負電荷胺基酸。

43. 如段落40、41或42之抗體κ輕鏈可變區，其中AHo位置141被取代成帶負電荷胺基酸。

44. 如段落40-43中任一者之抗體輕鏈，其中該帶正電荷胺基酸爲離胺酸。

45. 如段落34-44中任一者之抗體κ輕鏈可變區，其進一步包含κ輕鏈恆定區。

46. 如段落45之抗體κ輕鏈可變區，其中該κ輕鏈恆定區包含一或多個胺基酸添加、缺失或取代。

47. 如段落46之經分離抗體κ鏈可變區，其中取代某一胺基酸以將帶正電荷或帶負電荷胺基酸引入該κ輕鏈恆定區中。

48. 如段落47之經分離抗體κ鏈可變區，其中在Eu位置S176處引入該帶正電荷或帶負電荷胺基酸。

49. 如段落48之經分離抗體κ鏈可變區，其中Eu位置S176被取代成帶正電荷胺基酸。

50. 如段落49之經分離抗體κ鏈可變區，其中該取代爲S176K。

51. 如段落48之經分離抗體κ鏈可變區，其中Eu位置S176被取代

成帶負電荷胺基酸。

52. 如段落51之經分離抗體κ鏈可變區，其中該取代爲S176D。

53. 一種抗體λ輕鏈可變區，其在構架區內在AHo位置51或141處包含胺基酸取代，其中該取代在該位置處將帶正電荷或帶負電荷胺基酸引入該λ輕鏈可變區構架中。

54. 如段落53之抗體λ輕鏈可變區，其進一步包含λ輕鏈恆定區。

55. 如段落54之抗體λ輕鏈可變區，其中該λ輕鏈恆定區包含一或多個胺基酸添加、缺失或取代。

56. 如段落55之經分離抗體λ鏈可變區，其中取代某一胺基酸以將帶正電荷或帶負電荷胺基酸引入該λ輕鏈恆定區中。

57. 如段落56之經分離抗體λ鏈可變區，其中在Kabat位置S176處引入該帶正電荷或帶負電荷胺基酸。

58. 如段落57之經分離抗體λ鏈可變區，其中S176被取代成帶正電荷胺基酸。

59. 如段落58之經分離抗體λ鏈可變區，其中該取代爲S176K。

60. 如段落57之經分離抗體λ鏈可變區，其中S176被取代成帶負電荷胺基酸。

61. 如段落60之經分離抗體λ鏈可變區，其中該取代爲S176D或S176E。

62. 一種經分離核酸，其編碼如段落1-21中任一者之抗體重鏈可變區、如段落22-31中任一者之抗體重鏈、如段落34-52中任一者之抗體κ輕鏈可變區、或如段落53-61中任一者之抗體輕鏈可變區。

63. 一種表現載體，其包含可操作地連接於啓動子之如段落62之經分離核酸。

64. 一種重組宿主細胞，其包含如段落62之經分離核酸。

65. 一種重組宿主細胞，其包含如段落63之表現載體。

66. 一種抗原結合蛋白，其包含如段落1-21中任一者之經分離重鏈可變區及如段落22-31或34-52中任一者之經分離輕鏈可變區。

67. 如段落66之抗原結合蛋白，其中該抗原結合蛋白爲包含兩個重鏈及兩個輕鏈之抗體。

68. 如段落67之抗原結合蛋白，其中該抗體爲雙特異性抗體。

69. 一種醫藥組合物，其包含如段落66-68中任一者之抗原結合蛋白。

實例

實例1-藉由硬化蛋白抗體治療誘導DKK1表現

評估抗硬化蛋白抗體治療對不同動物模型之骨中之DKK1表現的影響。出乎意料的是在所有動物模型中，在用抗硬化蛋白抗體治療之動物之全骨提取物中偵測到DKK1表現顯著增加。在自正常動物、經絕期後骨質疏鬆動物模型及骨折癒合動物模型提取之骨中觀測到此表現增加。在抗硬化蛋白抗體治療後觀測之DKK1表現增加發生在所有三個測試物種(小鼠、大鼠及靈長類動物)中。

示範性研究詳情如下：每2週用4.5或22.5 mg/kg Ab-5(抗硬化蛋白抗體(SAB))治療13歲正常雄性食蟹獼猴(cynomolgus monkey)總計8週。在研究結束時，以人道方式使動物安樂死且收集組織，包括骨。自骨分離RNA且遵循製造商說明書，使用QuantiGene分支DNA(bDNA)分析(Affymetrix)及對食蟹獼猴DKK1 mRNA及持家基因具有特異性之探針組測定DKK1 RNA表現。圖8中說明之資料顯示在較低劑量(4.5 mg/kg)下肱骨中段中之DKK1表現增加且在最高劑量(22.5 mg/kg)下DKK1 mRNA受顯著誘導。亦在腰椎中觀測到DKK1表現增加。資料呈現爲相較於持家(HKG)基因HPRT之經校正表現(+/-標準偏差)。圖8之圖上方之括號表示$p<0.05$(ANOVA)。

本文呈現之資料顯示抗硬化蛋白抗體治療不依賴於疾病之發生

誘導DKK1表現且可能可適用於包括人類之所有物種。誘導DKK1可限制抗硬化蛋白抗體之活性，且表明抑制硬化蛋白與DKK1兩者之治療劑顯示較佳活性。此外，DKK1表現增加可充當硬化蛋白抗體治療之生物標記。

實例2-產生連接子體

以下實例描述產生異二聚抗體(具有IgG1骨架)，其中使用G4S連接子共價連接(a)抗硬化蛋白抗體及(b)抗DKK1抗體之輕鏈及重鏈以形成結合硬化蛋白之單一多肽鏈及結合DKK1之單一多肽鏈(「連接子體」)。接著經由在CH3域處進行電荷配對取代(亦即一個重鏈含有K392D及K409D取代且另一含有E356K及D399K取代)使針對DKK1及硬化蛋白目標之多肽鏈或半抗體裝配成雙特異性抗體。電荷配對取代採用本文所述之靜電操縱機制，藉此藉由CH3區中帶負電荷殘基與帶正電荷殘基之間的吸引促進異二聚體形成(DKK1 Ab-硬化蛋白Ab)且由於在CH3-CH3界面之相應區域處具有相同電荷之胺基酸之間的排斥而阻礙同二聚體(兩個DKK1 Ab臂或兩個硬化蛋白Ab臂)。亦在CH1-CL域界面處引入電荷配對取代以降低聚集程度(重鏈中之S183K/E及輕鏈中之S176E/K)。此外，一些連接子體亦在VL-VH界面處具有工程改造域間二硫鍵以進一步穩定化重鏈-輕鏈相互作用。此藉由使重鏈中之G44(Kabat)及輕鏈中之G100(Kabat)取代成半胱胺酸殘基來達成。

上述方法導致高度聚集，如藉由粒徑排阻層析(SEC)所測定。爲降低聚集程度，在輕鏈與重鏈之間在重鏈及輕鏈恆定區(CH1-CL1)中用電荷配對取代添加或置換G4S連接子。意欲聚集程度將由於向連接子體構築體中添加電荷配對取代而降低。

與CH1-CL界面中之電荷配對取代組合之連接子體設計仍然在若干構築體中產生非所要聚集問題。

實例3-產生無連接子之異二聚抗體

以下實例描述產生不具有連接子，但代之以在親本抗體之CH/CL界面與CH3/CH3界面兩者中包含電荷配對取代之異二聚抗體。在CH/CL及CH3/CH3界面中包含帶電荷取代之所得異二聚抗體在本文中稱爲異二聚抗體形式1或異Ig-v1。

簡言之，將以下取代引入DKK1抗體6.37.5中：CH3域中之K392D(EU)及K409D(EU)取代、CH1域中之S183K(EU)取代、及CL域中之S176E(EU)取代。將以下取代引入硬化蛋白抗體27H6中：CH3域中之E356K(EU)及D399K(EU)取代、CH1域中之S183E(EU)取代、及CL域中之S176K(EU)取代。IgG1骨架用於異二聚形式1設計中。

兩種不同抗體之各種輸入DNA比率用於使IgG產量最大且使聚集程度(高分子量物質)最小。使用兩種抗體之等量DNA導致聚集程度最小。

爲評估異Ig雙特異性抗體形成，純化物質且使其經受質譜分析。NR質量分析確認抗體產物具有兩個不同輕鏈及兩個不同重鏈。爲確認特定輕鏈-重鏈配對，經由蛋白水解(Pierce Fab微量製備套組)產生Fab片段。質量分析僅顯示兩種物質，一種對應於DKK1抗體重鏈及輕鏈配對且另一對應於硬化蛋白抗體之重鏈及輕鏈配對。質量分析確認存在在硬化蛋白/DKK1異二聚抗體之兩臂中均具有正確輕鏈及重鏈配對之異二聚抗體。

質量分析指示在純化樣品中存在單一抗體物質，其中觀測質量與異二聚抗體之計算質量匹配。所得異二聚抗體具有兩個輕鏈及兩個重鏈，其中異二聚抗體之抗硬化蛋白部分之重鏈在CH1域中具有S183E(EU)取代且抗硬化蛋白部分之輕鏈在CL域中具有S176K(EU)取代。異二聚抗體之抗DKK1部分之重鏈在CH1域中具有S183K(EU)取代且DKK1部分之輕鏈在CL域中具有S176E(EU)取代。異二聚抗體之抗硬化蛋白部分之CH3域具有E356K(EU)及D399K(EU)取代且抗DKK1部分

之CH3域在K392D(EU)及K409D(EU)處具有取代。

在獨立骨母細胞Wnt活化分析中評估產生之異二聚抗體在硬化蛋白及/或DKK1存在下活化典型Wnt信號傳導之能力，其中誘導細胞分化且以自分泌方式分泌活化Wnt信號傳導之因子。在分析中，MC3T3-E1細胞用Super-TOPFlash報導體構築體轉染，且選擇並評估穩定細胞株。MC3T3E1/TetONWnt1/螢光素酶爲一種使用慢病毒轉導，用T細胞因子反應螢光素酶構築體、Tet抑制子構築體及多西環素(doxycycline)誘導性Wnt-1構築體工程改造之小鼠骨母細胞細胞株。在多西環素存在下，MC3T3E1/TetONWnt1/Luc細胞表現Wnt-1且經由Wnt-1結合細胞表面LRP5/6及捲曲受體，從而導致螢光素酶表現來誘導信號轉導。當在硬化蛋白及/或DKK1存在下培育MC3T3E1/TetONWnt1/Luc#5細胞時，Wnt信號傳導由此等蛋白質經由Lrp5/6 β螺旋槳1基元加以抑制。生物分析量測用固定濃度之硬化蛋白及/或DKK1處理之異二聚抗體及親本抗體之細胞基報導體分析中的劑量依賴性刺激效應。

純系C10顯示在與純化硬化蛋白或DKK1蛋白質一起培育之後，報導體活性由於Wnt路徑活化受抑制而降低。在擴增培養基(含有10% FBS、1×青黴素-鏈黴素-Glu及1.0 ug/ml嘌呤黴素(puromycin)之α-MEM培養基)中培養細胞。當細胞達到80%匯合時，將培養基變換成分化培養基「DM」(擴增培養基、50 ug/ml抗壞血酸及10 mM β-甘油磷酸鹽)，持續4天。在分化之後，此細胞株以自分泌方式產生觸發典型Wnt活化之內源性蛋白質。吸出培養基且添加100 μl含有各種濃度之單特異性或異二聚抗體(在37℃下與DKK1一起預培育4小時及/或與硬化蛋白一起預培育45-60分鐘)之新鮮DM至孔中持續24小時。遵循製造商說明書(Promega之螢光素酶分析系統，目錄號：E4530)量測螢光素酶活性。測試之各種大鼠及人類雙特異性抗體能夠在硬化蛋白與DKK1兩者存在下以劑量依賴性方式活化骨母細胞典型Wnt路徑，從而進一步顯示

抗體可同時中和兩種可溶性蛋白質之Wnt抑制功能。

結果指示根據此實例中所述之方法產生之異二聚抗體與連接子體(其用作陽性對照)兩者均具有極類似活性，從而進一步確認輕鏈及重鏈之正確配對。

實例4-產生在CH3域、CH/CL域及VH/VL域中具有取代之異二聚抗體。

以下實例描述產生在CH3、CH/CL及VH/VL域之各者中具有一或多個取代以進一步有利於輕鏈及重鏈之正確配對的異二聚抗體。異二聚抗體之硬化蛋白部分係基於Ab-5及Ab-23且DKK1部分係基於抗體6.147及6.37.5。此處使用IgG2類別恆定域以防止ADCC且阻礙效應物功能。在VH/VL、CH/CL及CH3/CH3界面中包含帶電荷取代之所得異二聚抗體在本文中稱爲異二聚抗體形式2或異Ig-v2。

當在一種細胞內部共表現兩種不同抗體時，轉錄且轉譯四個不同鏈(HC1、LC1、HC2、LC2)。HC可形成同二聚體(HC1-HC1)或異二聚體(HC1-HC2)；LC可與兩個不同HC一起隨機裝配。總計，可存在十種不同組合[Paul Carter *J Immunological Methods* 248 (2001) 7-15]。可藉由工程改造C_H3區來使非所要重鏈同二聚體最少以僅形成異二聚體。此實例顯示不合需要LC/HC配對可藉由工程改造LC/HC之界面以增強LC與其同源HC之正確配對加以消除。靜電操縱機制用於引導LC/HC之配對及裝配；相反極性吸引所要複合物次單元，而同二聚體次單元之相同極性爲排斥性的。

當沿重鏈及輕鏈界面選擇殘基對用於經具有相反極性之帶電荷殘基(例如Asp或Lys)置換以控制LC與其同源HC之正確配對時，應用若干準則：1)所有位置在VL/VH界面與CL/C_H1界面兩者內均緊密鄰近定位；2)所有位置皆經包埋且在大多數(若非全部)不同抗體家族之中充分保守；3)所有位置對表現及抗原結合皆具有最小影響；及4)引入帶電

荷殘基不干擾侶伴蛋白BiP在抗體折疊及裝配過程中結合C_H1區。

在VL/VH及Cκ/C_H1界面處選擇用於工程改造之殘基列於表2中。在可變區中，VH中之主要AHo位置46(Q39 Kabat)、AHo位置51(Kabat G44)及AHo位置141(Kabat Q105)分別緊密鄰近於VL中之AHo位置46(Kabat Q38)、AHo位置141(Kabat Q100)及AHo位置51(Kabat A43)。在恆定區中，C_H1區中之A141(EU)、P171(EU)及S183(EU)分別接觸Ck中之殘基F116(EU)、S162(EU)及S176(EU)，但C_H1中之K147(EU)可與Ck區中之Q124(EU)、S131(EU)或T180(EU)相互作用。

表2：選擇位於VH/VL及CH1/Cκ界面處之胺基酸殘基用於引入電荷配對殘基。根據不同編號系統對VH及VL之生殖系殘基編號，粗體殘基為主要殘基。大多數抗體之VH/VL中之接觸殘基排列在同一列中。人類IgG1 CH1域之接觸Cκ區中之殘基的殘基亦用粗體表示且置於同一列中。FW：構架。

VH							**VL**					
IMGT #	Kabat #	Eu #	AHo#	FW	殘基	接觸	IMGT#	Kabat #	Eu #	AHo#	FW	殘基
44	39	39	46	*2*	**Q/R/T**	↔	44	38	38	46	*2*	**Q/G/H/L**
49	44	44	51	*2*	**G/R/A**	↔	*	100	100	141	4	**Q/G/P**
*	105	109	141	4	**Q/K/R/S**	↔	49	43	43	51	*2*	**A/G/S/P**

C_H1							**Cκ**					
IMGT#	Kabat #	Eu#	AHo#	Ref #	殘基	接觸	IMGT#	Kabat #	Eu#	AHo#	Ref#	殘基
20	139	141	*	176	**A**	↔	5	116	116	*	158	**F**
82	175	171	*	212	**P**	↔	81	162	162	*	211	**S**
86	188	183	*	230	**S**	↔	86	176	176	*	230	**S**
26	145	147	*	182	**K**	↔	13	124	124	*	166	**Q**
26	145	147	*	182	**K**	↔	20	131	131	*	176	**S**
26	145	147	*	182	**K**	↔	90	180	180	*	234	**T**

異二聚抗體之Wnt1驅動之骨母細胞報導體分析顯示在DKK1與硬化蛋白兩者存在下典型Wnt信號傳導受強健活化，而對照DKK1抗體(6.37.5、6.147)及對照硬化蛋白抗體(Ab-23)僅部分逆轉抑制。

工程改造異二聚抗體能夠中和DKK1且阻斷重組Wnt3a誘導之

TCF/LEF螢光素酶活性，如獨立細胞基分析中所見。在此分析中，在4℃下用100 ng/ml重組Wnt3a蛋白質(R&D Systems)誘導MC3T3 E1/STF-螢光素酶穩定細胞株中之Wnt信號傳導30分鐘。隨後用與對照PBS或異二聚抗體之起始於426.7 nM之兩倍連續稀釋液預混合的0.15 ug/ml人類DKK1蛋白質處理細胞。如上所述在24小時之後測定螢光素酶信號且藉由使用PRISM軟體繪製資料。結果指示可變區靶向硬化蛋白之環2區域(亦即SEQ ID NO: 1之胺基酸86-111)與DKK1兩者之異二聚抗體能夠中和硬化蛋白及DKK1且增加由Wnt3a驅動之報導體活性。

實例5-親本及異二聚抗體之功能分析

對針對硬化蛋白之環2區域之抗硬化蛋白親本抗體(Ab23、Ab5、20C3)及針對非環2抗原決定基之抗硬化蛋白親本抗體(27H6、Ab13、Ab-D、Ab-3)的功能分析揭示各組抗體之獨特作用機制。進行競爭α篩檢結合分析以量測遞增濃度之親本硬化蛋白抗體對含his標籤之LRP6與經生物素標記之人類硬化蛋白之間的相互作用的影響。此分析揭示當結合硬化蛋白之環2區域之抗硬化蛋白抗體強力抑制硬化蛋白與LRP6之間的相互作用時，針對硬化蛋白之非環2區域之抗體使此等蛋白質之間的相互作用增加。此外，工程改造異二聚抗體顯示類似現象，其中不同於針對硬化蛋白之環2區域之異二聚抗體，針對非環2硬化蛋白抗原決定基之異二聚抗體(亦即27H6-6.37.5、6.147-27H6)促進LRP6與硬化蛋白之結合增加。發現所有異二聚抗體皆與人類DKK1競爭結合LRP6。

為瞭解此現象對典型Wnt路徑活化之影響，在使用骨母細胞及293細胞之TCF報導體細胞基分析中研究親本抗體及異二聚抗體。用結合LRP6 β螺旋槳1基元之Wnt1或結合LRP6 β螺旋槳3基元之Wnt3a刺激細胞。典型Wnt路徑活化藉由螢光素酶活性增加加以量度。在分析中，添加硬化蛋白及/或DKK1以抑制報導體活性且研究不同抗硬化蛋白或

抗DKK1抗體之中和活性。儘管硬化蛋白抑制Wnt3a驅動之TCF報導體活化，但抗硬化蛋白非環2區域結合抗體(27H6)而非對照環2結合抗體(Ab5及Ab23)增強Wnt3a信號傳導。用含有針對硬化蛋白之非環2區域之抗硬化蛋白可變區的異二聚抗體獲得類似Wnt3a增強結果。相反，藉由硬化蛋白抑制，Wnt1活性由任一抗體恢復，如藉由不超過未處理對照之螢光素酶活性之螢光素酶活性增加所示。此等影響依賴於硬化蛋白之存在，因爲在不存在硬化蛋白下，用針對硬化蛋白之非環2區域之異二聚抗體未觀測到增強作用。對其他異二聚抗體之類似分析顯示包含結合硬化蛋白之環2之抗硬化蛋白部分的異二聚抗體未能增強Wnt3a，而含有結合硬化蛋白之非環2區域之可變區的異二聚抗體增強Wnt3a信號傳導。此外，包含結合硬化蛋白之非環2區域之可變區的異二聚抗體在DKK1存在下增強Wnt3a信號傳導，而單特異性非環2異二聚抗體增強作用在DKK1存在下受抑制。在單獨DKK1存在下，所有典型Wnt活化皆受抑制，此與顯示DKK1之C末端區域結合LRP6之β螺旋槳3基元且阻斷Wnt3a類別蛋白質與此區域之相互作用的新近報導(Cheng等人, Nature Structural Mol Biol, 2011; Anh Dev Cell 2011)一致。此等資料表明經由硬化蛋白結合於β螺旋槳域1之抗體-配體複合物可以增加Wnt3a/β螺旋槳3活性之方式影響受體之構形。先前已報導由抗LRP6 β螺旋槳1結合抗體達成之類似Wnt3a依賴性增強現象，其中此等抗體增加癌症細胞株中之促有絲分裂性及腫瘤異種移植物之生長(Ettenberg等人, PNAS 2010)。

亦觀測到由非環2結合抗硬化蛋白抗體在非骨母細胞中達成之Wnt3a增強作用。此結果提升硬化蛋白/非環2結合抗體複合物可活化表現LRP6之任何細胞類型中之Wnt信號傳導的可能性，其限制條件爲存在Wnt3類別蛋白質或β螺旋槳3結合蛋白且不存在DKK1。在異二聚抗體之情況下，增強作用可在DKK1存在下發生。基於此等觀測結果且爲

減小非骨母細胞中之促有絲分裂性之風險，用針對環2區域之在Wnt1骨母細胞TCF報導體分析中顯示使報導體活性強健增加之抗硬化蛋白可變區工程改造新穎異二聚抗體。

此外，結合硬化蛋白之非環2區域之親本抗硬化蛋白抗體不破壞硬化蛋白與其同源LRP受體之相互作用且保持LRP6相互作用或LRP4相互作用。儘管針對硬化蛋白之環2區域之親本硬化蛋白抗體及異二聚抗體抑制LRP6與硬化蛋白之間的相互作用，但其在共免疫沈澱實驗中未能抑制硬化蛋白與LRP4之間的相互作用。相反，含有抗非環2可變域之親本抗體或異二聚抗體皆使LRP4與硬化蛋白之間的結合降低(19D11、27H6、L8及N22)。在IgG2骨架中工程改造新穎異二聚抗體。

實例6-異二聚抗體顯示活體內活性。

以下實例顯示根據實例3及4中所述之方法產生之異二聚抗體在低骨礦物質密度之動物模型中使骨礦物質密度增加。

雄性10週齡B6D2F1小鼠用於此研究中。在研究開始時，將動物分成5組(n = 9/組)，各組在體重與股骨-脛骨區域處之藉由活體內DXA獲得之骨礦物質密度(BMD)兩者方面平衡。每週兩次持續3週用媒劑(脯胺酸)或硬化蛋白-Ab(Scl-Ab)、或DKK1-Ab或Scl-Ab與DKK1-Ab(組合)之組合或異二聚抗體(異Ig)皮下注射小鼠。抗體在12.5 mg/ml下給藥。每週藉由活體內DXA掃描動物以監測腰椎及股骨-脛骨區域處藥物治療之骨合成代謝活性。隨後在研究結束時使小鼠安樂死。收集股骨以藉由μCT進行離體密度測定及進行骨強度分析。

圖1說明以下異二聚抗體之活體內研究設計：(1)Ab23-Ab6.147 v2，(2)Ab5-Ab6.37.5 v1，及(3)Ab5-Ab6.147 v1。Ab-5用作單藥療法對照且DVD Ig 6.147-Ab23(描述於國際公開案第WO 2012/118903號中)用作此研究中之雙特異性抗體對照。由於分子量高於單藥療法對照及異二聚抗體，所以DVD Ig之劑量略微較高(17 mg/kg)。此處必須注意異

二聚抗體形式針對各目標為單價，而DVD針對各目標為二價。因此，儘管就體積莫耳濃度而言，給藥含量使得DVD及異二聚抗體(異Ig)相等，但其在結合位點(互補位)之數目方面不同。

圖2比較上述單特異性Ig(Ab5)、雙特異性DVD(6.147-Ab23)及異二聚抗體1、2及3之間的在第3週在小鼠之腰椎及腿中達成的骨物質密度(BMD)增加百分比。

圖2中所示之資料明確顯示異二聚抗體Ab5-6.37.5 v1(異二聚抗體2-「異Ig2」)及785-6.147 v1(異二聚抗體3-「異Ig3」)使骨物質密度增加。然而，在可變域界面(VH/VL)中具有額外電荷配對取代之異二聚抗體Ab23-6.147 v2(異二聚抗體1-「異Ig1」)不增加BMD。預期在可變域中添加其他電荷配對取代將有助於達成輕鏈及重鏈之特定配對(例如Ab5輕鏈與Ab5重鏈配對)。但似乎在此情況下，可變域中之其他電荷配對取代導致異二聚抗體之穩定性不良。在此PD研究之後的PK研究實際上顯示異二聚抗體Ab23-6.147之DKK1臂具有不良活體內穩定性。

實例7-藥物動力學資料

進行四種不同藥物動力學分析(亦即硬化蛋白/DKK1分析；硬化蛋白/Fc分析；DKK1/硬化蛋白分析；及FC/FC橋式ELISA分析)以捕捉並偵測血清樣品中之異二聚抗體。

硬化蛋白/DKK1分析：簡言之，半區域盤用含1 μg/ml人類硬化蛋白之1× PBS塗佈且在4℃下培育隔夜。用I-Block緩衝液阻斷各盤至少1小時。於大鼠血清樣品中製備標準物(Std)及品質控制樣品(QC)。以1:30於緩衝液(1× PBS、1 M NaCl、0.5%吐溫20(tween 20)及10 mg/ml BSA)中稀釋標準物、QC及血清樣品。接著將稀釋Std、QC及樣品裝載入ELISA盤中且培育90分鐘。接著洗滌ELISA盤且添加含200 ng/ml生物素化人類DKK1之緩衝液並培育90分鐘。將盤洗滌且添加200 ng/ml結合有HRP之抗生蛋白鏈菌素(Streptavidin)並培育30分鐘。在將盤洗滌之

後，添加TMB受質。在15分鐘之後藉由添加1 M硫酸終止反應。接著藉由SpectraMax盤讀取器讀取盤。

硬化蛋白/FC分析：半區域盤用含1 μg/ml人類硬化蛋白之1× PBS塗佈且在4℃下培育隔夜。用I-Block緩衝液阻斷各盤至少1小時。於大鼠血清樣品中製備標準物(Std)及品質控制樣品(QC)。以1:30於緩衝液(1× PBS、1 M NaCl、0.5%吐溫20及10 mg/ml BSA)中稀釋標準物、QC及血清樣品。接著將稀釋Std、QC及樣品裝載入ELISA盤中且培育90分鐘。接著洗滌ELISA盤且添加10 ng/ml結合有HRP之抗人類Fc抗體Mab 1.35.1並培育90分鐘。在將盤洗滌之後，添加TMB受質。在15分鐘之後藉由添加1 M硫酸終止反應。接著藉由SpectraMax盤讀取器讀取盤。

DKK1/FC分析：半區域盤用含1 μg/ml人類DKK1之1× PBS塗佈且在4℃下培育隔夜。用I-Block緩衝液阻斷各盤至少1小時。於大鼠血清樣品中製備標準物(Std)及品質控制樣品(QC)。以1:30於緩衝液(1× PBS、1 M NaCl、0.5%吐溫20及10 mg/ml BSA)中稀釋標準物、QC及血清樣品。接著將稀釋Std、QC及樣品裝載入ELISA盤中且培育90分鐘。接著洗滌ELISA盤且添加10 ng/ml結合有HRP之抗hu Fc抗體Mab 1.35.1並培育90分鐘。在將盤洗滌之後，添加TMB受質。在15分鐘之後藉由添加1 M硫酸終止反應。接著藉由SpectraMax盤讀取器讀取盤。

FC/FC橋式ELISA分析：簡言之，半區域盤用含0.2 μg/ml抗人類Fc抗體Mab 1.35.1之1 × PBS塗佈並在4℃下培育隔夜。用I-Block緩衝液阻斷各盤至少1小時。於大鼠血清樣品中製備標準物(Std)及品質控制樣品(QC)。以1:30於緩衝液(1 × PBS、1 M NaCl、0.5%吐溫20及10 mg/ml BSA)中稀釋標準物、QC及血清樣品。接著，將稀釋Std、QC及樣品裝載入ELISA盤中且培育90分鐘。接著洗滌ELISA盤且添加50 ng/ml結合有HRP之抗人類Fc抗體Mab 1.35.1並培育30分鐘。在將盤洗滌之後，添

加TMB受質。在10分鐘之後藉由添加1 M硫酸終止反應。接著藉由SpectraMax盤讀取器讀取盤。

圖3顯示測試之四種硬化蛋白-DKK1異二聚抗體(亦即Ab23-6.37.5 v1、Ab5-6.37.5 v1、Ab5-6.147 v2及Ab23-6.147 v2)之藥物動力學(PK)概況。結果指示在VH/VL域中包含帶電荷胺基酸取代之異二聚抗體負性影響穩定性，因為基於硬化蛋白/DKK1及DKK1/Fc分析之PK概況偏離硬化蛋白/Fc及Fc/Fc分析之PK概況。

實例8：在產生異二聚抗體期間藉由靜電操縱機制控制輕鏈與其同源重鏈之正確配對

當在一種細胞內部共表現兩種不同抗體時，轉錄且轉譯四個不同鏈(HC1、LC、HC2、LC2)。HC可形成同二聚體或異二聚體；LC可與兩個不同HC一起隨機裝配。可存在十種不同組合[Paul Carter J Immunological Methods 248 (2001) 7-15]。可藉由工程改造CH3區來使源於重鏈同二聚體之非所要副產物最少以僅形成異二聚體。此實例顯示不合需要LC/HC配對可藉由工程改造LC/HC之界面以增強LC與其同源HC之正確配對加以消除。靜電操縱機制用於引導LC/HC之配對及裝配，因為相反極性為吸引性的，而相同極性為排斥性的。

當沿重鏈及輕鏈界面選擇經具有相反極性之帶電荷殘基(例如Asp或Lys)置換以控制LC與其同源HC之正確配對的殘基對時，應用若干準則：1)所有位置在VL/VH界面與CL/CH1界面兩者內均緊密鄰近定位；2)所有位置皆經包埋且在大多數(若非全部)不同抗體家族之中充分保守；3)所有位置對表現及抗原結合皆具有最小影響；及4)引入帶電荷殘基不干擾侶伴蛋白BiP在抗體折疊及裝配過程中結合CH1區。

在VL/VH及Cκ/CH1界面處選擇用於工程改造Her2/EGFR異二聚抗體之殘基列於表2中。在可變區中，VH中之主要Q39(Kabat編號；AHo位置46)、G44(AHo位置51)及Q105(AHo位置141)分別緊密鄰近於VL中

之Q38(Kabat編號；AHo位置46)、Q100(AHo位置141)及A43(AHo位置51)。在恆定區中，CH1區中之A141(Eu編號)、P171及S183分別接觸Ck中之殘基F116(Eu編號)、S162及S176，但CH1中之K147(Eu編號)可與Ck區中之Q124、S131或T180(Eu編號)相互作用。

使用來自抗EGFR抗體及抗HER2抗體之v基因構築概念驗證異二聚IgG。圖4顯示構成異二聚抗體變異體之不同組態。一個Fc鏈在CH2域中具有ADCC增強取代S298T + A330M + K334V且在CH3域中具有異二聚化取代K392D + K409D，而另一Fc鏈在下部鉸鏈區及CH2域中具有ADCC增強取代L234Y + K290Y + Y296W以及在CH3域中具有異二聚化取代E356K + D399K。抗體優先形成當以其Fab區特異性結合腫瘤細胞時可誘導強烈ADCC殺傷性之異二聚體。

表2：選擇位於VH/VL及CH1/Cκ界面處之胺基酸殘基用於引入電荷配對殘基。根據不同編號系統對VH及VL之生殖系殘基編號，粗體殘基為主要殘基。大多數抗體之VH/VL中之接觸殘基排列在同一列中。人類IgG1 CH1域之接觸Cκ區中之殘基的殘基亦用粗體表示且置於同一列中。FW：構架。

表2.

VH							**VL**					
IMGT #	Kabat #	Eu #	AHo#	FW	殘基	接觸	IMGT #	Kabat #	Eu #	AHo#	FW	殘基
44	39	39	46	*2*	**Q/R/T**	↔	44	38	38	46	*2*	**Q/G/H/L**
49	44	44	51	*2*	**G/R/A**	↔	*	100	100	141	*4*	**Q G/P**
*	105	109	141	4	**Q/K/R/S**	↔	49	43	43	51	*2*	**A/G/S/P**

C_H1							**CK**					
IMGT #	Kabat #	Eu#	AHo#	Ref #	殘基	接觸	IMGT #	Kabat #	Eu#	AHo#	Ref#	殘基
20	139	141	*	176	**A**	↔	5	116	116	*	158	**F**
82	175	171	*	212	**P**	↔	81	162	162	*	211	**S**
86	188	183	*	230	**S**	↔	86	176	176	*	230	**S**
26	145	147	*	182	**K**	↔	13	124	124	*	166	**Q**
26	145	147	*	182	**K**	↔	20	131	131	*	176	**S**
26	145	147	*	182	**K**	↔	90	180	180	*	234	**T**

在一概念驗證研究中，將Fn3標籤(12 KDa)插入在抗EGFr Ab2 HC之N末端處且使Fn3-Flag-His6標籤(14 KDa)同框融合於抗EGFr Ab2 LC之C末端，因此LC/HC之4種不同組合可在SDS-PAGE凝膠中根據不同尺寸加以區分：所要LC1/HC1::LC2-Fn3-FH/Fn3-HC2或非所要LC2-Fn3-FH/HC1::LC1/Fn3-HC2為176 KDa；非所要LC1/HC1::LC1/Fn3-HC2為162 KDa；且非所要LC2-Fn3-FH/HC1::LC2-Fn3-FH/Fn3-HC2為190 KDa。176 KDa產物之組合物隨後在部分還原下藉由質譜加以確定。雙抗原結合盤ELISA用於篩檢具有較佳LC/HC配對之有利變異體。

研究不同變異體(表3)以獲得雙抗原結合性最高及LC/HC配對正確之最佳組合。當相較於不產生任何結合信號之單特異性抗Her2 Ab1(C01)或抗EGFr Ab2(C07)、及由LC/HC隨機配對之四個規則鏈構成之內部對照C11時，變異體1C02、1C04、2A05、2B04、2B05及5D03顯示與雙抗原(Her2及EGFr細胞外域)之結合以劑量依賴性方式改良。變異體2B05及5D03具有最強烈結合，因為曲線向左移動最多。在SDS-PAGE凝膠中，此等變異體亦主要形成全長異二聚體IgG1。表現測試指示添加調節劑XBP1略微加強異二聚抗體變異體之表現量，而另一調節劑ERP23很少加強表現。

表3：藉由靜電操縱機制製備之變異體。呈異二聚IgG1形式之抗Her2 Ab1及抗EGFr Ab2之VH/VL及CH1/CL界面的胺基酸變化，其中Ab1之HC在CH2域中具有S298T+A330M+K334V且在CH3域中具有K392D+K409D；Ab2之HC在下部鉸鏈及CH2域中具有L234Y+K209Y+Y296W且在CH3域中具有E356K+D399K。將Fn3標籤插入在抗EGFr Ab2 HC之N末端處且使Fn3-Flag-His6標籤同框融合於抗EGFr Ab2 LC之C末端。可變區(VH或VL)中之殘基係根據Kabat編號系統來編號，而恆定區(CH1或CL)中之殘基係根據Eu編號系統來編號。

	抗Her2 Ab1 HC (K392D + K409D)		抗Her2 Ab1 LC		抗EGFr Ab2 HC (E356K + D399K)		抗EGFr Ab2 LC	
變異體	VH1	CH1	VL1	CL	VH2	CH1	VL2	CL
C12	Q39K+ G44K		Q38D+ Q100D		Q39D+G44D		Q38K+ G100K	
C13	Q39K+ G44K		Q38D+ Q100D		Q39D+Q105D		Q38K+ A43K	
C14	Q39K+ G44K		Q38D+ Q100D		G44D+Q105D		G100K+ A43K	
C15	Q39K+ Q105K		Q38D+ A43D		Q39D+G44D		Q38K+ G100K	
C16	Q39K+ Q105K		Q38D+ A43D		Q39D+Q105D		Q38K+ A43K	
C17	Q39K+ Q105K		Q38D+ A43D		G44D+Q105D		G100K+ A43K	
C18	G44K+ Q105K		Q100D+ A43D		Q39D+G44D		Q38K+G 100K	
C19	G44K+ Q105K		Q100D+ A43D		Q39D+Q105D		Q38K+A 43K	
C20	G44K+ Q105K		Q100D+ A43D		G44D+Q105D		G100K+ A43K	
1A01		K147K + S183K		Q124D+ S176D		K147D + S183D		Q124K + S176K
1A02		K147K + S183K		Q124D+ S176D		K147D + S183D		S131K + S176K
1A03		K147K + S183K		Q124D+ S176D		K147D + S183D		S176K + T180K
1A04		K147K + S183K		S131D+ S176D		K147D + S183D		Q124K + S176K
1A05		K147K + S183K		S131D+ S176D		K147D + S183D		S131K + S176K
1A06		K147K + S183K		S131D+ S176D		K147D + S183D		S176K + T180K
1B01		K147K + S183K		S176D+ T180D		K147D + S183D		Q124K + S176K
1B02		K147K + S183K		S176D+ T180D		K147D + S183D		S131K + S176K
1B03		K147K + S183K		S176D+ T180D		K147D + S183D		S176K + T180K
1B04	Q39K+ Q105K	K147D + S183D	Q38D + A43D	Q124K + S176K	G44D + Q105D	S183K	G100K + A43K	Q124D + S176D

1B05	Q39K+ Q105K	K147D + S183D	Q38D + A43D	Q124K + S176K	G44D + Q105D	S183K	G100K + A43K	S131D + S176D
1B06	Q39K+ Q105K	K147D + S183D	Q38D + A43D	Q124K + S176K	G44D + Q105D	S183K	G100K + A43K	S176D + T180D
1C01	Q39K+ Q105K	K147D + S183D	Q38D + A43D	S131K + S176K	G44D + Q105D	S183K	G100K + A43K	Q124D + S176D
1C02	Q39K+ Q105K	K147D + S183D	Q38D + A43D	S131K + S176K	G44D + Q105D	S183K	G100K + A43K	S131D + S176D
1C03	Q39K+ Q105K	K147D + S183D	Q38D + A43D	S131K + S176K	G44D + Q105D	S183K	G100K + A43K	S176D + T180D
1C04	Q39K+ Q105K	K147D + S183D	Q38D + A43D	S176K + T180K	G44D + Q105D	S183K	G100K + A43K	Q124D + S176D
1C05	Q39K+ Q105K	K147D + S183D	Q38D + A43D	S176K + T180K	G44D + Q105D	S183K	G100K + A43K	S131D + S176D
1C06	Q39K+ Q105K	K147D + S183D	Q38D + A43D	S176K + T180K	G44D + Q105D	S183K	G100K + A43K	S176D + T180D
1D01		K147K		Q124D		K147D		Q124K
1D02		K147K		Q124D		K147D		S131K
1D03		K147K		Q124D		S183D		S176K
1D04		K147K		S131D		K147D		Q124K
1D05		K147K		S131D		K147D		S131K
1D06		K147K		S131D		S183D		S176K
2A01		S183K		S176D		K147D		Q124K
2A02		S183K		S176D		K147D		S131K
2A03		S183K		S176D		S183D		S176K
2A04	Q39K+ Q105K	K147D	Q38D + A43D	Q124K	G44D + Q105D	K147K	G100K + A43K	Q124D
2A05	Q39K+ Q105K	K147D	Q38D + A43D	Q124K	G44D + Q105D	K147K	G100K + A43K	S131D
2A06	Q39K+ Q105K	K147D	Q38D + A43D	Q124K	G44D + Q105D	S183K	G100K + A43K	S176D
2B01	Q39K+ Q105K	K147D	Q38D + A43D	S131K	G44D + Q105D	K147K	G100K + A43K	Q124D
2B02	Q39K+ Q105K	K147D	Q38D + A43D	S131K	G44D + Q105D	K147K	G100K + A43K	S131D
2B03	Q39K+ Q105K	K147D	Q38D + A43D	S131K	G44D + Q105D	S183K	G100K + A43K	S176D
2B04	Q39K+ Q105K	K147D	Q38D + A43D	T180K	G44D + Q105D	K147K	G100K + A43K	Q124D
2B05	Q39K+ Q105K	K147D	Q38D + A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
2B06	Q39K+ Q105K	K147D	Q38D + A43D	T180K	G44D + Q105D	S183K	G100K + A43K	S176D
2C01	Q39K+ Q105K	S183D	Q38D + A43D	S176K	G44D + Q105D	K147K	G100K + A43K	Q124D
2C02	Q39K+ Q105K	S183D	Q38D + A43D	S176K	G44D + Q105D	K147K	G100K + A43K	S131D
2C03	Q39K+	S183D	Q38D +	S176K	G44D +	S183K	G100K +	S176D

	Q105K		A43D		Q105D		A43K	
5A01	Q39K+ Q105K	A141D	Q38D + A43D	F116K	Q39D + Q105D	A141K	Q38K + A43K	F116D
5A02	Q39K+ Q105K	A141D	Q38D + A43D	F116K	Q39D + Q105D	P171K	Q38K + A43K	S162D
5A03	Q39K+ Q105K	A141D	Q38D + A43D	F116K	Q39D + Q105D	K147K	Q38K + A43K	S131D
5A04	Q39K+ Q105K	A141D	Q38D + A43D	F116K	Q39D + Q105D	S183K	Q38K + A43K	S176D
5A05	Q39K+ Q105K	P171D	Q38D + A43D	S162K	Q39D + Q105D	A141K	Q38K + A43K	F116D
5A06	Q39K+ Q105K	P171D	Q38D + A43D	S162K	Q39D + Q105D	P171K	Q38K + A43K	S162D
5B01	Q39K+ Q105K	P171D	Q38D + A43D	S162K	Q39D + Q105D	K147K	Q38K + A43K	S131D
5B02	Q39K+ Q105K	P171D	Q38D + A43D	S162K	Q39D + Q105D	S183K	Q38K + A43K	S176D
5B03	Q39K+ Q105K	K147D	Q38D + A43D	S131K	Q39D + Q105D	A141K	Q38K + A43K	F116D
5B04	Q39K+ Q105K	K147D	Q38D + A43D	S131K	Q39D + Q105D	P171K	Q38K + A43K	S162D
5B05	Q39K+ Q105K	K147D	Q38D + A43D	S131K	Q39D + Q105D	K147K	Q38K + A43K	S131D
5B06	Q39K+ Q105K	K147D	Q38D + A43D	S131K	Q39D + Q105D	S183K	Q38K + A43K	S176D
5C01	Q39K+ Q105K	S183D	Q38D + A43D	S176K	Q39D + Q105D	A141K	Q38K + A43K	F116D
5C02	Q39K+ Q105K	S183D	Q38D + A43D	S176K	Q39D + Q105D	P171K	Q38K + A43K	S162D
5C03	Q39K+ Q105K	S183D	Q38D + A43D	S176K	Q39D + Q105D	K147K	Q38K + A43K	S131D
5C04	Q39K+ Q105K	S183D	Q38D + A43D	S176K	Q39D + Q105D	S183K	Q38K + A43K	S176D
5C05	Q39K+ Q105K	A141D	Q38D + A43D	F116K	G44D + Q105D	A141K	G100K + A43K	F116D
5C06	Q39K+ Q105K	A141D	Q38D + A43D	F116K	G44D + Q105D	P171K	G100K + A43K	S162D
5D01	Q39K+ Q105K	A141D	Q38D + A43D	F116K	G44D + Q105D	K147K	G100K + A43K	S131D
5D02	Q39K+ Q105K	A141D	Q38D + A43D	F116K	G44D + Q105D	S183K	G100K + A43K	S176D
5D03	Q39K+ Q105K	P171D	Q38D + A43D	S162K	G44D + Q105D	A141K	G100K + A43K	F116D
5D04	Q39K+ Q105K	P171D	Q38D + A43D	S162K	G44D + Q105D	P171K	G100K + A43K	S162D
5D05	Q39K+ Q105K	P171D	Q38D + A43D	S162K	G44D + Q105D	K147K	G100K + A43K	S131D
5D06	Q39K+ Q105K	P171D	Q38D + A43D	S162K	G44D + Q105D	S183K	G100K + A43K	S176D
6A01	Q39K+ Q105K	K147D	Q38D + A43D	S131K	G44D + Q105D	A141K	G100K + A43K	F116D
6A02	Q39K+ Q105K	K147D	Q38D + A43D	S131K	G44D + Q105D	P171K	G100K + A43K	S162D
6A03	Q39K+ Q105K	K147D	Q38D + A43D	S131K	G44D + Q105D	K147K	G100K + A43K	S131D
6A04	Q39K+	K147D	Q38D +	S131K	G44D +	S183K	G100K +	S176D

	Q105K		A43D		Q105D		A43K	
6A05	Q39K+ Q105K	S183D	Q38D + A43D	S176K	G44D + Q105D	A141K	G100K + A43K	F116D
6A06	Q39K+ Q105K	S183D	Q38D + A43D	S176K	G44D + Q105D	P171K	G100K + A43K	S162D
6B01	Q39K+ Q105K	S183D	Q38D + A43D	S176K	G44D + Q105D	K147K	G100K + A43K	S131D
6B02	Q39K+ Q105K	S183D	Q38D + A43D	S176K	G44D + Q105D	S183K	G100K + A43K	S176D

藉由短暫轉染HEK 2936E細胞來製備變異體1C02、1C04、2A05、2B05及5D03，且用蛋白質A管柱純化，接著用Superdex 200粒徑排阻管柱精製。自900 mL上清液，藉由分析型SEC獲得1.2~6.8 mg純度約100%之最終產物。在非還原SDA-PAGE凝膠中(圖4，左側)，所有變異體皆具有極主要全長IgG1，其中Fn3標籤插入在抗EGFr Ab2 HC之N末端處且Fn3-Flag-His6標籤同框融合於抗EGFr Ab2 LC之C末端。變異體2B05及5D03之純度最大，伴有極少量較小亮帶。在還原條件下，歸因於其不同尺寸分離四個不同鏈(Fn3-HC2在61 KDa處；HC1在50 KDa處；LC2-Fn3-Flag-His6在36 KDa處；LC1在23 KDa處)。四個不同鏈顯示在裝配之全長IgG1抗體中爲1:1:1:1比率。藉由質譜確認組分及正確LC/HC配對。

實例9-Her2/EGFR異二聚抗體維持親本抗體之阻斷功能

此實例顯示實例7中所述之異二聚抗體維持製備其所始於之個別抗體之阻斷功能。此外，異二聚抗體能夠介導針對目標表現性細胞之ADCC。

除雙抗原結合之外，選擇變異體2B05及5D03以藉由細胞基分析測試其功能性。CHO細胞株用人類EGFr穩定轉染。當在培養基中添加配體EGF時，CHO細胞表面上之受體EGFr經活化且經磷酸化，從而打開下游信號路徑，諸如MAPK、ERK1/2、PI3K、JAK/STAT及PKC。2B05及5D03所源於之抗EGFr抗體阻斷配體EGF結合受體EGFr且在IC50 = 2.7 nM下抑制受體EGFr磷酸化。抗EGFr抗體與抗Her2抗體之組合在

IC50 = 3.2 nM下類似地起作用。抗EGFr×Her2異二聚抗體變異體2B05與5D03兩者在受體EGFr磷酸化方面類似，IC50分別爲4.2 nM及4.6 nM，從而指示異二聚抗體變異體2B05及5D03之抗EGFr Fab臂之作用與野生型抗EGFr抗體類似。

BT474爲一種人類乳房腫瘤細胞株。BT474細胞在表面上表現Her2(Erb2)與Her3(Erb3)兩者。抗Her2抗體可結合Her2之域IV，從而觸發受體內化及降解[Wehrman TS, 等人 (2006) PNAS 103(50):19063-19068及Buschenfelde CM等人 (2002) Cancer Res 62(8):2244-2247]。因此，抗體阻斷下游信號傳導路徑[Yakes FM,等人 (2002) Cancer Res 62(14):4132-4141及Scotti ML等人 (2008) Breast Cancer Res Treat 111(2):241-50]，諸如Raf/MEK 1及2/ERK 1及2及PI3K/Akt路徑。在BT474細胞中，抗Her2抗體不降低Her2磷酸化但抑制基底Her3磷酸化。當不在BT474細胞培養基中添加配體時，單獨Her2抗體在IC50 = 2.8 nM下阻斷Her3磷酸化。抗EGFr抗體與抗Her2抗體之組合在IC50 = 5.2 nM下類似地起作用。抗EGFr×Her2異二聚抗體變異體2B05與5D03兩者分別在IC50 = 3.0 nM及IC50 = 3.6 nM下抑制受體Her3基底程度磷酸化，從而指示抗Her2臂在起作用。

以上兩種不同細胞基分析之組合資料表明抗EGFr×Her2異二聚抗體變異體2B05及5D03之兩個臂在抑制EGFr及Her2之活化方面均恰當地起作用。

實例10-Her2/EGFR異二聚抗體能夠介導對腫瘤細胞之ADCC殺傷

N87爲一種表現高含量Her2及中等含量EGFr之人類胃腫瘤細胞株。無關人類IgG1用作對照。抗EGFr×Her2異二聚抗體變異體2B05及5D03已在其Fc區中併入ADCC增強取代及異二聚化取代。進行ADCC分析以測試異二聚抗體變異體是否結合其特定抗原且誘導對N87細胞之殺傷。在1 μg/mL下，無關人類IgG1對照抗體具有本底溶解30%且在

其經向下滴定時不顯示劑量依賴性反應。變異體2B05與5D03兩者在1 μg/mL濃度下均具有高得多之特異性溶解且以EC50分別爲0.10 pM及0.19 pM顯示劑量依賴性反應。資料顯示異二聚抗體變異體2B05及5D03可結合目標EGFr及Her2，且藉由嚙合NK細胞來誘導對N87細胞之強烈殺傷。

實例11-替代性變異體亦可指導正確LC/HC配對

靜電操縱可與其他操縱技術組合。舉例而言，探究用一對半胱胺酸殘基置換VH/VL界面中之一對帶電荷殘基。該對半胱胺酸殘基緊密鄰近(4~5.6 Å)以形成二硫鍵，因此鎖定正確配對之LC/HC。藉由短暫轉染哺乳動物2936E細胞進行基於變異體2B05之電荷配對及Cys-Cys配對的七種不同組合(表4)。藉由SDS-PAGE凝膠分離上清液。儘管內部對照C11顯示介於148 KDa與250 KDa之間的四個不同亮帶，但變異體2C04及2C06主要產生全長IgG1；在各別Fab臂中之Q105C-A43C及G44C-G100C處具有不同二硫鍵之變異體2D04僅裝配成全長IgG1抗體，從而暗示電荷配對殘基及半胱胺酸配對殘基之組合可合作起作用以製備正確配對且折疊之異二聚抗體。

表4：藉由在可變區中組合電荷配對殘基及半胱胺酸配對殘基製備之變異體。可變區(VH或VL)中之殘基係根據Kabat編號系統來編號，而恆定區(CH1或CL)中之殘基係根據Eu編號系統來編號。將Fn3標籤插入在抗EGFr Ab2 HC之N末端處且使Fn3-Flag-His6標籤同框融合於抗EGFr Ab2 LC之C末端。

	抗Her2 Ab1 HC (K392D + K409D)		**抗Her2 Ab1 LC**		**抗EGFr Ab2 HC (E356K + D399K)**		**抗EGFr Ab2 LC**	
變異體	VH1	C_H1	VL1	CL	VH2	C_H1	VL2	CL
2C04	Q39C + Q105K	K147D	Q38C + A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
2C05	Q39K+ Q105C	K147D	Q38D + A43C	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
2C06	Q39K + Q105K	K147D	Q38D + A43D	T180K	G44C + Q105D	K147K	G100C + A43K	S131D

2D01	Q39K + Q105K	K147D	Q38D + A43D	T180K	G44D + Q105C	K147K	G100K + A43C	S131D
2D02	Q39C + Q105K	K147D	Q38C + A43D	T180K	G44C + Q105D	K147K	G100C + A43K	S131D
2D03	Q39C + Q105K	K147D	Q38C + A43D	T180K	G44D + Q105C	K147K	G100K + A43C	S131D
2D04	Q39K + Q105C	K147D	Q38D + A43C	T180K	G44C + Q105D	K147K	G100C + A43K	S131D

亦測試用一對大/小殘基置換VH/VL界面中之一對帶電荷殘基[Zamyatnin AA (1972) Prog. Biophos. Mol. Biol. 24:107-123；Chothia C (1975) J. Mol. Biol. 105:1-14]。大/小殘基對可施加鈕入孔效應，從而在靜電操縱機制之組合中引導正確LC/HC配對。大殘基，例如色胺酸(W)具有體積227.8 Å3及可及表面積255 Å2；酪胺酸(Y)具有體積193.6 Å3及可及表面積230 Å2。小殘基丙胺酸(A)僅具有體積88.6 Å3及可及表面積115 Å2，而絲胺酸(S)類似地具有體積89 Å3及可及表面積115 Å2。製備且藉由西方墨點術測試基於異二聚抗體變異體2B05之一系列64個變異體(表5)。在藉由SDS-PAGE凝膠分離之後，變異體3A01、3A02、3A03、3A04、3A05、3A06、3B01、3B02、3B03、3B04、8A03及8A04僅顯示單一亮帶，從而指示四個不同鏈可裝配成全長異二聚抗體。在藉由SDS-PAGE凝膠分離之後，其他變異體具有多個亮帶，表明此等LC在與其同源HC配對方面可具有一些問題。

表5. 藉由在可變區中組合電荷配對殘基及大/小配對殘基製備之變異體。此處大殘基表示色胺酸(W)或酪胺酸(Y)，而小殘基表示丙胺酸(A)或絲胺酸(S)。可變區(VH或VL)中之殘基係根據Kabat編號系統來編號，而恆定區(CH1或CL)中之殘基係根據Eu編號系統來編號。將Fn3標籤插入在抗EGFr Ab2 HC之N末端處且使Fn3-Flag-His6標籤同框融合於抗EGFr Ab2 LC之C末端。

	抗Her2 Ab1 HC (K392D + K409D)		抗Her2 Ab1 LC		抗EGFr Ab2 HC (E356K + D399K)		抗EGFr Ab2 LC	
變異體	VH1	CH1	VL1	CL	VH2	CH1	VL2	CL
3A01	Q39A + Q105K	K147D	Q38W + A43D	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3A02	Q39A + Q105K	K147D	Q38Y + A43D	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3A03	Q39S + Q105K	K147D	Q38W + A43D	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3A04	Q39S + Q105K	K147D	Q38Y+ A43D	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3A05	Q39K + Q105A	K147D	Q38D+ A43W	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3A06	Q39K + Q105A	K147D	Q38D+ A43Y	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3B01	Q39K + Q105S	K147D	Q38D+ A43W	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3B02	Q39K + Q105S	K147D	Q38D+ A43Y	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3B03	Q39W + Q105K	K147D	Q38A+ A43D	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3B04	Q39W + Q105K	K147D	Q38S+ A43D	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3B05	Q39Y + Q105K	K147D	Q38A+ A43D	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3B06	Q39Y + Q105K	K147D	Q38S+ A43D	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3C01	Q39K + Q105W	K147D	Q38D+ A43S	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3C02	Q39K + Q105Y	K147D	Q38D+ A43S	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
3C03	Q39A + Q105K	K147D	Q38W + A43D	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
3C04	Q39A + Q105K	K147D	Q38Y + A43D	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
3C05	Q39S + Q105K	K147D	Q38W + A43D	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
3C06	Q39S + Q105K	K147D	Q38Y+ A43D	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
3D01	Q39K + Q105A	K147D	Q38D+ A43W	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
3D02	Q39K + Q105A	K147D	Q38D+ A43Y	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
3D03	Q39K + Q105S	K147D	Q38D+ A43W	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
3D04	Q39K + Q105S	K147D	Q38D+ A43Y	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
3D05	Q39W + Q105K	K147D	Q38A+ A43D	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
3D06	Q39W + Q105K	K147D	Q38S+ A43D	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
4A01	Q39Y + Q105K	K147D	Q38A+ A43D	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
4A02	Q39Y + Q105K	K147D	Q38S+ A43D	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
4A03	Q39K + Q105W	K147D	Q38D+ A43S	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D

4A04	Q39K + Q105Y	K147D	Q38D+ A43S	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
7A01	Q39A+ Q105K	K147D	Q38W+ A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7A02	Q39A+ Q105K	K147D	Q38Y+ A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7A03	Q39S+ Q105K	K147D	Q38W+ A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7A04	Q39S+ Q105K	K147D	Q38Y+ A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7A05	Q39K+ Q105A	K147D	Q38D+ A43W	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7A06	Q39K+ Q105A	K147D	Q38D+ A43Y	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7B01	Q39K+ Q105S	K147D	Q38D+ A43W	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7B02	Q39K+ Q105S	K147D	Q38D+ A43Y	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7B03	Q39W+ Q105K	K147D	Q38A+ A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7B04	Q39W+ Q105K	K147D	Q38S+ A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7B05	Q39Y+ Q105K	K147D	Q38A+ A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7B06	Q39Y+ Q105K	K147D	Q38S+ A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7C01	Q39K+ Q105W	K147D	Q38D+ A43S	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7C02	Q39K+ Q105Y	K147D	Q38D+ A43S	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
7C03	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44A + Q105D	K147K	G100W + A43K	S131D
7C04	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44A + Q105D	K147K	G100Y + A43K	S131D
7C05	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44S + Q105D	K147K	G100W + A43K	S131D
7C06	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44S + Q105D	K147K	G100Y + A43K	S131D
7D01	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44D + Q105A	K147K	G100K + A43W	S131D
7D02	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44D + Q105A	K147K	G100K + A43Y	S131D
7D03	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44D + Q105S	K147K	G100K + A43W	S131D
7D04	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44D + Q105S	K147K	G100K + A43Y	S131D
7D05	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44W+ Q105D	K147K	G100A + A43K	S131D
7D06	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44W+ Q105D	K147K	G100S + A43K	S131D
8A01	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44Y+ Q105D	K147K	G100A + A43K	S131D
8A02	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44Y+ Q105D	K147K	G100S + A43K	S131D
8A03	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44D + Q105W	K147K	G100K + A43S	S131D
8A04	Q39K + Q105K	K147D	Q38D+ A43D	T180K	G44D + Q105Y	K147K	G100K + A43S	S131D
8A05	Q39A+	K147D	Q38W+	T180K	G44W +	K147K	G100A +	S131D

	Q105K		A43D		Q105D		A43K	
8A06	Q39A+ Q105K	K147D	Q38W+ A43D	T180K	G44Y + Q105D	K147K	G100A + A43K	S131D
8B01	Q39A+ Q105K	K147D	Q38W+ A43D	T180K	G44W + Q105D	K147K	G100S + A43K	S131D
8B02	Q39A+ Q105K	K147D	Q38W+ A43D	T180K	G44Y + Q105D	K147K	G100S + A43K	S131D
8B03	Q39W+ Q105K	K147D	Q38A+ A43D	T180K	G44A + Q105D	K147K	G100W + A43K	S131D
8B04	Q39W+ Q105K	K147D	Q38A+ A43D	T180K	G44A + Q105D	K147K	G100Y + A43K	S131D
8B05	Q39Y+ Q105K	K147D	Q38A+ A43D	T180K	G44A + Q105D	K147K	G100W + A43K	S131D
8B06	Q39Y+ Q105K	K147D	Q38A+ A43D	T180K	G44A + Q105D	K147K	G100Y + A43K	S131D

實例12-在不存在標籤下使異二聚抗體最佳化

移除抗EGFr x Her2變異體2B05及5D03之標籤且藉由用四種DNA轉染哺乳動物2936E細胞以製備全長抗體或僅用兩種DNA轉染哺乳動物2936E細胞以評估錯配LC/HC配對之耐受性加以測試。當存在所有四個不同鏈時，兩種變異體均產生全長抗體，伴有大量半抗體。用編碼匹配LC1+HC1或LC2+HC2之兩種質體進行轉染亦產生全長同二聚體抗體，伴有大量半抗體。當LC2與其非同源HC1錯誤配對(LC2+HC1)時，存在少量產物顯示於凝膠中，而當LC1與其非同源HC2錯誤配對(LC1+HC2)時，不形成產物。表現測試暗示抗EGFr抗體之LC2耐受抗Her2抗體之HC1，而抗Her2抗體之LC1不耐受抗EGFr抗體之HC2。為使靜電操縱效應最大，藉由在相同空間位置處，但以相反極性引入電荷配對殘基來研究一系列新穎變異體(表6)。LC/HC界面互為相反的，當相同極性殘基靠近時為排斥的，或當相反極性殘基鄰近時為吸引的。

在轉錄且轉譯四個不同鏈之後，變異體V15及V20主要表現為完整抗體。在匹配HC/LC(亦即LC1+HC1或LC2+HC2)存在下，產生半抗體及同二聚體全長抗體。當錯配HC/LC(例如LC2+HC1)經共表現時，未觀測到產物，表明LC2不可與HC1相容。然而，LC1由HC2耐受以形成半抗體或同二聚體抗體，從而暗示V15及V20之LC1可與非同源HC2配

對且得以裝配，接著分泌。相反，在轉錄且轉譯四個不同鏈之後，變異體V21、V23及V25主要表現爲完整抗體。在兩個匹配鏈(亦即LC1+HC1或LC2+HC2)存在下，產生完整IgG抗體，從而指示LC可與其同源HC相容。在錯配LC2+HC1或LC1+HC2存在下，不形成產物，表明LC不耐受非同源HC。變異體V22不如同V21、V23及V25一般有效，因爲當迫使錯配LC與非同源HC配對時觀測到次要產物。質譜分析顯示變異體V12、V21、V23及V25存在四個不同鏈(LC1+HC1+LC2+HC2)及正確LC/HC配對(LC1+HC1及LC2+HC2)。

表6. 呈異二聚IgG1形式之抗Her2 Ab1及抗EGFr Ab2之VH/VL及CH1/CL界面的採用相互排斥/吸引機制之胺基酸變化。抗Her2 Ab1之HC在CH2域中具有S298T+A330M+K334V且在CH3域中具有K392D+K409D；抗EGFr Ab2之HC在下部鉸鏈/CH2域中具有L234Y+K209Y+Y296W且在CH3域中具有E356K+D399K。可變區(VH或VL)中之殘基係根據Kabat編號系統來編號，而恆定區(CH1或CL)中之殘基係根據Eu編號系統來編號。

	抗Her2 Ab1 HC (K392D + K409D)		**抗Her2 Ab1 LC**		**抗EGFr Ab2 HC (E356K + D399K)**		**抗EGFr Ab2 LC**	
變異體	VH1	CH1	VL1	CL	VH2	CH1	VL2	CL
V01	Q39K+Q105K	K147D	Q38D + A43D	T180K	G44D + Q105D	K147K	G100K + A43K	S131D
V02 *	Q39K+Q105C	K147D	Q38D + A43C	T180K	G44C + Q105D	K147K	G100C + A43K	S131D
V03	Q39K+Q105K	P171D	Q38D + A43D	S162K	G44D + Q105D	A141K	G100K + A43K	F116D
V04	Q39K+Q105K	P171D	Q38D + A43D	S162K	Q105D	A141K	A43K	F116D
V05	Q39K+Q105K	P171D	Q38D + A43D	S162K	Q39D + Q105D	A141K	Q38K + A43K	F116D
V06	Q39K+Q105K	K147D	Q38D + A43D	T180K	G44D + Q105D		G100K + A43K	
V07	Q39K	P171D	Q38D	S162K	Q39D	A141K	Q38K	F116D
V08	Q39K	A141D	Q38D	F116K	Q39D	P171K	Q38K	S162D
V09	Q39K	A141D	Q38D	F116K	Q39D	A141K	Q38K	F116D
V10	Q39K	P171D	Q38D	S162K	Q39D	P171K	Q38K	S162D
V11	Q105K	A141D	A43D	F116K	Q105D	A141K	A43K	F116D

V12	Q105K	P171D	A43D	S162K	Q105D	P171K	A43K	S162D
V13	Q105K	A141D	A43D	F116K	Q105D	P171K	A43K	S162D
V14	Q105K	P171D	A43D	S162K	Q105D	A141K	A43K	F116D
V15	Q39K	S183D	Q38D	S176K	Q39D	S183K	Q38K	S176D
V16	Q105K	S183D	A43D	S176K	Q105D	S183K	A43K	S176D
V17	Q39K	S183D	Q38D	S176K	Q105D	S183K	A43K	S176D
V18	Q105K	S183D	A43D	S176K	Q39D	S183K	Q38K	S176D
V19	Q39K	A141D + S183K	Q38D	F116K + S176D	Q39D	A141K + S183D	Q38K	F116D + S176K
V20	Q39K	A141D + P171K	Q38D	F116K + S162D	Q39D	A141K + P171D	Q38K	F116D + S162K
V21	Q39K+ Q105K	K147D	Q38D + A43D	T180K	Q39D + Q105D	K147K	Q38K + A43K	T180D
V22	Q39K+ Q105K	K147D	Q38D + A43D	T180K	Q39D + Q105D	K147K	Q38K + A43K	S131D
V23	Q39K+ Q105K	S183D	Q38D + A43D	S176K	Q39D + Q105D	S183K	Q38K + A43K	S176D
V24	Q39K+ Q105K	P171D	Q38D + A43D	S162K	Q39D + Q105D	P171K	Q38K + A43K	S162D
V25	G44K + Q105K	S183D	Q100D + A43D	S176K	G44D + Q105D	S183K	G100K + A43K	S176D

實例13-最佳化EGFR/Her2異二聚抗體變異體顯示熱穩定性

藉由示差掃描熱析法(DSC)評估抗EGFr IgG2、抗Her2 IgG1、抗Her2去海藻糖基化IgG1及四種抗EGFr×Her2異二聚抗體變異體在相同溶劑條件下的溫度誘導展開。各蛋白質之熱分析圖由2或3個變遷組成。野生型抗Her2抗體顯示Fab/CH3之Tm在82℃下且CH2之Tm在72℃下；抗Her2抗體之無海藻糖基化形式不改變各別域之Tm但使焓略微降低。抗EGFr抗體具有類似溫度誘導展開概況。所有四種抗EGFr×Her2異二聚抗體變異體皆具有略微降低之在68℃下之CH2/CH3 Tm，因為其皆在CH2域中具有ADCC增強取代且在CH3域中具有異二聚化取代。就Fab域之Tm而言，變異體V12及V24具有自82℃至72℃之最大顯著降低；變異體V25具有在72℃及78℃下之兩個各別峰，而變異體V23具有在78℃下之單一峰。總之，四種異二聚抗體變異體顯示良好熱穩定性。資料表明所選用於在Fab區中引入電荷配對殘基之位置在某種程度上影響完整異二聚抗體之穩定性，其中各別域之Tm高於68℃。

實例14-靶向同一抗原之兩個不同抗原決定基之異二聚抗體

為顯示製備異二聚抗體之相同方法可應用於不同抗體，自兩種不

同抗Her2抗體產生異二聚IgG。一種抗體結合Her2之域IV而另一結合Her2之域II。藉由用四種DNA轉染以製備全長抗體或僅用兩種DNA轉染以評估錯配LC/HC配對之耐受性來測試以相反方式引入VH/VL中之兩對電荷殘基及CH1/CL中之一對電荷殘基的變異體V23(表6)。類似於抗EGFr x Her異二聚抗體變異體V23，在轉譯且裝配四個不同鏈之後，抗Her2 x Her2異二聚抗體V23主要表現為完整抗體。在兩個匹配鏈(亦即LC1+HC1或LC2+HC2)存在下，產生半抗體及同二聚體抗體，從而指示LC可與其同源HC相容。在錯配鏈LC2+HC1或LC1+HC2存在下，完全不形成產物，表明LC不耐受其非同源HC。

實例15-帶電荷殘基之不同組合影響異二聚抗體表現及LC/HC配對

為研究電荷殘基之不同組合是否產生不同表現量或影響LC/HC配對，藉由在相同位置處以不同組合引入電荷配對殘基(表7)來製備若干抗Her2 x Her2異二聚抗體變異體。儘管V23B如同V23A一般具有正確LC/HC配對，但完整抗體或半抗體形式之表現量下降。然而，V23C及V23D耐受LC/HC錯配。總之，此組資料表明靜電操縱不為指導正確LC/HC配對之唯一因素；諸如形狀互補性之其他機制可在過程中起作用。

表7. 在VH/VL及CH1/CL界面之相同位置處之不同電荷配對組合的比較。可變區(VH或VL)中之殘基係根據Kabat編號系統來編號，而恆定區(CH1或CL)中之殘基係根據Eu編號系統來編號。抗Her2 Ab1之HC在CH2域中具有ADCC增強取代S298T+A330M+K334V且在CH3域中具有異二聚化變化K392D+K409D；抗Her2 Ab2之HC在下部鉸鏈/CH2域中具有ADCC增強取代L234Y+K209Y+Y296W且在CH3域中具有異二聚化變化E356K+D399K。

	抗Her2 Ab1 HC (K392D + K409D)		抗Her2 Ab1 LC		抗Her2 Ab2 HC (E356K + D399K)		抗Her2 Ab2 LC	
變異體	VH1	CH1	VL1	CL	VH2	CH1	VL2	CL
V23A	Q39K+ Q105K	S183D	Q38D + A43D	S176K	Q39D + Q105D	S183K	Q38K + A43K	S176D
V23B	Q39D+ Q105K	S183K	Q38K + A43D	S176D	Q39K + Q105D	S183D	Q38D + A43K	S176K
V23C	Q39K+ Q105D	S183K	Q38D + A43K	S176D	Q39D + Q105K	S183D	Q38K + A43D	S176K
V23D	Q39D+ Q105D	S183K	Q38K + A43K	S176D	Q39K + Q105K	S183D	Q38D + A43D	S176K

實例16-穩定性及黏度研究

對包含本文所述之代表性異二聚抗體之組合物進行穩定性研究，且將抗體組合物之特徵與類似DVD(雙可變域)抗體組合物進行比較。抗體樣品於A52Su調配物(亦即10 mM乙酸鹽、9%蔗糖，pH 5.2)中儲存在4℃或40℃下兩週或兩個月之時期。使用例如SE-HPLC、CEX-HPLC、HIAC(次可見粒子)及目視檢查將抗體聚集量測為穩定性之替代物。結果以單體峰之百分比形式(亦即100%將指示未觀測到聚集)概述於表8中。

表8.

抗體類型	抗體名稱	在4℃下持續兩週之單體峰%	在40℃下持續兩週之單體峰%
異Ig	Ab-5-6.147v1	99.2	95.3
異Ig	Ab-23-6.147v1	99.6	98.0
異Ig	Ab-23-6.147v2	99.7	98.7
異Ig	Ab-5-6.37.5v1	99.6	96.1
異Ig	Ab-23-6.37.5v1	99.6	98.7
DVD	Ab-23-6.147	N/A	62
DVD	Ab-5-6.147	N/A	15
DVD	Ab-23-6.37.5	N/A	89
DVD	Ab-20C3-6.147	N/A	53

如藉由表8中所述之結果所顯示，相較於當儲存在類似條件下時A52Su中11%-85%之DVD抗體形成聚集體的測試DVD抗體，當在40℃下儲存兩週時，A52Su中小於5%之異Ig抗體形成聚集體。當在4℃下儲存兩週時，小於1%之測試異Ig抗體形成聚集體。

進行單獨研究以研究A52Su調配物中之DVD及異二聚抗體之黏度與不同濃度(70 mg/mL或150 mg/mL)之間的關係。使用具有錐/板幾何

尺寸之流變儀(RV III+型，Brookfield Engineering Labs公司，Middleboro, Mass.)量測黏度。在量測期間用水浴維持樣品溫度在25℃下。主軸速度在15至125 rpm之範圍內，增量為10 rpm。用Rheocalc™軟體第2.7版進行資料收集。於A52Su調配物中測試之各種抗體之黏度量測結果以下提供於表9中。

表9.

抗體類型	抗體名稱	在70 mg/mL下之黏度(cP)	在150 mg/mL下之黏度(cP)
異Ig	Ab-5-6.147v1	4.5	35.7
異Ig	Ab-23-6.147v1	3.5	15.6
異Ig	Ab-23-6.147v2	4.2	16.8
異Ig	Ab-5-6.37.5v1	3.1	51.5
異Ig	Ab-23-6.37.5v1	2.1	13.7
DVD	Ab-23-6.147	4.3	94
DVD	Ab-5-6.147	4.4	65
DVD	Ab-23-6.37.5	4.6	43
DVD	Ab-20C3-6.147	4.6	15

如表9中所示，包含測試異二聚抗體或DVD抗體(70 mg/mL)之一的各組合物之黏度小於6 cP。當異二聚抗體在濃度150 mg/mL下存在於組合物中時，三種組合物之黏度小於17 cP。與異二聚抗體調配物不同，當DVD抗體在濃度150 mg/mL下存在時，僅一種DVD抗體調配物之黏度小於16 cP。

上述實例顯示本文所述之異二聚抗體比測試之雙特異性DVD抗體更穩定(亦即當在4℃下儲存兩週時，組合物中小於1%之抗體形成聚集體)。包含此等異二聚抗體之調配物亦滿足較佳黏度規範，且因此特別適於大規模製造。

實例17-靶向硬化蛋白及DKK1之異二聚抗體促進靈長類動物中之骨合成代謝

為顯示靶向硬化蛋白及DKK1之異二聚抗體促進靈長類動物中之骨合成代謝，在40隻未處理4至6歲雌性食蟹獼猴中進行9週PK/PD研究。將動物分成三組，各組投與不同異二聚抗體。

每兩週向各組動物投與總計三次劑量(第1天及第15天投與IV劑量

25 mg/kg，隨後在第43天投與一次25 mg/kg皮下劑量)。歷經研究之過程數次抽取血液。短暫離心、等分且冷凍血清以供隨後分析。對照包括未治療動物及用單一抗硬化蛋白抗體(Ab-5)或針對硬化蛋白及DKK1之中和異二聚抗體(形式1)或針對硬化蛋白及DKK1之雙可變域(DVD)抗體(6.147-AbL-Ab23)治療之動物。在基線時使用血清骨形成標記物量測結果(CICP、BSAP及骨鈣蛋白)及體重將所有動物隨機分組。

收集初始40個動物之血清樣品以進行預篩檢骨轉換標記物(BTM)評估。選擇23個動物且基於平衡之生物標記物概況及體重分配至治療組中。在基線(BL)預篩檢時，各組之間在所有BTM濃度方面皆不存在顯著差異(表10)。

表10. 在BL預篩檢時之血清BTM蛋白質濃度

BL預篩檢	TRACP 5b (U/L)	OC (ng/ml)	BAP (U/L)	C1CP (ng/ml)	DKK1 (pg/ml)
	平均值 ±SEM	平均值 ±SEM	平均值 ±SEM	平均值 ±SEM	平均值 ±SEM
所有 n=40	8.3 ± 0.6	24.9 ± 1.4	221.5 ± 13.0	90.5 ± 8.1	907.5 ± 42.3
對照 n=2	7.0 ± 2.6	28.7 ± 12.0	167.1 ± 41.9	83.9 ± 53.0	969.3 ± 456.3
1/Ab-5 n=3	6.9 ± 0.6	23.9 ± 5.6	216.8 ± 64.9	78.6 ± 13.7	1004.8 ± 157.0
2/6.147-AbL-Ab23, n=4	11.1 ± 4.6	21.0 ± 3.3	219.1 ± 30.4	83.2 ± 22.6	949.6 ± 153.4
3/Ab-23-6.37.5.v.1 n=3	8.1 ± 1.8	25.0 ± 2.7	202.8 ± 36.2	73.6 ± 29.8	837.6 ± 55.2
4/Ab-5-6.37.5.v.1 n=4	5.5 ± 0.2	22.6 ± 2.3	179.5 ± 22.8	90.7 ± 20.6	790.9 ± 75.9
5/Ab-5-6.147.v.1 n=3	7.2 ± 1.1	25.6 ± 2.4	264.8 ± 62.4	64.4 ± 9.0	895.5 ± 173.0

絕對血清酒石酸抗性酸性磷酸酶5b(TRACP 5b)資料顯示於表11中。TRACP為一種由骨再吸收破骨細胞以高量表現之酶。已顯示TRACP 5b適用作破骨細胞數目及骨再吸收之標記物。參見Halleen等人, Clin. Lab., 52:499-509, 2006，其揭露內容以全文引用的方式併入本

文中。對相對於給藥前之TRACP 5b變化百分比之分析(表11及圖9)揭示DVD抗體6.147-AbL-Ab23及異二聚抗體Ab-23-6.37.5治療在第5天及第7天導致TRACP 5b顯著降低(相較於Ab-5治療之動物)。

表11. 血清TRACP 5b(自第1天給藥前開始之變化%)

研究之時間點	TRACP 5b(自第1天給藥前開始之變化%)					
	組0 對照 n=2	組1 Ab-5 n=3	組2 Ab-2 n=4	組3 Ab-23-6.37.5 n=3	組4 Ab-5-6.37.5 n=4	組5 Ab-5-6.147 n=3
	平均值 ±SEM	平均值 ±SEM	平均值 ±SEM	平均值±SEM	平均值 ±SEM	平均值 ±SEM
第5天	N/A	-4.2 ± 5.0	-19.1 ± 1.7**	-16.7 ± 1.8*	-5.0 ± 0.7	-11.4 ± 2.2
第7天	N/A	-8.8 ± 2.9	-25.3 ± 4.1*	-25.9 ± 2.2*	-8.4 ± 3.5	-17.5 ± 4.3
第14天	1.2 ± 10.2	-19.5 ± 11.1	-33.6 ± 3.2	-38.0 ± 7.4	-15.8 ± 2.2	-25.5 ± 10.2
第21天	N/A	-29.0 ± 8.3	-39.9 ± 3.1	-39.8 ± 11.4	-24.8 ± 2.6	-24.6 ± 10.3
第28天	6.3 ± 10.0	-24.2 ± 7.7	-33.5 ± 1.9	-32.0 ± 17.1	-27.0 ± 5.1	-26.1 ± 11.9
第36天	N/A	-19.3 ± 4.2	-7.8 ± 3.7	-13.0 ± 15.3	-13.4 ± 5.6	-9.9 ± 5.7
第43天	N/A	-10.1 ± 6.3	-6.9 ± 3.5	-2.9 ± 15.1	-8.1 ± 6.1	-9.9 ± 8.3
第45天	N/A	-20.6 ± 5.6	-20.7 ± 3.1	-15.0 ± 14.4	-3.5 ± 4.8	-18.9 ± 6.1
第50天	N/A	-20.7 ± 2.3	-37.9 ± 2.7	-32.4 ± 12.0	-4.3 ± 6.7	-27.1 ± 4.0
第57天	8.0 ± 20.0	-24.1 ± 1.3	-30.0 ± 5.1	-36.7 ± 9.4	-9.9 ± 5.4	-23.7 ± 6.5
第64天	-5.2 ± 13.4	-25.6 ± 3.1	-18.2 ± 8.1	-22.4 ± 9.4	-6.7 ± 5.8	-24.0 ± 6.9

相較於組1，* $p<0.05$，** $p<0.01$

相較於Ab-5治療之動物，在研究之第36、43及57天，異二聚抗體Ab-5-6.147之血清骨鈣蛋白(OC)濃度(表12及圖10)顯著較高。對相對於給藥前之血清OC變化之分析(表10及圖9)揭示異二聚抗體Ab-23-6.37.5治療導致此分析物持續自第21天至第45天之測試時間點顯著升高。相較於Ab-5-6.147治療之動物，用異二聚抗體Ab-5-6.147治療導致自第21天至第43天及在第50天及第57天OC顯著增加。

表12. 血清OC(自第1天給藥前開始之變化%)

研究之時間點	OC(自第1天給藥前開始之變化%)					
	組0 對照 n=2	組1 Ab-5 n=3	組2 Ab-2 n=4	組3 Ab-14-6.37.5 n=3	組4 Ab-5-6.37.5 n=4	組5 Ab-5-6.147 n=3
	平均值 ±SEM	平均值 ±SEM	平均值 ±SEM	平均值 ±SEM	平均值 ±SEM	平均值 ±SEM
第5天	N/A	3.1 ± 0.5	-9.2 ± 11.8	5.4 ± 27.3	4.0 ± 21.5	28.6 ± 17.5
第7天	N/A	59.9 ± 36.1	71.8 ± 27.6	24.2 ± 32.1	26.7 ± 24.5	38.7 ± 14.2
第14天	10.2 ± 11.8	83.0 ± 21.4	57.5 ± 5.3	146.0 ± 6.5	143.7 ± 22	156.2 ± 35.4
第21天	N/A	76.8 ± 8.0	127 ± 21.8	152.1 ± 21.8	178.5 ± 25.6*	193.4 ± 23.7*
第28天	31.2 ± 3.4	78.9 ± 25.2	49.5 ± 4.5	99.3 ± 34.7	195.9 ± 27.0*	184.5 ± 20.2*
第36天	N/A	46.3 ± 37.4	9.3 ± 7.8	39.2 ± 21.2	175.5 ± 19.2**	158.2 ± 19.3*
第43天	N/A	-5.0 ± 7.0	-7.9 ± 8.1	23.0 ± 16.3	83.7 ± 10.4***	91.9 ± 10.9***
第45天	N/A	-7.2 ± 20.5	-18.0 ± 6.3	-11.9 ± 11.7	48.2 ± 14.1*	44.8 ± 2.2
第50天	N/A	10.1 ± 13.4	43.9 ± 11.9	57.1 ± 20.3	62.6 ± 25.7	124.1 ± 6.8**
第57天	39.9 ± 31.8	23.3 ± 20.8	12.0 ± 3.4	34.4 ± 26.6	72.4 ± 20.2	136.7 ± 21.1**
第64天	46.2 ± 49.2	3.6 ± 20.0	-19.4 ± 12.0	2.6 ± 16.8	66.9 ± 8.9	65.1 ± 16.7

相較於組1，* $p<0.05$，** $p<0.01$，*** $p<0.001$

分析血清骨鹼性磷酸酶(BAP)超過給藥前之變化百分比，其結果顯示於表13及圖11中。結果指示在第5天，異二聚抗體Ab-23-6.37.5治療之動物中之BAP顯著升高(相對於Ab-5組)。

表13. 血清BAP(自第1天給藥前開始之變化%)

研究之時間點	BAP (自第1天給藥前開始之變化%)					
	組0 對照 n=2	組1 Ab-5 n=3	組2 Ab-2 n=4	組3 Ab-23-6.37.5 n=3	組4 Ab-5-6.37.5 n=4	組5 Ab-5-6.147 n=3
	平均值 ±SEM	平均值 ±SEM	平均值 ±SEM	平均值±SEM	平均值 ±SEM	平均值±SEM
第5天	N/A	3.5 ± 0.8	35.2 ± 6.4	47.9 ± 17.2*	15.1 ± 4.6	38.5 ± 10.3
第7天	N/A	26.6 ± 9.6	60.7 ± 9.3	67.7 ± 16.7	24.2 ± 6.3	60.6 ± 11.0
第14天	-15.9 ± 2.1***	125.2 ± 23.1	89.4 ± 8.0	153.6 ± 20.6	77.3 ± 9.8	129.8 ± 11.8
第21天	N/A	118.7 ± 24.4	123.7 ± 20.2	158.1 ± 21.3	110.2 ± 16.5	165.7 ± 8.1
第28天	-14.3 ± 4.0*	109.2 ± 15.9	82.2 ± 14.5	133.4 ± 26.0	119.8 ± 27.2	136.8 ± 13.4
第36天	N/A	72.5 ± 30.9	27.5 ± 10.1	34.6 ± 17.8	83.7 ± 34.5	80.0 ± 23.9
第43天	N/A	10.4 ± 19.7	-8.6 ± 8.0	6.6 ± 9.7	41.6 ± 24.7	25.5 ± 10.7

第45天	N/A	-7.6 ± 17.1	-9.9 ± 7.4	3.7 ± 10.5	43.7 ± 25.9	28.4 ± 15.1
第50天	N/A	48.7 ± 14.7	90.4 ± 19.1	121.3 ± 21.6	80.9 ± 20.5	110.5 ± 7.2
第57天	-11.0 ± 20.2	67.3 ± 14.1	59.5 ± 14.3	108.0 ± 35.9	103.9 ± 21.6	110.7 ± 13.5
第64天	-2.3 ± 28.5	46.4 ± 16.3	7.5 ± 7.9	35.2 ± 26.3	66.9 ± 22.5	62.3 ± 11.8

相較於組1，* $p<0.05$，*** $p<0.001$

血清C1CP資料呈現於表14中。相較於Ab-5治療之動物，在第14天，DVD抗體6.147-AbL-Ab23治療組具有超過給藥前之顯著較低C1CP變化百分比(表14及圖12)。

表14. 血清C1CP(自第1天給藥前開始之變化%)

研究之時間點	C1CP(自第1天給藥前開始之變化%)					
	組0 對照 n=2	**組1 Ab-5 n=3**	**組2 Ab-2 n=4**	**組3 Ab-23-6.37.5 n=3**	**組4 Ab-5-6.37.5 n=4**	**組5 Ab-5-6.147 n=3**
	平均值 ±SEM	**平均值 ±SEM**	**平均值 ±SEM**	**平均值±SEM**	**平均值±SEM**	**平均值 ±SEM**
第5天	N/A	140.9 ± 31.9	197.1 ± 67.6	246.0 ± 119.2	59.6 ± 42.9	224.6 ± 67.5
第7天	N/A	392.0 ± 87.6	439.3 ± 168.8	569.2 ± 263.6	218.2 ± 64.2	317.5 ± 72.1
第14天	49.8 ± 7.2*	386.9 ± 80.9	96.0 ± 27.4*	346.3 ± 70.7	377.1 ± 103.8	332.3 ± 26.8
第21天	N/A	298.7 ± 33	515.2 ± 129.3	609.6 ± 135.7	450.3 ± 72.5	397.5 ± 11.2
第28天	80.9 ± 15.7	276.8 ± 76.7	103.4 ± 21.7	267.2 ± 130.4	519.3 ± 122.3	433.0 ± 71.1
第36天	N/A	46.6 ± 74.4	-49.0 ± 7.0	-44.9 ± 8.9	208.6 ± 64.5	54.4 ± 32.6
第43天	N/A	-55.5 ± 5.1	-60.1 ± 8.8	-54.3 ± 11.3	5.0 ± 38.0	-29.0 ± 8.1
第45天	N/A	31.7 ± 28.8	63.0 ± 18.1	52.8 ± 29.0	50.5 ± 35.3	105.5 ± 34.7
第50天	N/A	103.7 ± 33.6	248.9 ± 98.5	357.1 ± 153.6	130.4 ± 68.1	219.1 ± 24.3
第57天	38.2 ± 42.5	36.4 ± 19.5	-30.9 ± 12.4	7.5 ± 64.3	49.3 ± 45.1	47.4 ± 1.4
第64天	48.4 ± 62.8	-24.8 ± 25.4	-59.4 ± 4.2	-60.7 ± 9.9	-20.3 ± 10.6	-28.1 ± 12.5

相較於組1，* $p<0.05$

在對照與Ab-5治療之動物之間，跨越量測之所有時間點，絕對血清DKK1濃度以及相對於給藥前之變化百分比(表17)不顯著不同。

表17. 未處理雌性食蟹獼猴持續研究之持續時間的DKK1於血清中之濃度及自第1天給藥前開始之變化%

研究之時間點	DKK1(pg/ml)		研究之時間點	DKK1(自第1天給藥前開始之變化%)	
	組0 對照 n=2	組1 Ab-5 n=3		組0 對照 n=2	組1 Ab-5 n=3
	平均值 ±SEM	平均值 ±SEM		平均值 ±SEM	平均值 ±SEM
第天1給藥前	1263.7 ± 366.9	1532.5 ± 140.8			
第5天	N/A	1088.9 ± 117.4	第5天	N/A	-29.2 ± 1.8
第7天	N/A	1080.5 ± 136.9	第7天	N/A	-29.9 ± 2.5
第14天	1077.5 ± 452.9	1239.8 ± 142.5	第14天	0.8 ± 25.5	-19.3 ± 5.1
第21天	N/A	1288.1 ± 47.1	第21天	N/A	-14.8 ± 6.8
第28天	1199.3 ± 430.0	1438.3 ± 23.3	第28天	17.8 ± 37.6	-4.8 ± 7.3
第36天	N/A	1769.4 ± 32.3	第36天	N/A	17.6 ± 11.9
第43天	N/A	1895.6 ± 52.8	第43天	N/A	25.8 ± 12.5
第45天	N/A	1607.6 ± 99.8	第45天	N/A	7.7 ± 15.5
第50天	N/A	1523.5 ± 95.9	第50天	N/A	1.4 ± 13.1
第57天	1370.6 ± 427.0	1607.2 ± 91	第57天	39.5 ± 51.1	7.6 ± 15.6
第64天	1353.2 ± 440.0	1826.1 ± 146.9	第64天	36.4 ± 48.1	21.9 ± 18.4

總之，相較於Ab-5治療，DVD抗體6.147-AbL-Ab23治療在第5天($p<0.01$)及第7天($p<0.05$)短暫降低血清TRACP 5b(就相對於給藥前之變化百分比而言)。相較於Ab-5治療之動物，在第14天，DVD抗體6.147-AbL-Ab23治療組中之C1CP(就相對於給藥前之變化百分比而言)顯著降低($p<0.05$)。血清OC及BAP濃度不受DVD抗體6.147-AbL-Ab23治療影響。

相較於單獨Ab-5治療，在第5天及第7天，異二聚抗體Ab-23-6.37.5治療亦顯著降低血清TRACP 5b(就自給藥前開始之變化百分比而言)($p<0.05$)。相較於Ab-5治療組，在第5天，用異二聚抗體Ab-23-6.37.5治療之動物顯示BAP顯著較高(就相對於給藥前之變化百分比而言)($p<0.05$)，但未見OC及C1CP含量有顯著差異。

相較於單獨Ab-5治療，用異二聚抗體Ab-5-6.37.5治療在評估之任何時間點皆對血清TRAP5b、BAP或CICP無影響。然而，相較於Ab-5治療組，在第21天($p<0.05$)、第28天($p<0.05$)、第36天($p<0.01$)、第43天($p<0.001$)及第45天($p<0.05$)，異二聚抗體Ab-5-6.37.5治療組中之OC(就相對於給藥前之變化百分比而言)顯著增加。

類似地，相對於單獨Ab-5治療，TRAPCP 5b、BAP及C1CP濃度不受異二聚抗體Ab-5-6.147治療影響。相較於Ab-5治療組，在第36天($p<0.05$)、第43天($p<0.05$)及第57天($p<0.01$)，此組中之血清OC濃度顯著升高。相較於Ab-5治療組，在第21天、第28天、第36天(分別$p<0.05$)、第43天($p<0.001$)、第50天及第57天(分別$p<0.01$)，Ab-5-6.147治療組中之就相對於給藥前之變化百分比而言的血清OC顯著增加。

在對照與Ab-5治療之動物之間，跨越評估之所有時間點，血清DKK1濃度不顯著不同。

此實例中提供之此等資料顯示針對DKK1及硬化蛋白之異二聚抗體具有與親本Ab Ab-5類似之IgG樣藥物動力學性質，且在於食蟹獼猴中投藥之後導致特定骨形成標記物出眾增加。在非人類靈長類動物及齧齒動物中觀測之雙重DKK1及硬化蛋白抑制效應強調異二聚抗體治療骨病症之治療功效。

實例18-異二聚抗體之藥物動力學性質

在研究中表徵三種異二聚抗體(Ab23-6.37.5 v.1、Ab-5-6.37.5 v.1及Ab-5-6.147 v.1)之藥物動力學(PK)概況。

將食蟹獼猴分成藉由在第1天及第15天靜脈內投藥及在第43天皮下投藥來接受25 mg/kg Ab-5(組1)、34.4 mg/kg DVD抗體6.147-AbL-Ab23(組2)、或25 mg/kg Ab-23-6.37.5.v.1(組3)、Ab-5-6.37.5.v.1(組4)或Ab-5-6.147.v.1(組5)之各者的5個治療組。在第1研究日開始收集662個血清樣品(歷經64天)以供PK分析，其中亦在第15

天及第43天獲取樣品。

使用如上在實例7中所述之四種不同酶聯免疫吸附分析(ELISA)(硬化蛋白/DKK1分析；硬化蛋白/Fc分析；DKK1/硬化蛋白分析；及FC/FC橋式ELISA分析)分析血清樣品。使用利用一對針對Ab-5之抗特應抗體進行之ELISA來分析來自組1之在完整Ab-5濃度之情況下的血清樣品。使用以下兩種不同ELISA分析來自組2之血清樣品：一種用以量測完整抗DKK1 Mab且一種用以量測總Mab濃度。使用以下三種不同ELISA分析來自組3、4及5之血清樣品：一種用以量測完整抗DKK1 Mab，一種用以量測完整抗硬化蛋白(SOST)Mab，且一種用以量測總Mab濃度。藉由ELISA測定完整(DKK1)血清Mab濃度，其中重組人類DKK1及抗人類Fc分別用作捕捉試劑及偵測試劑。藉由ELISA測定完整(SOST)血清Mab濃度，其中重組人類SOST及抗人類Fc用作捕捉試劑及偵測試劑。另外，藉由ELISA測定總血清Mab濃度，其中一對抗人類IgG Fc抗體用作捕捉試劑及偵測試劑。

三種異二聚抗體及陽性對照之PK概況描述於圖13中，且由第一IV劑量資料獲得之PK參數以下概述於表18中。

表18. Ab23-6.37.5 v.1、Ab-5-6.37.5 v.1及Ab-5-6.147 v.1異Ig候選物在食蟹獼猴中之由第1 IV劑量間隔獲得之PK參數估計值。

化合物 (完整)	劑量 (mg/kg)	$T_{1/2}$ (天)	C0_μM (μM)	AUC0_無窮 (天*μM)	CL_預測 (mL/h/kg)	F (%)
Ab-5	25	4.6	4.24	18.0	0.394	63
DVD 6.147-AbL-Ab23	34.4	1.5	3.68	8.3	0.869	78
Ab-23-6.37.5.v.1	25	3.2	3.49	12.6	0.553	83
Ab-5-6.37.5.v.1	25	5.5	3.91	18.4	0.379	78
Ab-5-6.147.v.1	25	3.5	4.0	13.8	0.527	78

此研究中之5只猴產生針對不同Mab之結合性抗藥物抗體

(ADA)，其使藥物暴露量降低；因此自分析排除此等個體。異二聚抗體Ab-5-6.37.5 v.1、Ab-5-6.147 v.1及Ab23-6.37.5 v.1之終末半衰期($T_{1/2}$)分別估計為5.5、3.5及3.2天。Ab-5-6.37.5 v.1之暴露量與Ab-5類似(AUC 0-無窮-18.4天*μM相較於18.0天*μM)，而相較於Ab-5，其他兩種異Ig之暴露量降低約25-30%。三種異Ig之生物可用性(F)類似，在78-83%之範圍內。

實例19-其他活體內實驗

在10週齡完整小鼠中進行三週研究以比較異二聚抗體(Ab-5-6.37.5.v.1)與親本Ab DKK1 Ab 6.37.5及Ab-5之各者及與兩種親本抗體(IgG)之組合的骨合成代謝活性(每組n = 6)。鑒於異二聚抗體為硬化蛋白及DKK1之單價抑制劑，評估兩個劑量之異二聚抗體(亦即25 mg/kg及12.5 mg/kg)以相對於用作對照之二價分子衡量價數對生物活性之影響。

一週兩次在12.5 mg/kg下用單藥療法(Ab-5及DKK1 Ab 6.37.5，分開投與)及異二聚抗體療法各自皮下給藥，且在對照組中類似地投與DKK1 Ab(6.37.5，12.5 mg/kg)加抗硬化蛋白Ab(Ab-5，12.5 mg/kg)之組合。此外，用異二聚抗體在25 mg/kg下給藥以相對於研究中使用之二價對照校正價數。一週一次藉由DXA量測骨礦物質密度。

圖14中說明之結果顯示由異二聚抗體治療介導之腰椎骨物質增加顯著優於兩種單藥療法。用降低劑量之異二聚抗體觀測之骨合成代謝活性不顯著不同於在用組合療法治療之小鼠中量測者。較高劑量之異二聚抗體略微優於組合療法，但此差異不顯著。在股骨中觀測到類似骨物質增加(資料未顯示)。

相較於用單獨抗硬化蛋白抗體或抗DKK1抗體進行之治療，在齧齒動物中觀測之同時雙重DKK1及硬化蛋白抑制強調異二聚抗體治療骨病症之治療功效。

【符號說明】

無

【生物材料寄存】

國內寄存資訊【請依寄存機構、日期、號碼順序註記】

無

國外寄存資訊【請依寄存國家、機構、日期、號碼順序註記】

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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> 9
<211> 236
<212> PRT
<213> 小鼠

<400> 9

Met Asn Thr Arg Ala Pro Ala Glu Phe Leu Gly Phe Leu Leu Leu Trp
1 5 10 15

Phe Leu Gly Ala Arg Cys Asp Val Gln Met Ile Gln Ser Pro Ser Ser
20 25 30

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

Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr
210 215 220

Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230 235

<210> 10
<211> 711
<212> DNA
<213> 小鼠

<400> 10
atgaacacga gggcccctgc tgagttcctt gggttcctgt tgctctggtt tttaggtgcc 60

agatgtgatg tccagatgat tcagtctcca tcctccctgt ctgcatcttt gggagacata 120

gtcaccatga cttgccaggc aagtcagggc actagcatta atttaaactg gtttcagcaa 180

aaaccaggga aggctcctaa gctcctgatc tatggttcaa gcaacttgga agatggggtc 240

ccatcaaggt tcagtggcag tagatatggg acagatttca ctctcaccat cagcagcctg 300

gaggatgaag atctggcaac ttatttctgt ctacaacata gttatctccc gtacacgttc 360

ggaggggga ccaagctgga aataaaacgg gctgatgctg caccaactgt atccatcttc 420

ccaccatcca gtgagcagtt aacatctgga ggtgcctcag tcgtgtgctt cttgaacaac 480

ttctacccca aagacatcaa tgtcaagtgg aagattgatg gcagtgaacg acaaaatggc 540

gtcctgaaca gttggactga tcaggacagc aaagacagca cctacagcat gagcagcacc 600

ctcacgttga ccaaggacga gtatgaacga cataacagct atacctgtga ggccactcac 660

aagacatcaa cttcacccat tgtcaagagc ttcaacagga atgagtgtta g 711

<210> 11
<211> 443
<212> PRT
<213> 小鼠

<400> 11

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

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

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

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

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

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
325 330 335

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
405 410 415

Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His
420 425 430

Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
435 440

<210> 12
<211> 1332
<212> DNA
<213> 小鼠

<400> 12
gaggtccagc tgcaacagtc tggacctgaa ctggtgacgc ctggggcttc agtgaagata 60

tcttgtaagg cttctggata cacattcact gaccactaca tgagctgggt gaagcagagt 120

catggaaaaa gccttgagtg gattggagat attaatccct attctggtga aactacctac 180

aaccagaagt tcaagggcac ggccacattg actgtagaca agtcttccag tatagcctac 240

atggagatcc gcggcctgac atctgaggac tctgcagtct attactgtgc aagagatgat 300

tacgacgcct ctccgtttgc ttactggggc caagggactc tggtcactgt ctctgcagcc 360

aaaacgacac ccccatctgt ctatccactg gcccctggat ctgctgccca aactaactcc 420

atggtgaccc tgggatgcct ggtcaagggc tatttccctg agccagtgac agtgacctgg 480

aactctggat ccctgtccag cggtgtgcac accttcccag ctgtcctgca gtctgacctc 540

tacactctga gcagctcagt gactgtcccc tccagcacct ggcccagcga gaccgtcacc 600

tgcaacgttg cccacccggc cagcagcacc aaggtggaca agaaaattgt gcccagggat 660

tgtggttgta agccttgcat atgtacagtc ccagaagtat catctgtctt catcttcccc 720

ccaaagccca aggatgtgct caccattact ctgactccta aggtcacgtg tgttgtggta 780

gacatcagca aggatgatcc cgaggtccag ttcagctggt ttgtagatga tgtggaggtg 840

cacacagctc agacgcaacc ccgggaggag cagttcaaca gcactttccg ctcagtcagt 900

gaacttccca tcatgcacca ggactggctc aatggcaagg agttcaaatg cagggtcaac 960

agtccagctt tccctgcccc catcgagaaa accatctcca aaaccaaagg cagaccgaag 1020

gctccacagg tgtacaccat tccacctccc aaggagcaga tggccaagga taaagtcagt 1080

ctgacctgca tgataacaga cttcttccct gaagacatta ctgtggagtg gcagtggaat 1140

gggcagccag cggagaacta caagaacact cagcccatca tggacacaga tggctcttac 1200

ttcatctaca gcaagctcaa tgtgcagaag agcaactggg aggcaggaaa tactttcacc 1260

tgctctgtgt tacatgaggg cctgcacaac caccatactg agaagagcct ctcccactct 1320

cctggtaaat ga 1332

<210> 13
<211> 462
<212> PRT
<213> 小鼠

<400> 13

Met Arg Cys Arg Trp Ile 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 Val Thr
20 25 30

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

Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His
210 215 220

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

Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His
435 440 445

Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
450 455 460

<210> 14
<211> 1389
<212> DNA
<213> 小鼠

<400> 14
atgagatgca ggtggatctt tctctttctc ctgtcaggaa ctgcaggtgt cctctctgag 60

gtccagctgc aacagtctgg acctgaactg gtgacgcctg gggcttcagt gaagatatct 120

tgtaaggctt ctggatacac attcactgac cactacatga gctgggtgaa gcagagtcat 180

ggaaaaagcc ttgagtggat tggagatatt aatccctatt ctggtgaaac tacctacaac 240

cagaagttca agggcacggc cacattgact gtagacaagt cttccagtat agcctacatg 300

gagatccgcg gcctgacatc tgaggactct gcagtctatt actgtgcaag agatgattac 360

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

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 gccccatcg 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 gagggcctgc acaaccacca tactgagaag 1380

agcctctccc actctcctgg taaatga 1407

<210> 23
<211> 217
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 兔-小鼠嵌合物

<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
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

<210> 24
<211> 654
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<220>
<221> misc_feature
<223> 兔-小鼠嵌合物

<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 ggaccgaggt 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> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 兔-小鼠嵌合物

<400> 25

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
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> 人工序列

<220>
<223> 合成多肽

<220>
<221> misc_feature
<223> 兔-小鼠嵌合物

<400> 26
atggacacga gggccccac 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> 合成聚核苷酸

<220>
<221> MISC_FEATURE
<223> 人類化抗體

<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> 合成聚核苷酸

<220>

<221> misc_feature
<223> 人類化抗體

<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 ccggggacac 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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體

<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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體

<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 cttcccccca 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 ctgcccccat 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> 小鼠

<400> 36
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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 tttccctgag 480

ccagtgacag tgacctggaa ctctggatcc ctgtccagcg gtgtgcacac cttcccagct 540

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cccagcgaga ccgtcacctg caacgttgcc cacccggcca gcagcaccaa ggtggacaag 660

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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
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

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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
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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
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> 小鼠

<400> 38
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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 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 cttacttcgt ctacagcaag ctcaatgtgc agaagagcaa ctgggaggca 1320

ggaaatactt tcacctgctc tgtgttacat gagggcctgc acaaccacca tactgagaag 1380

agcctctccc actctcctgg taaatga 1407

<210> 39
<211> 5
<212> PRT

<213> 小鼠

<400> 39

Asp His Tyr Met Ser
1 5

<210> 40
<211> 17
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 41

Asp Asp Tyr Asp Ala Ser Pro Phe Ala Tyr
1 5 10

<210> 42
<211> 11
<212> PRT
<213> 小鼠

<400> 42

Gln Ala Ser Gln Gly Thr Ser Ile Asn Leu Asn
1 5 10

<210> 43
<211> 7
<212> PRT
<213> 小鼠

<400> 43

Gly Ser Ser Asn Leu Glu Asp
1 5

<210> 44
<211> 9
<212> PRT
<213> 小鼠

<400> 44

Leu Gln His Ser Tyr Leu Pro Tyr Thr
1 5

<210> 45
<211> 5
<212> PRT
<213> 小鼠

<400> 45

Asp Cys Tyr Met Asn
1 5

<210> 46
<211> 17
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 49

Ala Ala Ser Asn Leu Glu Ser
1 5

<210> 50
<211> 9
<212> PRT
<213> 小鼠

<400> 50

Gln Gln Ser Asn Glu Asp Pro Trp Thr
1 5

<210> 51
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 兔-小鼠嵌合物

<400> 51

Ser Tyr Trp Met Asn
1 5

<210> 52
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 兔-小鼠嵌合物

<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> 人工序列

<220>
<223> 合成多肽

<400> 53

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

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 兔-小鼠嵌合物

<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> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 兔-小鼠嵌合物

<400> 55

Asp Ala Ser Asp Leu Ala Ser
1 5

<210> 56
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 兔-小鼠嵌合物

<400> 56

Gln Gly Ala Tyr Asn Asp Val Ile Tyr Ala
1 5 10

<210> 57
<211> 7
<212> PRT
<213> 小鼠

<400> 57

Thr Ser Gly Met Gly Val Gly
1 5

<210> 58
<211> 16
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 60

Ser Ala Ser Ser Ser Val Ser Phe Val Asp
1 5 10

<210> 61
<211> 7
<212> PRT
<213> 小鼠

<400> 61

Arg Thr Ser Asn Leu Gly Phe
1 5

<210> 62
<211> 9
<212> PRT
<213> 小鼠

<400> 62

Gln Gln Arg Ser Thr Tyr Pro Pro Thr
1 5

<210> 63
<211> 20
<212> PRT
<213> 智人

<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> 智人

<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> 智人

<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> 智人

<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> 智人

<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> 智人

<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> 智人

<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> 智人

<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> 智人

<400> 71

Leu Val Ala Ser Cys Lys Cys
1 5

<210> 72

<211> 8
<212> PRT
<213> 智人

<400> 72

Cys Arg Glu Leu His Phe Thr Arg
1 5

<210> 73
<211> 7
<212> PRT
<213> 智人

<400> 73

Cys Ile Pro Asp Arg Tyr Arg
1 5

<210> 74
<211> 399
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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〉 合成聚核苷酸

〈220〉
〈221〉 misc_feature
〈223〉 人類化抗體序列

〈400〉 76
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccactgtgag 60

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

5

<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 小鼠

<400> 79

Tyr Thr Ser Arg Leu Leu Ser
1 5

<210> 80
<211> 9
<212> PRT
<213> 小鼠

<400> 80

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 81
<211> 11
<212> PRT
<213> 小鼠

<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

<210> 88
<211> 23
<212> PRT
<213> 褐鼠

<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

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
210

<210> 99
<211> 7
<212> PRT
<213> 小鼠

<400> 99

Tyr Thr Ser Arg Leu His Ser
1 5

<210> 100

<211> 9
<212> PRT
<213> 小鼠

<400> 100

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 101
<211> 11
<212> PRT
<213> 小鼠

<400> 101

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

<210> 102
<211> 7
<212> PRT
<213> 小鼠

<400> 102

Tyr Thr Ser Arg Leu His Ser
1 5

<210> 103
<211> 9
<212> PRT
<213> 小鼠

<400> 103

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 104

<211> 11
<212> PRT
<213> 小鼠

<400> 104

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

<210> 105
<211> 7
<212> PRT
<213> 小鼠

<400> 105

Tyr Thr Ser Arg Leu Leu Ser
1 5

<210> 106
<211> 9
<212> PRT
<213> 小鼠

<400> 106

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 107
<211> 11
<212> PRT
<213> 小鼠

<400> 107

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

<210> 108

<211> 7
<212> PRT
<213> 小鼠

<400> 108

Tyr Thr Ser Arg Leu Phe Ser
1 5

<210> 109
<211> 9
<212> PRT
<213> 小鼠

<400> 109

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 110
<211> 11
<212> PRT
<213> 小鼠

<400> 110

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

<210> 111
<211> 7
<212> PRT
<213> 小鼠

<400> 111

Tyr Thr Ser Arg Leu Leu Ser
1 5

<210> 112

<211> 9
<212> PRT
<213> 小鼠

<400> 112

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 113
<211> 11
<212> PRT
<213> 小鼠

<400> 113

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

<210> 114
<211> 7
<212> PRT
<213> 小鼠

<400> 114

Tyr Thr Ser Thr Leu Gln Ser
1 5

<210> 115
<211> 9
<212> PRT
<213> 小鼠

<400> 115

Gln Gln Gly Asp Thr Leu Pro Tyr Thr
1 5

<210> 116

<211> 12
<212> PRT
<213> 小鼠

<400> 116

Ser Val Ser Ser Ser Ile Ser Ser Ser Asn Leu His
1 5 10

<210> 117
<211> 213
<212> PRT
<213> 小鼠

<400> 117

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

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

<210> 118
<211> 642
<212> DNA
<213> 小鼠

<400> 118
caaattgttc tctcccagtc tccagcaatc ctgtctacat ctccagggga gaaggtcaca 60

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

acttcaccca ttgtcaagag cttcaacagg aatgagtgtt ag 642

<210> 119
<211> 235
<212> PRT
<213> 小鼠

<400> 119

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

<210> 120
<211> 708
<212> DNA
<213> 小鼠

<400> 120
atggattttc aagtgcagat tttcagcttc ctgctaatca gtgcttcagt cattatgtcc 60

aggggacaaa ttgttctctc ccagtctcca gcaatcctgt ctacatctcc aggggagaag 120

gtcacaatga cttgcagggc cagctcaagt gtatattaca tgcactggta ccagcagaag 180

ccaggatcct ccccccaaacc 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

acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag 660

acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag 708

<210> 121
<211> 445
<212> PRT
<213> 小鼠

<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 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 gtaaatga 1338

<210> 123
<211> 464
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 124
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> 小鼠

<400> 126

gaaattgtgc tcacccagtc tccagcactc atggctgcat ctccggggga 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> 小鼠

<400> 128
atggattttc atgtgcagat tttcagcttc atgctaatca gtgtcacagt cattttgtcc 60

agtggagaaa ttgtgctcac ccagtctcca gcactcatgg ctgcatctcc ggggggagaag 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

5

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> 小鼠

<400> 130
gaggttcagc tgcagcagtc tggggctgaa cttgtgaggc caggggcctt 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 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> 131
<211> 468
<212> PRT
<213> 小鼠

<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 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 gagggcctgc acaaccacca tactgagaag 1380

agcctctccc actctcctgg taaatga 1407

<210> 133
<211> 214

<212> PRT
<213> 小鼠

<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 caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 645

<210> 135
<211> 234
<212> PRT
<213> 小鼠

<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

5

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> 小鼠

<400> 138
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 tggcccctgg atctgctgcc 420

caaactaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg 480

acagtgacct ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg 540

cagtctgacc tctacactct gagcagctca gtgactgtcc ctccagcac 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> 139
<211> 466
<212> PRT
<213> 小鼠

<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

<210> 140
<211> 1401
<212> DNA
<213> 小鼠

<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 actgtccct 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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>

<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<400> 144
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

<210> 145
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<400> 145

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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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 ttccccctgg 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 gccccccatcg 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> 小鼠

<400> 150
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> 小鼠

<400> 151

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> 小鼠

<400> 154
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 ctccagcac 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 actgtccct 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 actgtccct 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

5

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 acccccatct 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> 小鼠

<400> 171

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 actgtccct 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

5

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> 小鼠

<400> 176
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 caccctcacg 600

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 702

<210> 177
<211> 450
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 182
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〉 小鼠

〈400〉 192
atggattttc 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

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

5

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〉 194

<211> 1338
<212> DNA
<213> 小鼠

<400> 194
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 gactctggt 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

ttccccccaa 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 gtaaatga 1338

<210> 195
<211> 464
<212> PRT
<213> 小鼠

<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 cacccccatc 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

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> 202
<211> 1344
<212> DNA
<213> 小鼠

<400> 202
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 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> 203
<211> 466
<212> PRT
<213> 小鼠

<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 actgtccct 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

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 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

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

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> 212
<211> 1392
<212> DNA
<213> 小鼠

<400> 212
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 cacccccatc 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 aa 1392

<210> 213
<211> 215
<212> PRT
<213> 人工序列

<220>

<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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〉 合成聚核苷酸

〈220〉
〈221〉 misc_feature
〈223〉 人類化抗體序列

〈400〉 220
atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60

gtgcagctgg tgcagagcgg cgccgaggtc aagaaacctg gagcaagcgt aaaggttagt 120

tgcaaagcat ctggatacac atttaccgac tactacatga attgggtacg acaagccccct 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 ggacccctga 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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<400> 221

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

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

<210> 222
<211> 645
<212> DNA
<213> 人工序列

<220>
<223> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<400> 222
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

<210> 223
<211> 237
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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〉 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<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 ccccccaaaa 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 ccccccatcga 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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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 ccggacccct 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

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1380

cagaagagcc tctccctgtc tccgggtaaa 1410

<210> 229
<211> 213
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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>
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<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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

5

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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<400> 234
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

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> 235
<211> 466
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<400> 235

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 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
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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<400> 236
atggactgga cctggaggat cctcttcttg gtggcagcag ccacaggagc ccactccgag 60

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 ggacccctga 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
<211> 7
<212> PRT
<213> 小鼠

<400> 237

Gly Thr Ser Asn Leu Ala Ser
1 5

<210> 238
<211> 8
<212> PRT
<213> 小鼠

<400> 238

Gln Gln Trp Thr Thr Thr Tyr Thr
1 5

<210> 239
<211> 11
<212> PRT
<213> 小鼠

<400> 239

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

<210> 240
<211> 7
<212> PRT
<213> 小鼠

<400> 240

Ser Thr Ser Arg Leu Asn Ser
1 5

<210> 241
<211> 8
<212> PRT
<213> 小鼠

<400> 241

Gln Gln Asp Ile Lys His Pro Thr
1 5

<210> 242
<211> 11
<212> PRT
<213> 小鼠

<400> 242

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

<210> 243
<211> 7
<212> PRT
<213> 小鼠

<400> 243

Trp Ala Ser Thr Arg His Thr
1 5

<210> 244
<211> 9
<212> PRT
<213> 小鼠

<400> 244

Gln Gln Tyr Ser Ser Tyr Pro Leu Thr
1 5

<210> 245
<211> 5
<212> PRT
<213> 小鼠

<400> 245

Asp Tyr Asn Met His
1 5

<210> 246
<211> 17
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 248

Asp Tyr Asn Met His
1 5

<210> 249
<211> 17
<212> PRT
<213> 小鼠

<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
<211> 14
<212> PRT
<213> 小鼠

<400> 250

Leu Val Tyr Asp Gly Ser Tyr Glu Asp Trp Tyr Phe Asp Val
1 5 10

<210> 251

<211> 5
<212> PRT
<213> 小鼠

<400> 251

Asp Tyr Asn Met His
1 5

<210> 252
<211> 17
<212> PRT
<213> 小鼠

<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
<211> 14
<212> PRT
<213> 小鼠

<400> 253

Leu Gly Tyr Val Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
1 5 10

<210> 254
<211> 5
<212> PRT
<213> 小鼠

<400> 254

Asp Tyr Asn Met His

1 5

<210> 255
<211> 17
<212> PRT
<213> 小鼠

<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
<211> 14
<212> PRT
<213> 小鼠

<400> 256

Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1 5 10

<210> 257
<211> 5
<212> PRT
<213> 小鼠

<400> 257

Asp Tyr Asn Met His
1 5

<210> 258
<211> 17
<212> PRT
<213> 小鼠

<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
<211> 14
<212> PRT
<213> 小鼠

<400> 259

Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
1 5 10

<210> 260
<211> 5
<212> PRT
<213> 小鼠

<400> 260

Asp Tyr Asn Met His
1 5

<210> 261
<211> 17
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 263

Asp Tyr Asn Met His
1 5

<210> 264
<211> 17
<212> PRT
<213> 小鼠

<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
<212> PRT

<213> 小鼠

<400> 265

Leu Gly Tyr Tyr Gly Asn Tyr Glu Asp Trp Tyr Phe Asp Val
1 5 10

<210> 266
<211> 5
<212> PRT
<213> 小鼠

<400> 266

Asp Tyr Tyr Ile His
1 5

<210> 267
<211> 17
<212> PRT
<213> 小鼠

<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
<211> 13
<212> PRT
<213> 小鼠

<400> 268

Glu Gly Leu Asp Tyr Gly Asp Tyr Tyr Ala Val Asp Tyr
1 5 10

<210> 269
<211> 5
<212> PRT
<213> 小鼠

<400> 269

Asp Tyr Ile Met His
1 5

<210> 270
<211> 17
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 272

Asp Tyr Tyr Met His
1 5

<210> 273
<211> 17
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 274

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

<210> 275
<211> 10
<212> PRT
<213> 小鼠

<400> 275

Arg Ala Ser Ser Ser Val Tyr Tyr Met His
1 5 10

<210> 276
<211> 7

<212> PRT
<213> 小鼠

<400> 276

Ala Thr Ser Asn Leu Ala Ser
1 5

<210> 277
<211> 9
<212> PRT
<213> 小鼠

<400> 277

Gln Gln Trp Ser Ser Asp Pro Leu Thr
1 5

<210> 278
<211> 12
<212> PRT
<213> 小鼠

<400> 278

Ser Val Ser Ser Thr Ile Ser Ser Asn His Leu His
1 5 10

<210> 279
<211> 7
<212> PRT
<213> 小鼠

<400> 279

Gly Thr Ser Asn Leu Ala Ser
1 5

<210> 280
<211> 9

<212> PRT
<213> 小鼠

<400> 280

Gln Gln Trp Ser Ser Tyr Pro Leu Thr
1 5

<210> 281
<211> 10
<212> PRT
<213> 小鼠

<400> 281

Arg Ala Ser Ser Ser Ile Ser Tyr Ile His
1 5 10

<210> 282
<211> 7
<212> PRT
<213> 小鼠

<400> 282

Ala Thr Ser Asn Leu Ala Ser
1 5

<210> 283
<211> 9
<212> PRT
<213> 小鼠

<400> 283

Gln Gln Trp Ser Ser Asp Pro Leu Thr
1 5

<210> 284
<211> 12

<212> PRT
<213> 小鼠

<400> 284

Arg Ala Ser Ser Ser Val Thr Ser Ser Tyr Leu Asn
1 5 10

<210> 285
<211> 7
<212> PRT
<213> 小鼠

<400> 285

Ser Thr Ser Asn Leu Ala Ser
1 5

<210> 286
<211> 9
<212> PRT
<213> 小鼠

<400> 286

Gln Gln Tyr Asp Phe Phe Pro Ser Thr
1 5

<210> 287
<211> 5
<212> PRT
<213> 小鼠

<400> 287

Asp Tyr Phe Ile His
1 5

<210> 288
<211> 17

<212> PRT
<213> 小鼠

<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> 小鼠

<400> 290

Asp Phe Tyr Leu His
1 5

<210> 291
<211> 17
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 293

Asp Tyr Tyr Ile His
1 5

<210> 294
<211> 17
<212> PRT
<213> 小鼠

<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

<211> 12
<212> PRT
<213> 小鼠

<400> 295

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

<210> 296
<211> 5
<212> PRT
<213> 小鼠

<400> 296

Asp Tyr Tyr Met Asn
1 5

<210> 297
<211> 17
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 300
atggattttc aggtgcagat tttcagcttc atgctaatca gtgtcacagt catattgtcc 60

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> 小鼠

<400> 301

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 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> 小鼠

<400> 302
atgggatgga actggatcat cttcttcctg atggcagtgg ttacaggggt caattcagag 60

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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<400> 303

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 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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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 ctatacctttt 360

ggccagggca ccaaactgga aattaaacgt 390

<210> 305
<211> 141
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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〉 合成聚核苷酸

〈220〉
〈221〉 misc_feature
〈223〉 人類化抗體序列

〈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〉 人工序列

〈220〉
〈223〉 合成多肽

〈220〉
〈221〉 MISC_FEATURE
〈223〉 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<220>

<221> misc_feature
<223> 人類化抗體序列

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 小鼠

<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> 小鼠

<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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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> 合成聚核苷酸

<220>
<221> misc_feature
<223> 人類化抗體序列

<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> 320
<212> PRT
<213> 小鼠

<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

<210> 325
<211> 106
<212> PRT
<213> 智人

<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> 智人

<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〉 小鼠

〈400〉 334

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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
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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

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

<210> 336
<211> 108
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 340
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> 341
<211> 213
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 344
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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

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> 小鼠

<400> 346
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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> 小鼠

<400> 348

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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> 小鼠

<400> 349
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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> 小鼠

<400> 352

Ala Ala Ser Asn Leu Glu Ser
1 5

<210> 353
<211> 9
<212> PRT
<213> 小鼠

<400> 353

Gln Gln Ser Asn Glu Asp Pro Phe Thr
1 5

<210> 354
<211> 657
<212> DNA
<213> 小鼠

<400> 354
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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> 小鼠

<400> 356
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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

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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
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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> 小鼠

<400> 358

Thr Tyr Trp Met Asn
1 5

<210> 359
<211> 17
<212> PRT
<213> 小鼠

<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> 小鼠

<400> 360

Ser Gly Glu Trp Gly Ser Met Asp Tyr
1 5

<210> 361
<211> 1329
<212> DNA
<213> 小鼠

<400> 361
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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

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cttcccatca tgcaccagga ctggctcaat ggcaaggagt tcaaatgcag ggtcaacagt 960

gcagctttcc ctgcccccat 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> 小鼠

<400> 363
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

acaccccccat ctgtctatcc actggccccct 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 cccccaaag 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

<210> 364
<211> 106
<212> PRT
<213> 小鼠

<400> 364

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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<400> 392

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

5

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

〈210〉 393
〈211〉 446
〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成多肽

〈220〉
〈221〉 MISC_FEATURE
〈223〉 人類化抗體序列

〈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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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〉 合成多肽

〈220〉
〈221〉 MISC_FEATURE
〈223〉 人類化抗體序列

〈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> 合成多肽

<220>
<221> MISC_FEATURE
<223> 人類化抗體序列

<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

5

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

<210> 397
<211> 213
<212> PRT
<213> 智人

<400> 397

Met Gln Leu Pro Leu Ala Leu Cys Leu Val Cys Leu Leu Val His Thr
1 5 10 15

Ala Phe Arg Val Val Glu Gly Gln Gly Trp Gln Ala Phe Lys Asn Asp
20 25 30

Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
50 55 60

Pro Pro His His Pro Phe Glu Thr Lys Asp Val Ser Glu Tyr Ser Cys
65 70 75 80

Arg Glu Leu His Phe Thr Arg Tyr 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 Gly Lys Trp Trp Arg Pro Ser
115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
130 135 140

Gln Leu Leu Cys Pro Gly Gly Glu Ala Pro Arg Ala 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 Thr Glu Ala Ala Arg Pro Gln Lys Gly
180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Ser Ala Lys Ala Asn Gln Ala Glu
195 200 205

Leu Glu Asn Ala Tyr
210

<210> 398
<211> 444
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 398

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

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

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

Gly Thr Ile Tyr Pro Tyr His Asp Gly Thr Thr Tyr Ser Gln 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 Glu Glu Glu Asp Gly Gln Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 399
<211> 444
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 399

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

Ser Val Lys Val Ser Cys Lys Val Ser Gly Phe Pro Ile Lys Asp Thr
20 25 30

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

Gly Trp Ser Asp Pro Glu Ile Gly Asp Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp 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 Thr Gly Asp Thr Thr Tyr Lys Phe Asp Phe Trp Gly Gln Gly Thr
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 400
<211> 450
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 400

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Asp Phe Glu Ile Lys Asp Tyr
20 25 30

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

Gly Gln Ile Asp Ala Glu Asp Gly Glu Thr Glu Tyr Ala Pro Arg Phe
50 55 60

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

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

Ala Arg Glu Gly Tyr Tyr Tyr Asp Gly Arg Asp Tyr Trp Tyr Phe Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

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

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

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

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

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

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

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
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 Gln
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 Tyr
290 295 300

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

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

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

Tyr Thr Leu Pro Pro Ser Gln 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

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

Asp Lys Ser Arg Trp Gln Glu 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

Leu Gly
450

〈210〉 401
〈211〉 214
〈212〉 PRT
〈213〉 人工

<220>

<223> 雜項構築體

<400> 401

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 Ala Ser Gln Gly Ile Gln Trp 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 Ser Leu His 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 His Ser Lys Leu Pro Arg
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> 402
<211> 214
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 402

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 His 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 Trp 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 Asp Tyr Pro Trp
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〉 403
〈211〉 213
〈212〉 PRT
〈213〉 人工

<220>

<223> 雜項構築體

<400> 403

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

Glu Arg Ala Thr Leu Ser Cys Ser Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

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

Ser Thr Ser Glu Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
50 55 60

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

Asp Phe Ala Val Tyr Tyr Cys Gln Gln Leu Ser His Leu 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> 404
<211> 1332
<212> DNA
<213> 人工

<220>
<223> 雜項構築體

<400> 404
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc agtgaaggtt 60

tcctgcaagg catctggata cacattcact gactactttc tgaactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaact atttatcctt accatgatgg tactacctac 180

tctcagaagt tcaagggcag agtcaccatt accgcggaca aatccacgag cacagcctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagaggaa 300

gaggatggtc agttcgacta ctggggccaa ggaaccacgg tcaccgtctc ctcagcctcc 360

accaagggcc catcggtctt cccgctagcg ccctgctcca ggagcacctc cgagagcaca 420

gccgccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac 480

tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc 540

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa gacctacacc 600

tgcaacgtag atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat 660

ggtccccccat gcccaccctg cccagcacct gagttcctgg ggggaccatc agtcttcctg 720

ttcccccccaa aacccaagga cactctcatg atctcccgga cccctgaggt cacgtgcgtg 780

gtggtggacg tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg 840

gaggtgcata atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg 900

gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag 960

gtctccaaca aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag 1020

ccccgagagc cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag 1080

gtcagcctga cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggaa 1140

agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc 1200

tccttcttcc tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc 1260

ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc 1320

ctgtctctgg gt 1332

<210> 405
<211> 1332
<212> DNA
<213> 人工

<220>
<223> 雜項構築體

<400> 405
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tcctgcaagg tttccggctt ccccattaag gacacctttc agcactgggt gcgacaggct 120

cctggaaaag ggcttgagtg gatgggatgg agcgatcctg agatcggtga tactgaatat 180

gcctcgaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aacaggcgac 300

accacataca agtttgactt ctgggggcaa gggaccacgg tcaccgtctc ctcagcctcc 360

accaagggcc catcggtctt cccgctagcg ccctgctcca ggagcacctc cgagagcaca 420

gccgccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac 480

tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc 540

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa gacctacacc 600

tgcaacgtag atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat 660

ggtcccccat gcccaccctg cccagcacct gagttcctgg ggggaccatc agtcttcctg 720

ttcccccaa aacccaagga cactctcatg atctcccgga cccctgaggt cacgtgcgtg 780

gtggtggacg tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg 840

gaggtgcata atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg 900

gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag 960

gtctccaaca aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag 1020

ccccgagagc cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag 1080

gtcagcctga cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggaa 1140

agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc 1200

tccttcttcc tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc 1260

ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc 1320

ctgtctctgg gt 1332

<210> 406
<211> 1350

<212> DNA
<213> 人工

<220>
<223> 雜項構築體

<400> 406
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60

tcctgtaagg gttctgactt cgagattaaa gactactata tacattgggt gcgccagatg 120

cccgggaaag gcctggagtg gatggggcag attgatgctg aggatggtga aactgaatat 180

gccccgaggt tccagggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240

ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagagagggt 300

tattactacg atgggcgcga ctactggtac ttcgatgtct ggggccaagg gaccacggtc 360

accgtctcct cagcctccac caagggccca tcggtcttcc cgctagcgcc ctgctccagg 420

agcacctccg agagcacagc cgccctgggc tgcctggtca aggactactt ccccgaaccg 480

gtgacggtgt cgtggaactc aggcgccctg accagcggcg tgcacacctt cccggctgtc 540

ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc cagcagcttg 600

ggcacgaaga cctacacctg caacgtagat cacaagccca gcaacaccaa ggtggacaag 660

agagttgagt ccaaatatgg tcccccatgc ccaccctgcc cagcacctga gttcctgggg 720

ggaccatcag tcttcctgtt cccccaaaa cccaaggaca ctctcatgat ctcccggacc 780

cctgaggtca cgtgcgtggt ggtggacgtg agccaggaag accccgaggt ccagttcaac 840

tggtacgtgg atggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagttc 900

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaacggc 960

aaggagtaca agtgcaaggt ctccaacaaa ggcctcccgt cctccatcga gaaaaccatc 1020

tccaaagcca aagggcagcc ccgagagcca caggtgtaca ccctgccccc atcccaggag 1080

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta ccccagcgac 1140

atcgccgtgg agtgggaaag caatgggcag ccggagaaca actacaagac cacgcctccc 1200

gtgctggact ccgacggctc cttcttcctc tacagcaggc taaccgtgga caagagcagg 1260

tggcaggagg ggaatgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1320

acacagaaga gcctctccct gtctctgggt 1350

<210> 407
<211> 642
<212> DNA
<213> 人工

<220>
<223> 雜項構築體

<400> 407
gacatccaga tgacccagtc tccatcctct ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgca gtgcaagtca gggcattcag tggtatttaa actggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctattac acatcaagtt tacactcagg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcagcag catagtaaac ttcctcggac gttcggcgga 300

gggaccaagg tggagatcaa acggactgtg 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 gc 642

<210> 408
<211> 642

<212> DNA
<213> 人工

<220>
<223> 雜項構築體

<400> 408
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atcacttgca aggccagtca ggatgtgcac actgctgtag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctattgg gcatccaccc ggtggactgg agtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcagcaa tatagcgatt atccgtggac gttcggcgga 300

gggaccaagg tggagatcaa acggactgtg 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 gc 642

<210> 409
<211> 639
<212> DNA
<213> 人工

<220>
<223> 雜項構築體

<400> 409
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gtgccagctc aagtgtaagt tacatccact ggtaccaaca gaaacctggc 120

caggctccca ggctcctcat ctatagcaca tccgagctgg cttctggcat cccagccagg 180

ttcagtggca gtgggtctgg gacagacttc actctcacca tcagcagcct agagcctgaa 240

gattttgcag tttattactg tcagcagctt agtcatctcc cgctcacgtt cggcggaggg 300

accaaggtgg agatcaaacg aactgtggct 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 ggagagtgc 639

<210> 410
<211> 118
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 410

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

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

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

Gly Thr Ile Tyr Pro Tyr His Asp Gly Thr Thr Tyr Ser Gln 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 Glu Glu Glu Asp Gly Gln Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 411
<211> 118
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 411

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

Ser Val Lys Val Ser Cys Lys Val Ser Gly Phe Pro Ile Lys Asp Thr
20 25 30

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

Gly Trp Ser Asp Pro Glu Ile Gly Asp Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp 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 Thr Gly Asp Thr Thr Tyr Lys Phe Asp Phe Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

〈210〉 412
〈211〉 124
〈212〉 PRT
〈213〉 人工

〈220〉
〈223〉 雜項構築體

〈400〉 412

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Asp Phe Glu Ile Lys Asp Tyr
20 25 30

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

Gly Gln Ile Asp Ala Glu Asp Gly Glu Thr Glu Tyr Ala Pro Arg Phe
50 55 60

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

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

Ala Arg Glu Gly Tyr Tyr Tyr Asp Gly Arg Asp Tyr Trp Tyr Phe Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 413
<211> 107
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 413

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 Ala Ser Gln Gly Ile Gln Trp 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 Ser Leu His 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 His Ser Lys Leu Pro Arg
85 90 95

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

<210> 414
<211> 107
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 414

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 His 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 Trp 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 Asp Tyr Pro Trp
85 90 95

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

<210> 415
<211> 106
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 415

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

Glu Arg Ala Thr Leu Ser Cys Ser Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

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

Ser Thr Ser Glu Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
50 55 60

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

Asp Phe Ala Val Tyr Tyr Cys Gln Gln Leu Ser His Leu Pro Leu Thr
85 90 95

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

<210> 416
<211> 10
<212> PRT
<213> 人工

<220>

<223> 雜項構築體

<400> 416

Gly Tyr Thr Phe Thr Asp Tyr Phe Leu Asn
1 5 10

<210> 417
<211> 17
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 417

Thr Ile Tyr Pro Tyr His Asp Gly Thr Thr Tyr Ser Gln Lys Phe Lys
1 5 10 15

Gly

<210> 418
<211> 9
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 418

Glu Glu Glu Asp Gly Gln Phe Asp Tyr
1 5

<210> 419
<211> 11
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 419

Ser Ala Ser Gln Gly Ile Gln Trp Tyr Leu Asn
1 5 10

<210> 420
<211> 7
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 420

Tyr Thr Ser Ser Leu His Ser
1 5

<210> 421
<211> 9
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 421

Gln Gln His Ser Lys Leu Pro Arg Thr
1 5

<210> 422
<211> 10
<212> PRT
<213> 人工

<220>

<223> 雜項構築體

<400> 422

Gly Phe Pro Ile Lys Asp Thr Phe Gln His
1 5 10

<210> 423
<211> 17
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 423

Trp Ser Asp Pro Glu Ile Gly Asp Thr Glu Tyr Ala Ser Lys Phe Gln
1 5 10 15

Gly

<210> 424
<211> 9
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 424

Gly Asp Thr Thr Tyr Lys Phe Asp Phe
1 5

<210> 425
<211> 11
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 425

Lys Ala Ser Gln Asp Val His Thr Ala Val Ala
1 5 10

<210> 426
<211> 7
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 426

Trp Ala Ser Thr Arg Trp Thr
1 5

<210> 427
<211> 9
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 427

Gln Gln Tyr Ser Asp Tyr Pro Trp Thr
1 5

<210> 428
<211> 10
<212> PRT
<213> 人工

<220>

<223> 雜項構築體

<400> 428

Asp Phe Glu Ile Lys Asp Tyr Tyr Ile His
1 5 10

<210> 429
<211> 17
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 429

Gln Ile Asp Ala Glu Asp Gly Glu Thr Glu Tyr Ala Pro Arg Phe Gln
1 5 10 15

Gly

<210> 430
<211> 17
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 430

Gln Ile Asp Ala Glu Asp Gly Glu Thr Glu Tyr Ala Pro Arg Phe Gln
1 5 10 15

Gly

<210> 431
<211> 17
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 431

Gln Ile Asp Ala Glu Asp Gly Glu Thr Glu Tyr Ala Pro Arg Phe Gln
1 5 10 15

Gly

<210> 432
<211> 7
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 432

Ser Thr Ser Glu Leu Ala Ser
1 5

<210> 433
<211> 9
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 433

Gln Gln Leu Ser His Leu Pro Leu Thr
1 5

<210> 434
<211> 322
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 434

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
1 5 10 15

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
20 25 30

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
35 40 45

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

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
65 70 75 80

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
85 90 95

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

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
115 120 125

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
130 135 140

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
145 150 155 160

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
165 170 175

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
180 185 190

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
195 200 205

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
210 215 220

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
225 230 235 240

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
245 250 255

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
260 265 270

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
275 280 285

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
290 295 300

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
305 310 315 320

Leu Gly

<210> 435
<211> 970
<212> DNA
<213> 人工

<220>
<223> 雜項構築體

<400> 435
ggcccatcgg tcttcccgct agcgccctgc tccaggagca cctccgagag cacagccgcc 60

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 120

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 180

gctcagcagc gtggtgaccg tgccctccag cagcttgggc acgaagacct acacctgcaa 240

cgtagatcac aagcccagca acaccaaggt ggacaagaga gttgagtcca aatatggtcc 300

cccatgccca ccctgcccag cacctgagtt cctgggggga ccatcagtct tcctgttccc 360

cccaaaaccc aaggacactc tcatgatctc ccggacccct gaggtcacgt gcgtggtggt 420

ggacgtgagc caggaagacc ccgaggtcca gttcaactgg tacgtggatg gcgtggaggt 480

gcataatgcc aagacaaagc cgcgggagga gcagttcaac agcacgtacc gtgtggtcag 540

cgtcctcacc gtcctgcacc aggactggct gaacggcaag gagtacaagt gcaaggtctc 600

caacaaaggc ctcccgtcct ccatcgagaa aaccatctcc aaagccaaag ggcagccccg 660

agagccacag gtgtacaccc tgcccccatc ccaggaggag atgaccaaga accaggtcag 720

cctgacctgc ctggtcaaag gcttctaccc agcgacatc gccgtggagt gggaaagcaa 780

tgggcagccg gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt 840

cttcctctac agcaggctaa ccgtggacaa gagcaggtgg caggagggga atgtcttctc 900

atgctccgtg atgcatgagg ctctgcacaa ccactacaca cagaagagcc tctccctgtc 960

tctgggttga 970

<210> 436
<211> 444
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 436

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

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

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

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

Gln Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

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

Thr Thr Gly Glu Ser Asn Tyr Asp Phe Asp Phe Trp Gly Leu Gly Thr
100 105 110

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

Leu Ala Pro Gly Thr Ala Leu Lys Ser 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 Ala Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

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

Trp Pro Ser Gln 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 Asn Cys Gly Gly Asp Cys
210 215 220

Lys Pro Cys Ile Cys Thr Gly Ser 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 Gln Asp Asp Pro Glu Val His Phe
260 265 270

Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Arg Pro
275 280 285

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

Ile Leu His Gln Asp Trp Leu Asn Gly Arg Thr Phe Arg Cys Lys Val
305 310 315 320

Thr Ser Ala Ala Phe Pro Ser Pro Ile Glu Lys Thr Ile Ser Lys Pro
325 330 335

Glu Gly Arg Thr Gln Val Pro His Val Tyr Thr Met Ser Pro Thr Lys
340 345 350

Glu Glu Met Thr Gln Asn Glu Val Ser Ile Thr Cys Met Val Lys Gly
355 360 365

Phe Tyr Pro Pro Asp Ile Tyr Val Glu Trp Gln Met Asn Gly Gln Pro
370 375 380

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

Tyr Phe Leu Tyr Ser Lys Leu Asn Val Lys Lys Glu Lys Trp Gln Gln
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

<210> 437
<211> 214

<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 437

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

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

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

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

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

Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Ser Asn Tyr Pro Trp
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 Thr Glu Gln Leu Ala Thr Gly
115 120 125

Gly Ala Ser Val Val Cys Leu Met Asn Asn Phe Tyr Pro Arg Asp Ile
130 135 140

Ser Val Lys Trp Lys Ile Asp Gly Thr Glu Arg Arg Asp Gly Val Leu
145 150 155 160

Asp Ser Val Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
165 170 175

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

Thr Cys Glu Val Val His Lys Thr Ser Ser Ser Pro Val Val Lys Ser
195 200 205

Phe Asn Arg Asn Glu Cys
210

<210> 438
<211> 450
<212> PRT
<213> 人工

<220>
<223> 雜項構築體

<400> 438

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

Ser Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Tyr
20 25 30

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

Gly Arg Ile Asp Pro Glu Asp Gly Glu Thr Glu Tyr Ala Pro Arg Phe
50 55 60

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

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

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

Val Trp Gly Thr Gly Thr Thr Val Thr Val Ser Ser Ala Lys Thr Thr
115 120 125

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

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

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

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

Thr Val Pro Ser Ser Thr Trp Pro Ser Gln Thr Val Thr Cys Asn Val
195 200 205

Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
210 215 220

Asn Cys Gly Gly Asp Cys Lys Pro Cys Ile Cys Thr Gly Ser Glu Val
225 230 235 240

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

Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Gln Asp
260 265 270

Asp Pro Glu Val His Phe Ser Trp Phe Val Asp Asp Val Glu Val His
275 280 285

Thr Ala Gln Thr Arg Pro Pro Glu Glu Gln Phe Asn Ser Thr Phe Arg
290 295 300

Ser Val Ser Glu Leu Pro Ile Leu His Gln Asp Trp Leu Asn Gly Arg
305 310 315 320

Thr Phe Arg Cys Lys Val Thr Ser Ala Ala Phe Pro Ser Pro Ile Glu
325 330 335

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

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

Thr Cys Met Val Lys Gly Phe Tyr Pro Pro Asp Ile Tyr Val Glu Trp
370 375 380

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

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

Lys Glu Lys Trp Gln Gln Gly Asn Thr Phe Thr Cys Ser Val Leu His
420 425 430

Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
435 440 445

Gly Lys
450

<210> 439
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<220>
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<400> 439

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

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Leu Trp Ile Tyr
35 40 45

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

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn 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 Thr Glu Gln Leu Ala Thr Gly Gly
115 120 125

Ala Ser Val Val Cys Leu Met Asn Asn Phe Tyr Pro Arg Asp Ile Ser
130 135 140

Val Lys Trp Lys Ile Asp Gly Thr Glu Arg Arg Asp Gly Val Leu Asp
145 150 155 160

Ser Val Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
165 170 175

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

Cys Glu Val Val His Lys Thr Ser Ser Ser Pro Val Val Lys Ser Phe
195 200 205

Asn Arg Asn Glu Cys
210

<210> 440
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<400> 440

Gly Phe Thr Phe Ser Ser Tyr Val Met Asn

1 5 10

<210> 441
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<400> 441

Gly Phe Thr Phe Arg Ser His Trp Leu Ser
1 5 10

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Gly Phe Thr Phe Ser Ser Tyr Val Met Asn
1 5 10

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Gly Phe Thr Phe Arg Ser His Trp Leu Ser
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Gly Phe Thr Phe Arg Ser His Trp Leu Ser

1 5 10

<210> 445
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<400> 445

Gly Phe Thr Phe Arg Ser His Trp Leu Ser
1 5 10

<210> 446
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<400> 446

Gly Phe Thr Phe Arg Ser His Trp Leu Ser
1 5 10

<210> 447
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<400> 447

Gly Phe Thr Phe Arg Ser His Trp Leu Ser
1 5 10

<210> 448
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<400> 448

Gly Phe Thr Phe Arg Ser His Trp Leu Ser

1 5 10

<210> 449
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<400> 449

Gly Phe Thr Phe Arg Ser His Trp Leu Ser
1 5 10

<210> 450
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<400> 450

Gly Phe Thr Phe Arg Ser His Trp Leu Ser
1 5 10

<210> 451
<211> 20
<212> PRT
<213> 智人

<400> 451

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

Ser Val Lys Gly
20

<210> 452
<211> 20
<212> PRT
<213> 智人

<400> 452

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

Ser Val Lys Gly
20

<210> 453
<211> 20
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<400> 453

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

Ser Val Lys Gly
20

<210> 454
<211> 20
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<400> 454

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

Ser Val Lys Gly
20

<210> 455
<211> 19
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<213> 智人

<400> 455

Trp Val Ser Val Thr Gly Val His Gly Asp Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly

<210> 456
<211> 19
<212> PRT
<213> 智人

<400> 456

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

Val Lys Gly

<210> 457
<211> 19
<212> PRT
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<400> 457

Trp Val Ser Val Thr Thr His Gln Gly Tyr Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly

<210> 458
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<212> PRT
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<400> 458

Trp Val Ser Ala Thr Asn Arg Tyr Gly Tyr Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly

<210> 459
<211> 20
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<400> 459

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

Ser Val Lys Gly
20

<210> 460
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<212> PRT
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<400> 460

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

Val Lys Gly

<210> 461

<211> 19
<212> PRT
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<400> 461

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

Val Lys Gly

<210> 462
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<213> 智人

<400> 462

Thr Phe Met His Gly His Leu Gly Gly Gly Leu Ser Met Asp Phe
1 5 10 15

<210> 463
<211> 8
<212> PRT
<213> 智人

<400> 463

Asp Thr Tyr Leu His Phe Asp Tyr
1 5

<210> 464
<211> 15
<212> PRT
<213> 智人

<400> 464

Thr Phe Met His Gly His Leu Gly Gly Gly Leu Ser Met Asp Phe

1 5 10 15

<210> 465
<211> 8
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<213> 智人

<400> 465

Asp Thr Tyr Leu His Phe Asp Tyr
1 5

<210> 466
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<400> 466

Asp Thr Tyr Leu His Phe Asp Tyr
1 5

<210> 467
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Asp Thr Tyr Leu His Phe Asp Tyr
1 5

<210> 468
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<400> 468

Asp Thr Tyr Leu His Phe Asp Tyr

1 5

<210> 469
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<212> PRT
<213> 智人

<400> 469

Asp Thr Tyr Leu His Phe Asp Tyr
1 5

<210> 470
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<400> 470

Asp Thr Tyr Leu His Phe Asp Tyr
1 5

<210> 471
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<400> 471

Asp Thr Tyr Leu His Phe Asp Tyr
1 5

<210> 472
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<400> 472

Asp Thr Tyr Leu His Phe Asp Tyr

5

1 5

<210> 473
<211> 11
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<400> 473

Ser Gly Asp Asn Ile Gly Ser Phe Tyr Val His
1 5 10

<210> 474
<211> 20
<212> PRT
<213> 智人

<400> 474

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

Ser Val Lys Gly
20

<210> 475
<211> 20
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<213> 智人

<400> 475

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

Ser Val Lys Gly
20

<210> 476
<211> 11
<212> PRT
<213> 智人

<400> 476

Ser Gly Asp Asn Ile Gly Ser Phe Tyr Val His
1 5 10

<210> 477
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<212> PRT
<213> 智人

<400> 477

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

<210> 478
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<212> PRT
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<400> 478

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

<210> 479
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<212> PRT
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<400> 479

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

<210> 480
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<400> 480

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

<210> 481
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<400> 481

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

<210> 482
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<400> 482

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

<210> 483
<211> 14
<212> PRT
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<400> 483

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

<210> 484
<211> 11
<212> PRT
<213> 智人

<400> 484

Leu Val Ile Tyr Asp Asp Asn Asn Arg Pro Ser
1 5 10

<210> 485
<211> 11
<212> PRT
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<400> 485

Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser
1 5 10

<210> 486
<211> 11
<212> PRT
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<400> 486

Leu Val Ile Tyr Asp Asp Asn Asn Arg Pro Ser
1 5 10

<210> 487
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<212> PRT
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<400> 487

Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser
1 5 10

<210> 488
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<212> PRT
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<400> 488

Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser
1 5 10

<210> 489
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<212> PRT
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<400> 489

Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser
1 5 10

<210> 490
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<400> 490

Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser
1 5 10

<210> 491
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<400> 491

Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser
1 5 10

<210> 492
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<212> PRT
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<400> 492

Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser
1 5 10

<210> 493
<211> 11
<212> PRT
<213> 智人

<400> 493

Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser
1 5 10

<210> 494
<211> 11
<212> PRT
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<400> 494

Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser
1 5 10

<210> 495
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<212> PRT
<213> 智人

<400> 495

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

<210> 496
<211> 10
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<400> 496

Ser Ser Tyr Gly Glu Ser Leu Thr Ser Tyr
1 5 10

<210> 497
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<400> 497

Ala Ser Trp Thr Gly Val Glu Pro Asp Tyr
1 5 10

<210> 498
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<212> PRT
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<400> 498

Gln Ser Tyr Ala Gly Ser Tyr Leu Ser Glu
1 5 10

<210> 499
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<400> 499

Ser Ser Tyr Gly Glu Ser Leu Thr Ser Tyr
1 5 10

<210> 500
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Ser Ser Tyr Gly Glu Ser Leu Thr Ser Tyr
1 5 10

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Ser Ser Tyr Gly Glu Ser Leu Thr Ser Tyr
1 5 10

<210> 502
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<400> 502

Ser Ser Tyr Gly Glu Ser Leu Thr Ser Tyr
1 5 10

<210> 503
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<400> 503

Ser Thr Tyr Asp Gly Pro Gly Leu Ser Glu
1 5 10

<210> 504
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<400> 504

Ser Ser Tyr Gly Glu Ser Leu Thr Ser Tyr
1 5 10

<210> 505
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<212> PRT
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<400> 505

Ser Ser Tyr Gly Glu Ser Leu Thr Ser Tyr
1 5 10

<210> 506
<211> 124
<212> PRT
<213> 智人

<400> 506

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

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

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

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

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

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

Ala Arg Thr Phe Met His Gly His Leu Gly Gly Gly Leu Ser Met Asp
100 105 110

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

<210> 507
<211> 117
<212> PRT
<213> 智人

<400> 507

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

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

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

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

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

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

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

Val Thr Val Ser Ser
115

<210> 508
<211> 124
<212> PRT
<213> 智人

<400> 508

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

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

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

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

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

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

Ala Arg Thr Phe Met His Gly His Leu Gly Gly Gly Leu Ser Met Asp

100 105 110

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

<210> 509
<211> 117
<212> PRT
<213> 智人

<400> 509

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

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

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

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

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

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

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

Val Thr Val Ser Ser
115

<210> 510
<211> 116
<212> PRT
<213> 智人

<400> 510

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

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

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

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

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

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

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

Thr Val Ser Ser
115

<210> 511
<211> 116
<212> PRT

<213> 智人

<400> 511

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

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

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

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

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

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

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

Thr Val Ser Ser
115

<210> 512
<211> 116
<212> PRT
<213> 智人

<400> 512

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

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

Ser Val Thr Thr His Gln Gly Tyr Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

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

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

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

Thr Val Ser Ser
115

<210> 513
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<213> 智人

<400> 513

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

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

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

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

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

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

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

Thr Val Ser Ser
115

<210> 514
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<212> PRT
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<400> 514

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

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

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

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

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

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

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

Val Thr Val Ser Ser
115

<210> 515
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<213> 智人

<400> 515

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

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

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

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

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

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

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

Thr Val Ser Ser
115

<210> 516
<211> 116
<212> PRT
<213> 智人

<400> 516

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

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

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

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

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

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

85 90 95

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

Thr Val Ser Ser
115

<210> 517
<211> 110
<212> PRT
<213> 智人

<400> 517

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

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

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

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

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

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

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

<210> 518
<211> 113
<212> PRT
<213> 智人

<400> 518

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

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

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

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

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Gly Glu Ser
85 90 95

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

Gln

<210> 519
<211> 110
<212> PRT

<213> 智人

<400> 519

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

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

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

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

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

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

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

<210> 520
<211> 113
<212> PRT
<213> 智人

<400> 520

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Asp Ile

20 25 30

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

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

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Ala Gly Ser
85 90 95

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

Gln

<210> 521
<211> 113
<212> PRT
<213> 智人

<400> 521

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

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

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

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

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Gly Glu Ser
85 90 95

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

Gln

<210> 522
<211> 113
<212> PRT
<213> 智人

<400> 522

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

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

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

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

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Gly Glu Ser
85 90 95

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

Gln

<210> 523
<211> 113
<212> PRT
<213> 智人

<400> 523

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

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

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

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

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Gly Glu Ser
85 90 95

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

Gln

<210> 524
<211> 113
<212> PRT
<213> 智人

<400> 524

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

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

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

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

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Gly Glu Ser
85 90 95

Leu Thr Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly

100 105 110

Gln

<210> 525
<211> 113
<212> PRT
<213> 智人

<400> 525

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

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

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

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

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

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

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

Gln

5

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<210> 526
<211> 113
<212> PRT
<213> 智人

<400> 526

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

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

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

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

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Gly Glu Ser
85 90 95

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

Gln

<210> 527
<211> 113
<212> PRT

<213> 智人

<400> 527

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

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

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

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

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

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

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

Gln

<210> 528
<211> 372
<212> DNA
<213> 智人

<400> 528
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agctgcgcgg cctccggatt tacctttct tcttatgtta tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcttt atctctggtg attctagcaa tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtactttt 300

atgcatggtc atcttggtgg tggtctttct atggattttt ggggccaagg caccctggtg 360

acggttagct ca 372

<210> 529
<211> 350
<212> DNA
<213> 智人

<400> 529
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtcta 60

gctgcgcggc ctccggattt acctttcgtt ctcattggct ttcttgggtg cgccaagccc 120

ctgggaaggg tctcgagtgg gtgagcaata tcaattatga tggtagctct acctattatg 180

cggatagcgt gaaaggccgt tttaccattt cacgtgataa ttcgaaaaac accctgtatc 240

tgcaaatgaa cagcctgcgt gcggaagata cggccgtgta ttattgcgcg cgtgatactt 300

atcttcattt tgattattgg ggccaaggca ccctggtgac ggttagctca 350

<210> 530
<211> 372
<212> DNA
<213> 智人

<400> 530
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agctgcgcgg cctccggatt tacctttct tcttatgtta tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcttt atctctggtg attctagcaa tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtactttt 300

atgcatggtc atcttggtgg tggtctttct atggattttt ggggccaagg caccctggtg 360

acggttagct ca 372

<210> 531
<211> 351
<212> DNA
<213> 智人

<400> 531
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agctgcgcgg cctccggatt tacctttcgt tctcattggc tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcaat atcaattatg atggtagctc tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatact 300

tatcttcatt ttgattattg gggccaaggc accctggtga cggttagctc a 351

<210> 532
<211> 348
<212> DNA
<213> 智人

<400> 532
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agctgcgcgg cctccggatt tacctttcgt tctcattggc tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt actggtgttc atggtgatac ttattatgct 180

gattctgtta agggtcgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg tgatacttat 300

cttcattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 533
<211> 348
<212> DNA
<213> 智人

<400> 533
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttcgt tctcattggc tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt attggtaatt ggggtgatac ttattatgct 180

gattctgtta agggtcgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg tgatacttat 300

cttcattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 534
<211> 348
<212> DNA
<213> 智人

<400> 534
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttcgt tctcattggc tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt attggtaatt ggggtgatac ttattatgct 180

gattctgtta agggtcgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg tgatacttat 300

cttcattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 535
<211> 348
<212> DNA

<213> 智人

<400> 535
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttcgt tctcattggc tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct actaatcgtt atggttatac ttattatgct 180

gattctgtta agggtcgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg tgatacttat 300

cttcattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 536
<211> 351
<212> DNA
<213> 智人

<400> 536
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttcgt tctcattggc tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcaat atcaattatg atggtagctc tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatact 300

tatcttcatt ttgattattg gggccaaggc accctggtga cggttagctc a 351

<210> 537
<211> 348
<212> DNA
<213> 智人

<400> 537
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agctgcgcgg cctccggatt tacctttcgt tctcattggc tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt attactcctt atggtgatac ttattatgct 180

gattctgtta agggtcgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg tgatacttat 300

cttcattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 538
<211> 348
<212> DNA
<213> 智人

<400> 538
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttcgt tctcattggc tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt attactcctt atggtgatac ttattatgct 180

gattctgtta agggtcgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

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cttcattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 539
<211> 330
<212> DNA
<213> 智人

<400> 539
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tcgtgtagcg gcgataatat tggttctttt tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cggttcttgg gctggttctt ctggttctta tgtgtttggc 300

ggccgcacga agttaaccgt tcttggccag 330

<210> 540
<211> 339
<212> DNA
<213> 智人

<400> 540
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt gatattaatg atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg gtgagtctct tacttcttat 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 541
<211> 330
<212> DNA
<213> 智人

<400> 541
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggttctttt tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cgcttcttgg actggtgttg agcctgatta tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag 330

<210> 542
<211> 339

<212> DNA
<213> 智人

<400> 542
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt gatattaatg atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg ctggttctta tctttctgag 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 543
<211> 339
<212> DNA
<213> 智人

<400> 543
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tcgtgtacgg gtactagcag cgatgttggt gatattaatg atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg gtgagtctct tacttcttat 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 544
<211> 339
<212> DNA
<213> 智人

<400> 544
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tcgtgtacgg gtactagcag cgatgttggt gatattaatg atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg gtgagtctct tacttcttat 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 545
<211> 339
<212> DNA
<213> 智人

<400> 545
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tcgtgtacgg gtactagcag cgatgttggt gatattaatg atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg gtgagtctct tacttcttat 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 546
<211> 339
<212> DNA
<213> 智人

<400> 546
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt gatattaatg atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg gtgagtctct tacttcttat 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 547
<211> 339
<212> DNA
<213> 智人

<400> 547
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt gatattaatg atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tctacttatg atggtcctgg tctttctgag 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 548
<211> 339
<212> DNA
<213> 智人

<400> 548
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt gatattaatg atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg gtgagtctct tacttcttat 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 549

<211> 339
<212> DNA
<213> 智人

<400> 549
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt gatattaatg atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tctacttatg atggtcctgg tctttctgag 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 550
<211> 469
<212> PRT
<213> 智人

<400> 550

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Ser Ser Tyr Val Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Phe Ile Ser Gly Asp Ser Ser Asn Thr Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Thr Phe Met His Gly His Leu Gly Gly Gly Leu
115 120 125

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

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
145 150 155 160

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
165 170 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
180 185 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
195 200 205

Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr
210 215 220

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
225 230 235 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro
245 250 255

Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
260 265 270

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
275 280 285

Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
290 295 300

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
305 310 315 320

Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
325 330 335

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala
340 345 350

Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro
355 360 365

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
370 375 380

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385 390 395 400

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
405 410 415

Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
420 425 430

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
435 440 445

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
450 455 460

Leu Ser Pro Gly Lys
465

<210> 551
<211> 462
<212> PRT
<213> 智人

<400> 551

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Arg Ser His Trp Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Asn Ile Asn Tyr Asp Gly Ser Ser Thr Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Asp Thr Tyr Leu His Phe Asp Tyr Trp Gly Gln
115 120 125

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

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
145 150 155 160

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
165 170 175

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
180 185 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
195 200 205

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
210 215 220

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
225 230 235 240

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
245 250 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
260 265 270

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
275 280 285

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
290 295 300

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
305 310 315 320

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
325 330 335

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
340 345 350

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
355 360 365

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
370 375 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385 390 395 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
405 410 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
420 425 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
435 440 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 552
<211> 469
<212> PRT
<213> 智人

<400> 552

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Ser Ser Tyr Val Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Phe Ile Ser Gly Asp Ser Ser Asn Thr Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Thr Phe Met His Gly His Leu Gly Gly Gly Leu
115 120 125

Ser Met Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala

130 135 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
145 150 155 160

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
165 170 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
180 185 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
195 200 205

Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr
210 215 220

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
225 230 235 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro
245 250 255

Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
260 265 270

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
275 280 285

Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
290 295 300

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser

305 310 315 320

Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
325 330 335

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala
340 345 350

Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro
355 360 365

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
370 375 380

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385 390 395 400

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
405 410 415

Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
420 425 430

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
435 440 445

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
450 455 460

Leu Ser Pro Gly Lys
465

<210> 553

<211> 462
<212> PRT
<213> 智人

<400> 553

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Arg Ser His Trp Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Asn Ile Asn Tyr Asp Gly Ser Ser Thr Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Asp Thr Tyr Leu His Phe Asp Tyr Trp Gly Gln
115 120 125

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

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
145 150 155 160

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
165 170 175

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
180 185 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
195 200 205

Ser Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
210 215 220

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
225 230 235 240

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
245 250 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
260 265 270

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
275 280 285

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
290 295 300

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
305 310 315 320

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
325 330 335

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
340 345 350

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
355 360 365

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
370 375 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385 390 395 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
405 410 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
420 425 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
435 440 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 554
<211> 461
<212> PRT
<213> 智人

<400> 554

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Arg Ser His Trp Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Val Thr Gly Val His Gly Asp Thr Tyr Tyr Ala Asp
65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
85 90 95

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Asp Thr Tyr Leu His Phe Asp Tyr Trp Gly Gln Gly
115 120 125

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

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145 150 155 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
165 170 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
180 185 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
195 200 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
210 215 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225 230 235 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
245 250 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
260 265 270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
275 280 285

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
290 295 300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
305 310 315 320

Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
325 330 335

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
340 345 350

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

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
370 375 380

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
385 390 395 400

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
405 410 415

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
420 425 430

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
435 440 445

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 555
<211> 461
<212> PRT
<213> 智人

<400> 555

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Arg Ser His Trp Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Val Ile Gly Asn Trp Gly Asp Thr Tyr Tyr Ala Asp
65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
85 90 95

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Asp Thr Tyr Leu His Phe Asp Tyr Trp Gly Gln Gly
115 120 125

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

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145 150 155 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
165 170 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
180 185 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
195 200 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
210 215 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225 230 235 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
245 250 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
260 265 270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
275 280 285

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
290 295 300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
305 310 315 320

Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
325 330 335

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
340 345 350

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

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
370 375 380

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
385 390 395 400

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
405 410 415

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
420 425 430

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
435 440 445

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 556
<211> 461
<212> PRT
<213> 智人

<400> 556

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Arg Ser His Trp Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Val Thr Thr His Gln Gly Tyr Thr Tyr Tyr Ala Asp
65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr

85 90 95

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Asp Thr Tyr Leu His Phe Asp Tyr Trp Gly Gln Gly
115 120 125

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

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145 150 155 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
165 170 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
180 185 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
195 200 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
210 215 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225 230 235 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
245 250 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu

5

260 265 270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
275 280 285

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
290 295 300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
305 310 315 320

Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
325 330 335

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
340 345 350

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

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
370 375 380

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
385 390 395 400

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
405 410 415

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
420 425 430

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

435 440 445

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 557
<211> 465
<212> PRT
<213> 智人

<400> 557

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Arg Ser His Trp Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ala Thr Asn Arg Tyr Gly Tyr Thr Tyr Tyr Ala Asp
65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
85 90 95

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Asp Thr Tyr Leu His Phe Asp Tyr Trp Gly Gln Gly
115 120 125

Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
130 135 140

Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu
145 150 155 160

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
165 170 175

Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
180 185 190

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
195 200 205

Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
210 215 220

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

Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro
245 250 255

Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser
260 265 270

Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp
275 280 285

Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr
290 295 300

Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val
305 310 315 320

Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu
325 330 335

Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg
340 345 350

Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val
355 360 365

Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr
370 375 380

Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr
385 390 395 400

Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu
405 410 415

Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys
420 425 430

Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu
435 440 445

Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly
450 455 460

Lys
465

<210> 558
<211> 462
<212> PRT
<213> 智人

<400> 558

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Arg Ser His Trp Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Asn Ile Asn Tyr Asp Gly Ser Ser Thr Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Asp Thr Tyr Leu His Phe Asp Tyr Trp Gly Gln
115 120 125

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

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
145 150 155 160

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
165 170 175

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
180 185 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
195 200 205

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
210 215 220

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
225 230 235 240

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
245 250 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
260 265 270

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
275 280 285

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
290 295 300

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
305 310 315 320

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
325 330 335

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
340 345 350

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
355 360 365

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
370 375 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385 390 395 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
405 410 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
420 425 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
435 440 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 559
<211> 461
<212> PRT
<213> 智人

<400> 559

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe
35 40 45

Arg Ser His Trp Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Val Ile Thr Pro Tyr Gly Asp Thr Tyr Tyr Ala Asp
65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
85 90 95

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Asp Thr Tyr Leu His Phe Asp Tyr Trp Gly Gln Gly
115 120 125

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

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145 150 155 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
165 170 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
180 185 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
195 200 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
210 215 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225 230 235 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
245 250 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
260 265 270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
275 280 285

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
290 295 300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
305 310 315 320

Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
325 330 335

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
340 345 350

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

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
370 375 380

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
385 390 395 400

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
405 410 415

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
420 425 430

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
435 440 445

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 560
<211> 461
<212> PRT
<213> 智人

<400> 560

Met Ala Trp Val Trp Thr Leu Pro Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Val Gln Ala Gln Val Gln Leu Val 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 Thr Phe

5

35 40 45

Arg Ser His Trp Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Val Ile Thr Pro Tyr Gly Asp Thr Tyr Tyr Ala Asp
65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
85 90 95

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Asp Thr Tyr Leu His Phe Asp Tyr Trp Gly Gln Gly
115 120 125

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

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145 150 155 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
165 170 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
180 185 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
195 200 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro

210 215 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225 230 235 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
245 250 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
260 265 270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
275 280 285

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
290 295 300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
305 310 315 320

Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
325 330 335

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
340 345 350

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

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
370 375 380

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln

5

385 390 395 400

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
405 410 415

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
420 425 430

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
435 440 445

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 561
<211> 130
<212> PRT
<213> 智人

<400> 561

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val
20 25 30

Ala Pro Gly Gln Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly
35 40 45

Ser Phe Tyr Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val
50 55 60

Leu Val Ile Tyr Asp Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg
65 70 75 80

Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly
85 90 95

Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Ala Gly
100 105 110

Ser Ser Gly Ser Tyr Val Phe Gly Gly Arg Thr Lys Leu Thr Val Leu
115 120 125

Gly Gln
130

<210> 562
<211> 237
<212> PRT
<213> 智人

<400> 562

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
20 25 30

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
35 40 45

Val Gly Asp Ile Asn Asp Val Ser Trp Tyr Gln Gln His Pro Gly Lys
50 55 60

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val
65 70 75 80

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
85 90 95

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
100 105 110

Tyr Gly Glu Ser Leu Thr Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145 150 155 160

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
165 170 175

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
180 185 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
195 200 205

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
210 215 220

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230 235

<210> 563
<211> 234
<212> PRT

<213> 智人

<400> 563

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val
20 25 30

Ala Pro Gly Gln Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly
35 40 45

Ser Phe Tyr Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val
50 55 60

Leu Val Ile Tyr Asp Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg
65 70 75 80

Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly
85 90 95

Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Thr Gly
100 105 110

Val Glu Pro Asp Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
115 120 125

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
145 150 155 160

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
165 170 175

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
180 185 190

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
195 200 205

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
210 215 220

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230

<210> 564
<211> 237
<212> PRT
<213> 智人

<400> 564

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
20 25 30

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
35 40 45

Val Gly Asp Ile Asn Asp Val Ser Trp Tyr Gln Gln His Pro Gly Lys
50 55 60

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val

65 70 75 80

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
85 90 95

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser
100 105 110

Tyr Ala Gly Ser Tyr Leu Ser Glu Val Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145 150 155 160

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
165 170 175

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
180 185 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
195 200 205

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
210 215 220

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230 235

<210> 565

<211> 237
<212> PRT
<213> 智人

<400> 565

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
20 25 30

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
35 40 45

Val Gly Asp Ile Asn Asp Val Ser Trp Tyr Gln Gln His Pro Gly Lys
50 55 60

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val
65 70 75 80

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
85 90 95

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
100 105 110

Tyr Gly Glu Ser Leu Thr Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145 150 155 160

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
165 170 175

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
180 185 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
195 200 205

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
210 215 220

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230 235

<210> 566
<211> 237
<212> PRT
<213> 智人

<400> 566

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
20 25 30

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
35 40 45

Val Gly Asp Ile Asn Asp Val Ser Trp Tyr Gln Gln His Pro Gly Lys
50 55 60

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val
65 70 75 80

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
85 90 95

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
100 105 110

Tyr Gly Glu Ser Leu Thr Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145 150 155 160

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
165 170 175

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
180 185 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
195 200 205

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
210 215 220

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230 235

<210> 567
<211> 237
<212> PRT
<213> 智人

<400> 567

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
20 25 30

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
35 40 45

Val Gly Asp Ile Asn Asp Val Ser Trp Tyr Gln Gln His Pro Gly Lys
50 55 60

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val
65 70 75 80

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
85 90 95

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
100 105 110

Tyr Gly Glu Ser Leu Thr Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145 150 155 160

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
165 170 175

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
180 185 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
195 200 205

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
210 215 220

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230 235

<210> 568
<211> 237
<212> PRT
<213> 智人

<400> 568

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
20 25 30

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
35 40 45

Val Gly Asp Ile Asn Asp Val Ser Trp Tyr Gln Gln His Pro Gly Lys

50 55 60

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val
65 70 75 80

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
85 90 95

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
100 105 110

Tyr Gly Glu Ser Leu Thr Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145 150 155 160

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
165 170 175

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
180 185 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
195 200 205

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
210 215 220

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser

225 230 235

<210> 569
<211> 237
<212> PRT
<213> 智人

<400> 569

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
20 25 30

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
35 40 45

Val Gly Asp Ile Asn Asp Val Ser Trp Tyr Gln Gln His Pro Gly Lys
50 55 60

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val
65 70 75 80

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
85 90 95

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Thr
100 105 110

Tyr Asp Gly Pro Gly Leu Ser Glu Val Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145 150 155 160

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
165 170 175

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
180 185 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
195 200 205

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
210 215 220

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230 235

<210> 570
<211> 237
<212> PRT
<213> 智人

<400> 570

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
20 25 30

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
35 40 45

Val Gly Asp Ile Asn Asp Val Ser Trp Tyr Gln Gln His Pro Gly Lys
50 55 60

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val
65 70 75 80

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
85 90 95

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
100 105 110

Tyr Gly Glu Ser Leu Thr Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145 150 155 160

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
165 170 175

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
180 185 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
195 200 205

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
210 215 220

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230 235

<210> 571
<211> 237
<212> PRT
<213> 智人

<400> 571

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
20 25 30

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
35 40 45

Val Gly Asp Ile Asn Asp Val Ser Trp Tyr Gln Gln His Pro Gly Lys
50 55 60

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val
65 70 75 80

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
85 90 95

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Thr
100 105 110

Tyr Asp Gly Pro Gly Leu Ser Glu Val Phe Gly Gly Gly Thr Lys Leu
115 120 125

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

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145 150 155 160

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
165 170 175

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
180 185 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
195 200 205

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
210 215 220

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230 235

<210> 572
<211> 1410
<212> DNA
<213> 智人

<400> 572
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gtgcagctgg tcgagtctgg cggcggactg gtgcagcctg gcggcagcct gagactgagc 120

tgcgccgcca gcggcttcac cttcagcagc tacgtgatga actgggtgcg gcaggccct 180

ggcaagggcc tggagtgggt gtccttcatc agcggcgaca gcagcaacac ctactacgcc 240

gacagcgtga agggccggtt caccatcagc cgggacaaca gcaagaacac cctgtacctg 300

cagatgaaca gcctgcgggc cgaggacacc gccgtgtact actgcgcccg gaccttcatg 360

cacggccacc tgggcggagg actgagcatg gatttctggg gccagggcac cctggtcacc 420

gtctcctcag cttccaccaa gggcccatcc gtcttccccc tggcgccctg ctccaggagc 480

acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 540

acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta 600

cagtcctcag gactctactc cctcagcagc gtggtgacag tgccctccag caacttcggc 660

acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 720

gttgagcgca aatgttgtgt cgagtgccca ccgtgcccag caccacctgt ggcaggaccg 780

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 840

gtcacgtgcg tggtggtgga cgtgagccac gaagaccccg aggtccagtt caactggtac 900

gtggacggcg tggaggtgca taatgccaag acaaagccac gggaggagca gttcaacagc 960

acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 1020

tacaagtgca aggtctccaa caaaggcctc ccagccccca tcgagaaaac catctccaaa 1080

accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1140

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1200

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg 1260

gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1320

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1380

aagagcctct ccctgtctcc gggtaaatga 1410

〈210〉 573
〈211〉 1389
〈212〉 DNA
〈213〉 智人

<400> 573

atggcttggg tgtggacctt gccattcctg atggcagctg cccaaggtgt ccaggcccag 60

gtgcagctgg tcgagagcgg cggagggctg gtgcagcctg gcggcagcct gagactgagc 120

tgcgccgcca gcggcttcac cttcagaagc cactggctgt cctgggtgcg gcaggcccct 180

ggcaagggcc tggaatgggt gtccaacatc aactacgacg gcagcagcac ctactacgcc 240

gacagcgtga agggccggtt caccatcagc cgggacaaca gcaagaacac cctgtacctg 300

cagatgaaca gcctgcgggc cgaggacacc gccgtgtact actgcgccag ggacacctac 360

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ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 540

gctctgacca gcggcgtgca caccttccca gctgtcctac agtcctcagg actctactcc 600

ctcagcagcg tggtgacagt gccctccagc aacttcggca cccagaccta cacctgcaac 660

gtagatcaca agcccagcaa caccaaggtg gacaagacag ttgagcgcaa atgttgtgtc 720

gagtgcccac cgtgcccagc accacctgtg gcaggaccgt cagtcttcct cttccccca 780

aaacccaagg acaccctcat gatctcccgg acccctgagg tcacgtgcgt ggtggtggac 840

gtgagccacg aagaccccga ggtccagttc aactggtacg tggacggcgt ggaggtgcat 900

aatgccaaga caaagccacg ggaggagcag ttcaacagca cgttccgtgt ggtcagcgtc 960

ctcaccgttg tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac 1020

aaaggcctcc cagcccccat cgagaaaacc atctccaaaa ccaaagggca gccccgagaa 1080

ccacaggtgt acaccctgcc cccatcccgg gaggagatga ccaagaacca ggtcagcctg 1140

acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga gagcaatggg 1200

cagccggaga acaactacaa gaccacacct cccatgctgg actccgacgg ctccttcttc 1260

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tccgtgatgc atgaggctct gcacaaccac tacacgcaga agagcctctc cctgtctccg 1380

ggtaaatga 1389

<210> 574
<211> 1410
<212> DNA
<213> 智人

<400> 574
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gtgcagctgg tcgagtctgg cggcggactg gtgcagcctg gcggcagcct gagactgagc 120

tgcgccgcca gcggcttcac cttcagcagc tacgtgatga actgggtgcg gcaggccct 180

ggcaagggcc tggagtgggt gtccttcatc agcggcgaca gcagcaacac ctactacgcc 240

gacagcgtga agggccggtt caccatcagc cgggacaaca gcaagaacac cctgtacctg 300

cagatgaaca gcctgcgggc cgaggacacc gccgtgtact actgcgcccg gaccttcatg 360

cacggccacc tgggcggagg actgagcatg gatttctggg gccagggcac cctggtcacc 420

gtctcctcag cttccaccaa gggcccatcc gtcttccccc tggcgccctg ctccaggagc 480

acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 540

acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta 600

cagtcctcag gactctactc cctcagcagc gtggtgacag tgccctccag caacttcggc 660

acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 720

gttgagcgca aatgttgtgt cgagtgccca ccgtgcccag caccacctgt ggcaggaccg 780

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 840

gtcacgtgcg tggtggtgga cgtgagccac gaagaccccg aggtccagtt caactggtac 900

gtggacggcg tggaggtgca taatgccaag acaaagccac gggaggagca gttcaacagc 960

acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 1020

tacaagtgca aggtctccaa caaaggcctc ccagccccca tcgagaaaac catctccaaa 1080

accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1140

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1200

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<211> 714
<212> DNA
<213> 智人

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agctgcaccg gcaccagcag cgacgtgggc gacatcaacg acgtgagctg gtatcagcag 180

caccccggca aggcccccaa gctgatgatc tacgacgtga acaaccggcc cagcggcgtg 240

agcaaccggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctc 300

caggccgagg acgaggccga ctactactgc cagagctacg ccggcagcta cctgagcgag 360

gtgttcggcg gagggaccaa gcttaccgtc ctaggtcagc ccaaggctgc cccctcggtc 420

actctgttcc cgccctcctc tgaggagctt caagccaaca aggccacact ggtgtgtctc 480

ataagtgact tctacccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 540

aaggcgggag tggagacaac cacaccctcc aaacaaagca acaacaagta cgcggccagc 600

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 660

acgcatgaag ggagcaccgt ggaaaagaca gtggccccta cagaatgttc atag 714

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caccccggca aggcccccaa gctgatgatc tacgacgtga acaaccggcc cagcggcgtg 240

agcaaccggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctc 300

caggccgagg acgaggccga ctactactgc agcagctacg gcgagagcct gaccagctac 360

gtgtttggcg gcggaaccaa gcttaccgtc ctaggtcagc ccaaggctgc cccctcggtc 420

actctgttcc cgccctcctc tgaggagctt caagccaaca aggccacact ggtgtgtctc 480

ataagtgact tctacccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 540

aaggcgggag tggagacaac cacaccctcc aaacaaagca acaacaagta cgcggccagc 600

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 660

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<210> 588
<211> 714
<212> DNA
<213> 智人

<400> 588
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agctgcaccg gcaccagcag cgacgtgggc gacatcaacg acgtgagctg gtatcagcag 180

caccccggca aggcccccaa gctgatgatc tacgacgtga acaaccggcc cagcggcgtg 240

agcaaccggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctc 300

caggccgagg acgaggccga ctactactgc agcagctacg gcgagagcct gaccagctac 360

gtgtttggcg gcggaaccaa gcttaccgtc ctaggtcagc ccaaggctgc cccctcggtc 420

actctgttcc cgccctcctc tgaggagctt caagccaaca aggccacact ggtgtgtctc 480

ataagtgact tctacccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 540

aaggcgggag tggagacaac cacaccctcc aaacaaagca acaacaagta cgcggccagc 600

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 660

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agctgcaccg gcaccagcag cgacgtgggc gacatcaacg acgtgagctg gtatcagcag 180

caccccggca aggcccccaa gctgatgatc tacgacgtga acaaccggcc cagcggcgtg 240

agcaaccggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctc 300

caggccgagg acgaggccga ctactactgc agcagctacg gcgagagcct gaccagctac 360

gtgtttggcg gcggaaccaa gcttaccgtc ctaggtcagc ccaaggctgc cccctcggtc 420

actctgttcc cgccctcctc tgaggagctt caagccaaca aggccacact ggtgtgtctc 480

ataagtgact tctacccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 540

aaggcgggag tggagacaac cacaccctcc aaacaaagca acaacaagta cgcggccagc 600

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 660

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<210> 590
<211> 714
<212> DNA
<213> 智人

<400> 590
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agctgcaccg gcaccagcag cgacgtgggc gacatcaacg acgtgagctg gtatcagcag 180

caccccggca aggcccccaa gctgatgatc tacgacgtga acaaccggcc cagcggcgtg 240

agcaaccggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctc 300

caggccgagg acgaggccga ctactactgc agcagctacg gcgagagcct gaccagctac 360

gtgtttggcg gcggaaccaa gcttaccgtc ctaggtcagc ccaaggctgc cccctcggtc 420

actctgttcc cgccctcctc tgaggagctt caagccaaca aggccacact ggtgtgtctc 480

ataagtgact tctacccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 540

aaggcgggag tggagacaac cacaccctcc aaacaaagca acaacaagta cgcggccagc 600

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 660

acgcatgaag ggagcaccgt ggaaaagaca gtggccccta cagaatgttc atag 714

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<213> 智人

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gacatcgccc tgacccagcc cgccagcgtg agcggcagcc ctggccagag catcaccatc 120

agctgcaccg gcaccagcag cgacgtgggc gacatcaacg acgtgagctg gtatcagcag 180

caccccggca aggcccccaa gctgatgatc tacgacgtga acaaccggcc cagcggcgtg 240

agcaaccggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctc 300

caggccgagg acgaggccga ctactactgc agcacctacg acggccctgg cctgagcgag 360

gtgttcggcg agggaccaa gcttaccgtc ctaggtcagc ccaaggctgc cccctcggtc 420

actctgttcc cgccctcctc tgaggagctt caagccaaca aggccacact ggtgtgtctc 480

ataagtgact tctacccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 540

aaggcgggag tggagacaac cacaccctcc aaacaaagca acaacaagta cgcggccagc 600

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 660

acgcatgaag ggagcaccgt ggaaaagaca gtggccccta cagaatgttc atag 714

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<213> 智人

<400> 592
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gacatcgccc tgacccagcc cgccagcgtg agcggcagcc ctggccagag catcaccatc 120

agctgcaccg gcaccagcag cgacgtgggc gacatcaacg acgtgagctg gtatcagcag 180

caccccggca aggcccccaa gctgatgatc tacgacgtga acaaccggcc cagcggcgtg 240

agcaaccggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctc 300

caggccgagg acgaggccga ctactactgc agcacctacg acggccctgg cctgagcgag 360

gtgttcggcg agggaccaa gcttaccgtc ctaggtcagc ccaaggctgc cccctcggtc 420

actctgttcc cgccctcctc tgaggagctt caagccaaca aggccacact ggtgtgtctc 480

ataagtgact tctacccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 540

aaggcgggag tggagacaac cacaccctcc aaacaaagca acaacaagta cgcggccagc 600

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 660

acgcatgaag ggagcaccgt ggaaaagaca gtggccccta cagaatgttc atag 714

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agctgcaccg gcaccagcag cgacgtgggc gacatcaacg acgtgagctg gtatcagcag 180

caccccggca aggcccccaa gctgatgatc tacgacgtga acaaccggcc cagcggcgtg 240

agcaaccggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctc 300

caggccgagg acgaggccga ctactactgc agcacctacg acggccctgg cctgagcgag 360

gtgttcggcg gagggaccaa gcttaccgtc ctaggtcagc ccaaggctgc cccctcggtc 420

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ataagtgact tctacccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 540

aaggcgggag tggagacaac cacaccctcc aaacaaagca acaacaagta cgcggccagc 600

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 660

acgcatgaag ggagcaccgt ggaaaagaca gtggccccta cagaatgttc atag 714

<210> 594
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<400> 594

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20 25 30

Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
50 55 60

Pro Pro His His Pro Phe Glu Thr Lys Asp Val Ser Glu Tyr Ser Cys
65 70 75 80

Arg Glu Leu His Phe Thr Arg Tyr 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 Gly Lys Trp Trp Arg Pro Ser
115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
130 135 140

Gln Leu Leu Cys Pro Gly Gly Glu Ala Pro Arg Ala 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 Thr Glu Ala Ala Arg Pro Gln Lys Gly
180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Ser Ala Lys Ala Asn Gln Ala Glu
195 200 205

Leu Glu Asn Ala Tyr
210

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Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
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Gly Gly Gly

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<223> CDR

<400> 611

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1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Pro Phe Ser Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Asp Ser Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
50 55 60

Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala
65 70 75 80

Val Tyr Arg Cys Tyr Phe Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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<210> 612
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<400> 612

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

Ser Leu Arg Leu Ser Cys Val Gly Ser Gly Arg Thr Phe Ser Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Leu Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asp Thr Ala Ser
50 55 60

Asn Arg Gly Tyr Leu His Met Asn Asn Leu Thr Pro Glu Asp Thr Ala
65 70 75 80

Val Tyr Tyr Cys Ala Ala Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr

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85 90 95

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

Ser Leu Lys Leu Ser Cys Ala Leu Thr Gly Gly Ala Phe Thr Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Thr Pro Gly Arg Glu Arg Glu Phe Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
50 55 60

Asn Met Val Tyr Leu Arg Met Asn Ser Leu Ile Pro Glu Asp Ala Ala
65 70 75 80

Val Tyr Ser Cys Ala Ala Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Leu Val Thr Val Ser Ser
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Glu Ala Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Glu Ser Pro Phe Arg Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Thr Ser Gly Gln Glu Arg Glu Phe Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys
50 55 60

Asn Thr Val Trp Leu His Gly Ser Thr Leu Lys Pro Glu Asp Thr Ala
65 70 75 80

Val Tyr Tyr Cys Ala Ala Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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Ala Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Gly Gly Gly
1 5 10 15

Ser Leu Arg Leu Ala Cys Ala Ala Ser Glu Arg Ile Phe Asp Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Tyr Arg Gln Gly Pro Gly Asn Glu Arg Glu Leu Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Met Asp Tyr Thr Lys
50 55 60

Gln Thr Val Tyr Leu His Met Asn Ser Leu Arg Pro Glu Asp Thr Gly
65 70 75 80

Leu Tyr Tyr Cys Lys Ile Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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Asp Val Lys Phe Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Asn Phe Asp Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Ser Glu Lys Asp Lys
50 55 60

Asn Ser Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala
65 70 75 80

Leu Tyr Ile Cys Ala Gly Xaa Xaa Xaa Xaa Xaa Trp Gly Arg Gly Thr
85 90 95

Gln Val Thr Val Ser Ser

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1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Ser Thr Tyr Thr Xaa Xaa
20 25 30

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

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ala Arg Asp Ser Thr Lys
50 55 60

Asp Thr Phe Cys Leu Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Ala
65 70 75 80

Val Tyr Tyr Cys Tyr Ala Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ser Asp Xaa Xaa

20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Ala Pro Gly Lys Pro Arg Glu Gly Val
35 40 45

Ser Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Thr Asp Asn Ala Lys
50 55 60

Asn Thr Val His Leu Leu Met Asn Arg Val Asn Ala Glu Asp Thr Ala
65 70 75 80

Leu Tyr Tyr Cys Ala Val Xaa Xaa Xaa Xaa Xaa Trp Gly Arg Gly Thr
85 90 95

Arg Val Thr Val Ser Ser
100

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1 5 10 15

Ser Leu Arg Leu Ser Cys Gln Ala Ser Gly Asp Ile Ser Thr Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Tyr Arg Gln Val Pro Gly Lys Leu Arg Glu Phe Val
35 40 45

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

Arg Ala Ile Tyr Leu Gln Met Asn Asn Leu Lys Pro Asp Asp Thr Ala
65 70 75 80

Val Tyr Tyr Cys Asn Arg Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Pro
100

<210> 620
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<400> 620

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

Ser Leu Arg Leu Phe Cys Ala Val Pro Ser Phe Thr Ser Thr Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asn Ala Thr Lys
50 55 60

Asn Thr Leu Thr Leu Arg Met Asp Ser Leu Lys Pro Glu Asp Thr Ala
65 70 75 80

Val Tyr Tyr Cys Ala Ala Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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<400> 621

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

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

Xaa Xaa Xaa Trp Phe Arg Gln Ala Pro Gly Glu Lys Arg Glu Phe Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ala Arg Glu Asn Ala Gly
50 55 60

Asn Met Val Tyr Leu Gln Met Asn Asn Leu Lys Pro Asp Asp Thr Ala
65 70 75 80

Leu Tyr Thr Cys Ala Ala Xaa Xaa Xaa Xaa Xaa Trp Gly Arg Gly Thr
85 90 95

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

Ser Gln Thr Leu Ser Cys Ala Ala Ser Gly Arg Thr Asn Ser Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Val Phe Leu

35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys
50 55 60

Asn Met Met Tyr Leu Gln Met Asn Asn Leu Lys Pro Gln Asp Thr Ala
65 70 75 80

Val Tyr Tyr Cys Ala Ala Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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Ala Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Val Ser Gly Leu Thr Ser Ser Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Thr Pro Trp Gln Glu Arg Asp Phe Val
35 40 45

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

Asp Thr Val Leu Leu Glu Met Asn Phe Leu Lys Pro Glu Asp Thr Ala
65 70 75 80

Ile Tyr Tyr Cys Ala Ala Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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Ala Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Ala
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Thr Arg Thr Leu Asp Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Ala Pro Gly Arg Asp Arg Glu Phe Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Val Ser Arg Asp Ser Ala Glu
50 55 60

Asn Thr Val Ala Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala
65 70 75 80

Val Tyr Tyr Cys Ala Ala Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Arg Val Thr Val Ser Ser
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<400> 625

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

Ser Leu Arg Leu Ser Cys Thr Val Ser Arg Leu Thr Ala His Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ala Val
35 40 45

Ser Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asp Tyr Ala Gly
50 55 60

Asn Thr Ala Phe Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Gly
65 70 75 80

Val Tyr Tyr Cys Ala Thr Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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<400> 626

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

Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Arg Asn Phe Val Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Phe Arg Arg Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Val Ser Arg Asp Asn Gly Lys

50 55 60

Asn Thr Ala Tyr Leu Arg Met Asn Ser Leu Lys Pro Glu Asp Thr Ala
65 70 75 80

Asp Tyr Tyr Cys Ala Val Xaa Xaa Xaa Xaa Xaa Leu Gly Ser Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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<400> 627

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

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

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

Ser Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
50 55 60

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala
65 70 75 80

Val Tyr Tyr Cys Val Lys Xaa Xaa Xaa Xaa Xaa Gly Ser Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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<400> 628

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

Ser Leu Arg Leu Ser Cys Val Cys Val Ser Ser Gly Cys Thr Xaa Xaa
20 25 30

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

Ser Xaa Xaa Xaa Xaa Xaa Arg Phe Lys Ile Ser Arg Asp Asn Ala Lys
50 55 60

Lys Thr Leu Tyr Leu Gln Met Asn Ser Leu Gly Pro Glu Asp Thr Ala
65 70 75 80

Met Tyr Tyr Cys Gln Arg Xaa Xaa Xaa Xaa Xaa Arg Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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<400> 629

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

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

Xaa Xaa Xaa Trp Val Arg His Thr Pro Gly Lys Ala Glu Glu Trp Val
35 40 45

Ser Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
50 55 60

Asn Thr Leu Tyr Leu Glu Met Asn Ser Leu Ser Pro Glu Asp Thr Ala
65 70 75 80

Met Tyr Tyr Cys Gly Arg Xaa Xaa Xaa Xaa Xaa Arg Ser Lys Gly Ile
85 90 95

Gln Val Thr Val Ser Ser
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Ala Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Xaa Xaa Xaa Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Xaa Xaa Xaa Xaa Xaa Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
50 55 60

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

65 70 75 80

Val Tyr Tyr Cys Ala Ala Xaa Xaa Xaa Xaa Xaa Arg Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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<400> 631

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Asp Xaa Xaa
20 25 30

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

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

Asn Met Leu Tyr Leu His Leu Asn Asn Leu Lys Ser Glu Asp Thr Ala
65 70 75 80

Val Tyr Tyr Cys Arg Arg Xaa Xaa Xaa Xaa Xaa Leu Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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<400> 632

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

Ser Leu Arg Leu Ser Cys Val Cys Val Ser Ser Gly Cys Thr Xaa Xaa
20 25 30

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

Ser Xaa Xaa Xaa Xaa Xaa Arg Phe Lys Ile Ser Arg Asp Asn Ala Lys
50 55 60

Lys Thr Leu Tyr Leu Gln Met Asn Ser Leu Gly Pro Glu Asp Thr Ala
65 70 75 80

Met Tyr Tyr Cys Gln Arg Xaa Xaa Xaa Xaa Xaa Arg Gly Gln Gly Thr
85 90 95

Gln Val Thr Val Ser Ser
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<400> 633

Gln Val Gln Arg Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

<210> 634
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<400> 634

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

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

<210> 635
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<400> 635

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

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

<210> 636
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<400> 636

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

Ser Leu Gly Leu Ser Cys Val Ala Ser Gly Arg Asp Phe Val
20 25 30

<210> 637
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<400> 637

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

Ser Leu Arg Leu Ser Cys Glu Val Leu Gly Arg Thr Ala Gly
20 25 30

<210> 638
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<400> 638

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Trp Val Gln Pro Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Thr Ile Leu Ser
20 25 30

<210> 639
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<212> PRT
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<400> 639

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

Ser Leu Asn Leu Ser Cys Val Ala Ser Gly Asn Thr Phe Asn
20 25 30

<210> 640
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<212> PRT
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<400> 640

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

Ser Leu Gln Leu Ser Cys Ser Ala Pro Gly Phe Thr Leu Asp
20 25 30

<210> 641

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<400> 641

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

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

<210> 642
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<400> 642

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

Ser Cys Ala Ala Ser Gly
20

<210> 643
<211> 22
<212> PRT
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<220>
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<400> 643

Val Asp Ser Gly Gly Gly Leu Val Gln Ala Gly Asp Ser Leu Lys Leu
1 5 10 15

Ser Cys Ala Leu Thr Gly
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<210> 644
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<400> 644

Val Asp Ser Gly Gly Gly Leu Val Gln Ala Gly Asp Ser Leu Arg Leu
1 5 10 15

Ser Cys Ala Ala Ser Gly
20

<210> 645
<211> 22
<212> PRT
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<400> 645

Val Asp Ser Gly Gly Gly Leu Val Glu Ala Gly Gly Ser Leu Arg Leu
1 5 10 15

Ser Cys Gln Val Ser Glu
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<400> 646

Gln Asp Ser Gly Gly Gly Ser Val Gln Ala Gly Gly Ser Leu Lys Leu
1 5 10 15

Ser Cys Ala Ala Ser Gly
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<210> 647
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<400> 647

Val Gln Ser Gly Gly Arg Leu Val Gln Ala Gly Asp Ser Leu Arg Leu
1 5 10 15

Ser Cys Ala Ala Ser Glu
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<210> 648
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<212> PRT
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<220>
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<400> 648

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

Ser Cys Ala Ser Ser Thr
20

<210> 649
<211> 22
<212> PRT
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<220>
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<400> 649

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

Ser Cys Val Ala Ser Gly
20

<210> 650
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<220>
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<400> 650

Gln Ala Ser Gly Gly Gly Leu Val Gln Ala Gly Gly Ser Leu Arg Leu
1 5 10 15

Ser Cys Ser Ala Ser Val

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<212> PRT
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<400> 651

Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val Ala
1 5 10

<210> 652
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<212> PRT
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<220>
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<400> 652

Trp Phe Arg Gln Thr Pro Gly Arg Glu Arg Glu Phe Val Ala
1 5 10

<210> 653
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<212> PRT
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<220>
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<400> 653

Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Met Val Ala
1 5 10

<210> 654
<211> 14
<212> PRT
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<400> 654

Trp Tyr Arg Gln Gly Pro Gly Lys Gln Arg Glu Leu Val Ala
1 5 10

<210> 655
<211> 14
<212> PRT
<213> 人工序列

<220>
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<400> 655

Trp Ile Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val Ser
1 5 10

<210> 656
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW2 序列

<400> 656

Trp Phe Arg Glu Ala Pro Gly Lys Glu Arg Glu Gly Ile Ser
1 5 10

<210> 657

<211> 14
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW2 序列

<400> 657

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

<210> 658
<211> 14
<212> PRT
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<220>
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<400> 658

Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Glu Val Ser
1 5 10

<210> 659
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW2 序列

<400> 659

Trp Phe Arg Gln Pro Pro Gly Lys Val Arg Glu Phe Val Gly
1 5 10

<210> 660
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<220>
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<400> 660

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Arg Cys Tyr Phe
20 25 30

<210> 661
<211> 32
<212> PRT
<213> 人工序列

<220>
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<400> 661

Arg Phe Ala Ile Ser Arg Asp Asn Asn Lys Asn Thr Gly Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Glu Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 662
<211> 32
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<220>
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<400> 662

Arg Phe Thr Val Ala Arg Asn Asn Ala Lys Asn Thr Val Asn Leu Glu

1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 663
<211> 32
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<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW3 序列

<400> 663

Arg Phe Thr Ile Ser Arg Asp Ile Ala Lys Asn Thr Val Asp Leu Leu
1 5 10 15

Met Asn Asn Leu Glu Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 664
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<212> PRT
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<220>
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<400> 664

Arg Leu Thr Ile Ser Arg Asp Asn Ala Val Asp Thr Met Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 665

<211> 32
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW3 序列

<400> 665

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln
1 5 10 15

Met Asp Asn Val Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ala Ala
20 25 30

<210> 666
<211> 32
<212> PRT
<213> 人工序列

<220>
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<400> 666

Arg Phe Thr Ile Ser Lys Asp Ser Gly Lys Asn Thr Val Tyr Leu Gln
1 5 10 15

Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Thr
20 25 30

<210> 667
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW3 序列

<400> 667

Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Met Met Tyr Leu Gln
1 5 10 15

Met Asn Asn Leu Lys Pro Gln Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 668
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW3 序列

<400> 668

Arg Phe Thr Ile Ser Arg Glu Asn Asp Lys Ser Thr Val Tyr Leu Gln
1 5 10 15

Leu Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 669
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW3 序列

<400> 669

Arg Phe Thr Ile Ser Arg Asp Tyr Ala Gly Asn Thr Ala Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr Tyr Cys Ala Thr
20 25 30

<210> 670
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW4 序列

<400> 670

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 671
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW4 序列

<400> 671

Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 672
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW4 序列

<400> 672

Arg Gly Gln Gly Thr Arg Val Thr Val Ser Ser
1 5 10

<210> 673

<211> 11
<212> PRT
<213> 人工序列

<220>
<223> KERE 類別奈米抗體 FW4 序列

<400> 673

Trp Gly Leu Gly Thr Gln Val Thr Ile Ser Ser
1 5 10

<210> 674
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW1 序列

<400> 674

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

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

<210> 675
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW1 序列

<400> 675

Glu Val His Leu Val Glu Ser Gly Gly Gly Leu Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Phe Gly Phe Ile Phe Lys
20 25 30

<210> 676
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW1 序列

<400> 676

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

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

<210> 677
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW1 序列

<400> 677

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

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

<210> 678
<211> 30
<212> PRT

<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW1 序列

<400> 678

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

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

<210> 679
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW1 序列

<400> 679

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

Ser Cys Ala Ala Ser Gly
20

<210> 680
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW1 序列

<400> 680

Glu Glu Ser Gly Gly Gly Leu Ala Gln Pro Gly Gly Ser Leu Arg Leu

1 5 10 15

Ser Cys Val Ala Ser Gly
20

<210> 681
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW1 序列

<400> 681

Val Glu Ser Gly Gly Gly Leu Ala Leu Pro Gly Gly Ser Leu Thr Leu
1 5 10 15

Ser Cys Val Phe Ser Gly
20

<210> 682
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW2 序列

<400> 682

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

<210> 683
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW2 序列

<400> 683

Trp Val Arg Arg Pro Pro Gly Lys Gly Leu Glu Trp Val Ser
1 5 10

<210> 684
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW2 序列

<400> 684

Trp Val Arg Gln Ala Pro Gly Met Gly Leu Glu Trp Val Ser
1 5 10

<210> 685
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW2 序列

<400> 685

Trp Val Arg Gln Ala Pro Gly Lys Glu Pro Glu Trp Val Ser
1 5 10

<210> 686
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW2 序列

<400> 686

Trp Val Arg Gln Ala Pro Gly Lys Asp Gln Glu Trp Val Ser
1 5 10

<210> 687
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW2 序列

<400> 687

Trp Val Arg Gln Ala Pro Gly Lys Ala Glu Glu Trp Val Ser
1 5 10

<210> 688
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW2 序列

<400> 688

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
1 5 10

<210> 689
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW2 序列

<400> 689

Trp Val Arg Gln Ala Pro Gly Arg Ala Thr Glu Trp Val Ser
1 5 10

<210> 690
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW3 序列

<400> 690

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Val Lys
20 25 30

<210> 691
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW3 序列

<400> 691

Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asp Ser Leu Ile Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Arg
20 25 30

<210> 692
<211> 32
<212> PRT

<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW3 序列

<400> 692

Arg Phe Thr Ser Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Asp Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Arg
20 25 30

<210> 693
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW3 序列

<400> 693

Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Gly Pro Glu Asp Thr Ala Met Tyr Tyr Cys Gln Arg
20 25 30

<210> 694
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW3 序列

<400> 694

Arg Phe Thr Ala Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln

1 5 10 15

Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Arg Tyr Tyr Cys Ala Arg
20 25 30

<210> 695
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW3 序列

<400> 695

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asp Asp Leu Gln Ser Glu Asp Thr Ala Met Tyr Tyr Cys Gly Arg
20 25 30

<210> 696
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW4 序列

<400> 696

Gly Ser Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 697
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW4 序列

<400> 697

Leu Arg Gly Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 698
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW4 序列

<400> 698

Arg Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 699
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW4 序列

<400> 699

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

<210> 700
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW4 序列

<400> 700

Trp Gly Lys Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 701
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> GLEW 類別奈米抗體 FW4 序列

<400> 701

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 702
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW1 序列

<400> 702

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

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

<210> 703
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW1 序列

<400> 703

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

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

<210> 704
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW1 序列

<400> 704

Glu Val His Leu Val Glu Ser Gly Gly Gly Leu Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Phe Gly Phe Ile Phe Lys
20 25 30

<210> 705
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW1 序列

<400> 705

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Arg Thr Ile Val Ser
20 25 30

<210> 706
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW1序列

<400> 706

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Arg Ile Phe Ser
20 25 30

<210> 707
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW1序列

<400> 707

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

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

<210> 708
<211> 30
<212> PRT

<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW1序列

<400> 708

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

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

<210> 709
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW1序列

<400> 709

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

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

<210> 710
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW1序列

<400> 710

Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly Ser Leu Arg Leu

1 5 10 15

Ser Cys Ala Ala Ser Gly
20

<210> 711
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW1序列

<400> 711

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

Ser Cys Ala Ala Ser Arg
20

<210> 712
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW2序列

<400> 712

Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val Ala
1 5 10

<210> 713
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW2序列

<400> 713

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

<210> 714
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW2序列

<400> 714

Trp Val Arg Arg Pro Pro Gly Lys Gly Leu Glu Trp Val Ser
1 5 10

<210> 715
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW2序列

<400> 715

Trp Ile Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val Ser
1 5 10

<210> 716
<211> 14
<212> PRT
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<220>
<223> P,R,S 103類別奈米抗體FW2序列

<400> 716

Trp Val Arg Gln Tyr Pro Gly Lys Glu Pro Glu Trp Val Ser
1 5 10

<210> 717
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW2 序列

<400> 717

Trp Phe Arg Gln Pro Pro Gly Lys Glu His Glu Phe Val Ala
1 5 10

<210> 718
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW2 序列

<400> 718

Trp Tyr Arg Gln Ala Pro Gly Lys Arg Thr Glu Leu Val Ala
1 5 10

<210> 719
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW2 序列

<400> 719

Trp Leu Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val Ser
1 5 10

<210> 720
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW2序列

<400> 720

Trp Leu Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 721
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW2序列

<400> 721

Trp Val Arg Gln Ala Pro Gly Lys Ala Glu Glu Phe Val Ser
1 5 10

<210> 722
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103類別奈米抗體FW3序列

<400> 722

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln

1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 723
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW3 序列

<400> 723

Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asp Ser Leu Ile Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Arg
20 25 30

<210> 724
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW3 序列

<400> 724

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Glu Met Tyr Leu Gln
1 5 10 15

Met Asn Asn Leu Lys Thr Glu Asp Thr Gly Val Tyr Trp Cys Gly Ala
20 25 30

<210> 725

<211> 32
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW3 序列

<400> 725

Arg Phe Thr Ile Ser Ser Asp Ser Asn Arg Asn Met Ile Tyr Leu Gln
1 5 10 15

Met Asn Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 726
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW3 序列

<400> 726

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Met Leu Tyr Leu His
1 5 10 15

Leu Asn Asn Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys Arg Arg
20 25 30

<210> 727
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW3 序列

<400> 727

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

Leu Asn Ser Leu Asn Pro Glu Asp Thr Ala Val Tyr Ser Cys Asn Leu
20 25 30

<210> 728
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW3 序列

<400> 728

Arg Phe Lys Ile Ser Arg Asp Asn Ala Lys Lys Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Gly Pro Glu Asp Thr Ala Met Tyr Tyr Cys Gln Arg
20 25 30

<210> 729
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> P,R,S 103 類別奈米抗體 FW3 序列

<400> 729

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

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Asp Tyr Tyr Cys Ala Val
20 25 30

<210> 730
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW4 序列

<400> 730

Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 731
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW4 序列

<400> 731

Leu Arg Gly Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 732
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW4 序列

<400> 732

Gly Asn Lys Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 733

<211> 11
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW4 序列

<400> 733

Ser Ser Pro Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 734
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW4 序列

<400> 734

Ser Ser Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 735
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> P, R, S 103 類別奈米抗體 FW4 序列

<400> 735

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

<210> 736
<211> 30
<212> PRT

<213> 人工序列

<220>
<223> FR1 序列

<400> 736

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

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

<210> 737
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> FR1 序列

<400> 737

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

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

<210> 738
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> FR1 序列

<400> 738

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly

1 5 10 15

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

<210> 739
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> FR1 序列

<400> 739

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

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

<210> 740
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> FR1 序列

<400> 740

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

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

<210> 741

<211> 30
<212> PRT
<213> 人工序列

<220>
<223> FR1 序列

<400> 741

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

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

<210> 742
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> FR1 序列

<400> 742

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

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

<210> 743
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> FR1 序列

<400> 743

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

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

<210> 744
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> FR1 序列

<400> 744

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

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

<210> 745
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<220>
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<400> 745

Asp Asn Val Met Gly
1 5

<210> 746
<211> 5
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<213> 人工序列

<220>
<223> CDR 序列

<400> 746

Ile Tyr Asn Met Asp
1 5

<210> 747
<211> 5
<212> PRT
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<220>
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<400> 747

Arg Phe Asp Met Ser
1 5

<210> 748
<211> 5
<212> PRT
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<220>
<223> CDR 序列

<400> 748

Ser Tyr Phe Met Gly
1 5

<210> 749
<211> 5
<212> PRT
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<220>
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<400> 749

Ile Tyr Asn Met Asp
1 5

<210> 750
<211> 5
<212> PRT
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<220>
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<400> 750

Arg Tyr Val Thr Gly
1 5

<210> 751
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<212> PRT
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<220>
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<400> 751

Ser Phe Val Ile Gly
1 5

<210> 752
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<212> PRT
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<220>
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<400> 752

Gln Tyr Thr Ile Thr
1 5

<210> 753
<211> 5
<212> PRT
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<220>
<223> CDR 序列

<400> 753

Ile Tyr Asn Met Asp
1 5

<210> 754
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> FR2 序列

<400> 754

Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val Ala
1 5 10

<210> 755
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> FR2 序列

<400> 755

Trp Phe Arg Gln Thr Pro Gly Lys Glu Arg Glu Leu Ile Ala
1 5 10

<210> 756
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> FR2 序列

<400> 756

Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Phe Ile Ala
1 5 10

<210> 757
<211> 14
<212> PRT
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<220>
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<400> 757

Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Val Val Ala
1 5 10

<210> 758
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<213> 人工序列

<220>
<223> FR2 序列

<400> 758

Trp Phe Leu Gln Ala Pro Gly Lys Glu Arg Glu Leu Ile Ala

1 5 10

<210> 759
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> FR2 序列

<400> 759

Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Val Val Ala
1 5 10

<210> 760
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<220>
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<400> 760

Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Val Val Ala
1 5 10

<210> 761
<211> 14
<212> PRT
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<220>
<223> FR2 序列

<400> 761

Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val Ala
1 5 10

5

<210> 762
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> FR2 序列

<400> 762

Trp Phe Arg Gln Gly Ser Gly Lys Gly Arg Glu Leu Ile Ala
1 5 10

<210> 763
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 763

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

<210> 764
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 764

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

Gly

<210> 765
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 765

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

<210> 766
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 766

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

Gly

<210> 767
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 767

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

Gly

<210> 768
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 768

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

Gly

<210> 769
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 769

Ser Ile Thr Ser Gly Gly Ser Thr Tyr Tyr Glu Asp Ser Gly Lys Gly
1 5 10 15

<210> 770
<211> 17
<212> PRT

<213> 人工序列

<220>
<223> CDR 序列

<400> 770

Ala Val Ser Trp Ser Gly Ser Ser Glu Ser Val Ser Asn Ser Val Lys
1 5 10 15

Gly

<210> 771
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 771

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

Gly

<210> 772
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> FR3 序列

<400> 772

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln

1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn Leu
20 25 30

<210> 773
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> FR3 序列

<400> 773

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ser Val Tyr Ile Cys Thr Ala
20 25 30

<210> 774
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> FR3 序列

<400> 774

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Cys Pro
20 25 30

<210> 775

<211> 32
<212> PRT
<213> 人工序列

<220>
<223> FR3 序列

<400> 775

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 776
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> FR3 序列

<400> 776

Arg Phe Thr Ile Ser Arg Gly Asn Ala Lys Asn Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr His Cys Thr Ala
20 25 30

<210> 777
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> FR3 序列

<400> 777

Arg Phe Ala Ile Ser Arg Asp Asn Ala Lys Asn Ala Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Asn Leu Glu Asp Thr Gly Val Tyr Tyr Cys Ala Glu
20 25 30

<210> 778
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> FR3 序列

<400> 778

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Arg Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 779
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> FR3 序列

<400> 779

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Ala Tyr Leu Ala
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
20 25 30

<210> 780
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> FR3 序列

<400> 780

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Asn Val Tyr His Cys Ala Ala
20 25 30

<210> 781
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 781

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

<210> 782
<211> 10
<212> PRT
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<220>
<223> CDR 序列

<400> 782

Gly Asp Thr Gly Gly Ala Ala Tyr Gly Tyr

1 5 10

<210> 783
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 783

Leu Gly Ile Glu Tyr Ala
1 5

<210> 784
<211> 9
<212> PRT
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<220>
<223> CDR 序列

<400> 784

Ala Lys Gly Ile Gly Val Tyr Gly Tyr
1 5

<210> 785
<211> 10
<212> PRT
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<220>
<223> CDR 序列

<400> 785

Gly Val Thr Gly Gly Ala Ala Tyr Gly Tyr
1 5 10

<210> 786
<211> 9
<212> PRT
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<220>
<223> CDR 序列

<400> 786

Ala Glu Leu Pro Gly Thr Tyr Asp Tyr
1 5

<210> 787
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 787

Ala Glu Pro Ala Gly Val Tyr Asp Val
1 5

<210> 788
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 788

Asp Arg Arg Gly Leu Ala Ser Thr Arg Ala Ala Asp Tyr Asp Tyr
1 5 10 15

<210> 789

<211> 10
<212> PRT
<213> 人工序列

<220>
<223> CDR 序列

<400> 789

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

<210> 790
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> FR4 序列

<400> 790

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 791
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> FR4 序列

<400> 791

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 792
<211> 11
<212> PRT

<213> 人工序列

<220>
<223> FR4 序列

<400> 792

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 793
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> FR4 序列

<400> 793

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 794
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> FR4 序列

<400> 794

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 795
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> FR4 序列

<400> 795

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 796
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> FR4 序列

<400> 796

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 797
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> FR4 序列

<400> 797

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 798
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> FR4 序列

<400> 798

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 799
<211> 120
<212> PRT
<213> 人工序列

<220>
<223> 奈米抗體

<400> 799

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Asp Asn
20 25 30

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

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

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

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

Leu Gly Thr Ile Val Thr Gly Thr Trp Arg Ser Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 800
<211> 119
<212> PRT
<213> 人工序列

<220>
<223> 奈米抗體

<400> 800

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

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

Asn Met Asp Trp Phe Arg Gln Thr Pro Gly Lys Glu Arg Glu Leu Ile
35 40 45

Ala Arg Leu Trp Trp Arg Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ser Val Tyr Ile Cys
85 90 95

Thr Ala Gly Asp Thr Gly Gly Ala Ala Tyr Gly Tyr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser

<210> 801
<211> 114
<212> PRT
<213> 人工序列

<220>
<223> 奈米抗體

<400> 801

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

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

Asp Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Phe Ile
35 40 45

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

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

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

Pro Leu Gly Ile Glu Tyr Ala Trp Gly Gln Gly Thr Gln Val Thr Val
100 105 110

Ser Ser

<210> 802
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> 奈米抗體

<400> 802

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

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

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

Ala Thr Ile Arg Trp Ser Asp Gly Ser Thr Tyr Tyr Glu Asp Ser Val
50 55 60

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

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

Ala Ala Ala Lys Gly Ile Gly Val Tyr Gly Tyr Trp Gly Gln Gly Thr
100 105 110

Gln Val Thr Val Ser Ser
115

<210> 803

<211> 119
<212> PRT
<213> 人工序列

<220>
<223> 奈米抗體

<400> 803

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

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

Asn Met Asp Trp Phe Leu Gln Ala Pro Gly Lys Glu Arg Glu Leu Ile
35 40 45

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

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

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr His Cys
85 90 95

Thr Ala Gly Val Thr Gly Gly Ala Ala Tyr Gly Tyr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser
115

<210> 804
<211> 118
<212> PRT

<213> 人工序列

<220>
<223> 奈米抗體

<400> 804

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

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

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

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

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

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

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

Gln Val Thr Val Ser Ser
115

<210> 805
<211> 117
<212> PRT
<213> 人工序列

<220>
<223> 奈米抗體

<400> 805

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

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

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

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

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

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

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

Val Thr Val Ser Ser
115

<210> 806
<211> 124
<212> PRT
<213> 人工序列

<220>
<223> 奈米抗體

<400> 806

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

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

Thr Ile Thr Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Val Ser Trp Ser Gly Ser Ser Glu Ser Val Ser Asn Ser Val
50 55 60

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

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

Ala Ala Asp Arg Arg Gly Leu Ala Ser Thr Arg Ala Ala Asp Tyr Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 807
<211> 119
<212> PRT
<213> 人工序列

<220>
<223> 奈米抗體

<400> 807

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

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

Asn Met Asp Trp Phe Arg Gln Gly Ser Gly Lys Gly Arg Glu Leu Ile
35 40 45

Ala Arg Ile Trp Trp Arg Ser Gly Glu Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Asn Val Tyr His Cys
85 90 95

Ala Ala Gly Asp Thr Gly Gly Ala Ser Tyr Gly Tyr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser
115

<210> 808
<211> 213
<212> PRT
<213> 智人

<400> 808

Met Gln Leu Pro Leu Ala Leu Cys Leu Val Cys Leu Leu Val His Thr
1 5 10 15

Ala Phe Arg Val Val Glu Gly Gln Gly Trp Gln Ala Phe Lys Asn Asp
20 25 30

Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
50 55 60

Pro Pro His His Pro Phe Glu Thr Lys Asp Val Ser Glu Tyr Ser Cys
65 70 75 80

Arg Glu Leu His Phe Thr Arg Tyr 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 Gly Lys Trp Trp Arg Pro Ser
115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Thr Val
130 135 140

Gln Leu Leu Cys Pro Gly Gly Glu Ala Pro Arg Ala 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 Thr Glu Ala Ala Arg Pro Gln Lys Gly
180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Ser Ala Lys Ala Asn Gln Ala Glu
195 200 205

Leu Glu Asn Ala Tyr
210

<210> 809
<211> 213
<212> PRT
<213> 人工序列

<220>
<223> 重組硬化蛋白

<400> 809

Met Pro Leu Leu Leu Leu Leu Pro Leu Leu Trp Ala Gly Ala Leu Ala
1 5 10 15

His His His His His His His Gln Gly Trp Gln Ala Phe Lys Asn Asp
20 25 30

Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
50 55 60

Pro Pro His His Pro Phe Glu Thr Lys Asp Val Ser Glu Tyr Ser Cys
65 70 75 80

Arg Glu Leu His Phe Thr Arg Tyr 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 Gly Lys Trp Trp Arg Pro Ser
115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
130 135 140

Gln Leu Leu Cys Pro Gly Gly Glu Ala Pro Arg Ala 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 Thr Glu Ala Ala Arg Pro Gln Lys Gly
180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Ser Ala Lys Ala Asn Gln Ala Glu
195 200 205

Leu Glu Asn Ala Tyr
210

<210> 810
<211> 798
<212> DNA
<213> 智人

<400> 810
atgatggctc tgggcgcagc gggagctacc cgggtctttg tcgcgatggt agcggcggct 60

ctcggcggcc accctctgct gggagtgagc gccaccttga actcggttct caattccaac 120

gctatcaaga acctgccccc accgctgggc ggcgctgcgg ggcacccagg ctctgcagtc 180

agcgccgcgc cgggaatcct gtacccgggc gggaataagt accagaccat tgacaactac 240

cagccgtacc cgtgcgcaga ggacgaggag tgcggcactg atgagtactg cgctagtccc 300

acccgcggag gggacgcagg cgtgcaaatc tgtctcgcct gcaggaagcg ccgaaaacgc 360

tgcatgcgtc acgctatgtg ctgccccggg aattactgca aaaatggaat atgtgtgtct 420

tctgatcaaa atcatttccg aggagaaatt gaggaaacca tcactgaaag ctttggtaat 480

gatcatagca ccttggatgg gtattccaga agaaccacct tgtcttcaaa aatgtatcac 540

accaaaggac aagaaggttc tgtttgtctc aggtcatcag actgtgcctc aggattgtgt 600

tgtgatagac acttctggtc caagatctgt aaacctgtcc tgaaagaagg tcaagtgtgt 660

accaagcata ggagaaaagg ctctcatgga ctagaaatat tccagcgttg ttactgtgga 720

gaaggtctgt cttgccggat acagaaagat caccatcaag ccagtaattc ttctaggctt 780

cacacttgtc agagacac 798

<210> 811
<211> 266
<212> PRT
<213> 智人

<400> 811

Met Met Ala Leu Gly Ala Ala Gly Ala Thr Arg Val Phe Val Ala Met
1 5 10 15

Val Ala Ala Ala Leu Gly Gly His Pro Leu Leu Gly Val Ser Ala Thr
20 25 30

Leu Asn Ser Val Leu Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro Pro
35 40 45

Leu Gly Gly Ala Ala Gly His Pro Gly Ser Ala Val Ser Ala Ala Pro
50 55 60

Gly Ile Leu Tyr Pro Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn Tyr
65 70 75 80

Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Thr Asp Glu Tyr
85 90 95

Cys Ala Ser Pro Thr Arg Gly Gly Asp Ala Gly Val Gln Ile Cys Leu
100 105 110

Ala Cys Arg Lys Arg Arg Lys Arg Cys Met Arg His Ala Met Cys Cys
115 120 125

Pro Gly Asn Tyr Cys Lys Asn Gly Ile Cys Val Ser Ser Asp Gln Asn
130 135 140

His Phe Arg Gly Glu Ile Glu Glu Thr Ile Thr Glu Ser Phe Gly Asn
145 150 155 160

Asp His Ser Thr Leu Asp Gly Tyr Ser Arg Arg Thr Thr Leu Ser Ser
165 170 175

Lys Met Tyr His Thr Lys Gly Gln Glu Gly Ser Val Cys Leu Arg Ser
180 185 190

Ser Asp Cys Ala Ser Gly Leu Cys Cys Asp Arg His Phe Trp Ser Lys
195 200 205

Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys Thr Lys His Arg
210 215 220

Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Tyr Cys Gly
225 230 235 240

Glu Gly Leu Ser Cys Arg Ile Gln Lys Asp His His Gln Ala Ser Asn
245 250 255

Ser Ser Arg Leu His Thr Cys Gln Arg His
260 265

<210> 812
<211> 816
<212> DNA
<213> 小鼠

<400> 812
atgatggttg tgtgtgcagc ggcagctgtc cggttcttgg ccgtgtttac aatgatggct 60

ctctgcagcc tccctctgct aggagccagt gccaccttga actcagttct catcaattcc 120

aacgcgatca agaacctgcc cccaccgctg ggtggtgctg gggggcagcc gggctctgct 180

gtcagtgtgg cgccgggagt tctctatgag ggcgggaaca agtaccagac tcttgacaac 240

taccagccct acccttgcgc tgaagatgag gagtgcggct ctgacgagta ctgctccagc 300

cccagccgcg gggcagccgg cgtcggaggt gtacagatct gtctggcttg ccgaaagcgc 360

aggaagcgct gcatgaggca cgctatgtgc tgccccggga actactgcaa aaatggaata 420

tgcatgccct ctgaccacag ccattttcct cgaggggaga ttgaggaaag catcattgaa 480

aaccttggta atgaccacaa cgccgccgcg ggggatggat atcccagaag aaccacactg 540

acttcaaaaa tatatcacac caaaggacaa gaaggctccg tctgcctccg atcatcagac 600

tgtgccgcag ggctgtgttg tgcaagacac ttctggtcca agatctgtaa acctgtcctt 660

aaagaaggtc aggtgtgcac caagcacaaa cggaaaggct cccacgggct ggagatattc 720

cagcgctgtt actgcgggga aggcctggct tgcaggatac agaaagatca ccatcaagcc 780

agcaattctt ctaggctcca cacctgccag agacac 816

<210> 813

<211> 272
<212> PRT
<213> 小鼠

<400> 813

Met Met Val Val Cys Ala Ala Ala Ala Val Arg Phe Leu Ala Val Phe
1 5 10 15

Thr Met Met Ala Leu Cys Ser Leu Pro Leu Leu Gly Ala Ser Ala Thr
20 25 30

Leu Asn Ser Val Leu Ile Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro
35 40 45

Pro Leu Gly Gly Ala Gly Gly Gln Pro Gly Ser Ala Val Ser Val Ala
50 55 60

Pro Gly Val Leu Tyr Glu Gly Gly Asn Lys Tyr Gln Thr Leu Asp Asn
65 70 75 80

Tyr Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Ser Asp Glu
85 90 95

Tyr Cys Ser Ser Pro Ser Arg Gly Ala Ala Gly Val Gly Gly Val Gln
100 105 110

Ile Cys Leu Ala Cys Arg Lys Arg Arg Lys Arg Cys Met Arg His Ala
115 120 125

Met Cys Cys Pro Gly Asn Tyr Cys Lys Asn Gly Ile Cys Met Pro Ser
130 135 140

Asp His Ser His Phe Pro Arg Gly Glu Ile Glu Glu Ser Ile Ile Glu
145 150 155 160

Asn Leu Gly Asn Asp His Asn Ala Ala Ala Gly Asp Gly Tyr Pro Arg
165 170 175

Arg Thr Thr Leu Thr Ser Lys Ile Tyr His Thr Lys Gly Gln Glu Gly
180 185 190

Ser Val Cys Leu Arg Ser Ser Asp Cys Ala Ala Gly Leu Cys Cys Ala
195 200 205

Arg His Phe Trp Ser Lys Ile Cys Lys Pro Val Leu Lys Glu Gly Gln
210 215 220

Val Cys Thr Lys His Lys Arg Lys Gly Ser His Gly Leu Glu Ile Phe
225 230 235 240

Gln Arg Cys Tyr Cys Gly Glu Gly Leu Ala Cys Arg Ile Gln Lys Asp
245 250 255

His His Gln Ala Ser Asn Ser Ser Arg Leu His Thr Cys Gln Arg His
260 265 270

<210> 814
<211> 810
<212> DNA
<213> 玄鼠

<400> 814
atgacggttg tgcgtgcagt ggcagctgtc cggttcttgg tcgtgcttac aacgatggct 60

ctctgcagcc tccctccgct cggagtcagc gccactttga actcagttct catcaattcc 120

aacgcgatca agaacctgcc cccaccgctg ggtggtgctg gggggcagcc gggctctgct 180

gtcagcgtgg cgcccggagt cctctatgag ggcgggaaca agtaccagac tcttgacaac 240

taccagccct acccttgcgc ggaggatgag gagtgcggca ctgacgagta ctgctccagt 300

cccagccgcg gggcagccgg cgtgggaggt gtacaaatct gcctggcttg ccgaaagcgc 360

aggaaacgct gcatgaggca cgctatgtgc tgccccggga attactgcaa aaacggaata 420

tgcatgccct ctgaccacag ccatttacct cgaggggaaa tcgaggaagg catcattgaa 480

aaccttggca atgaccacgg tgccggggat ggatatccca gaagaaccac actgacttca 540

aaaatatatc acaccaaagg gcaagaaggc tctgtctgcc tccgatcatc agactgcgcc 600

acagggctgt gttgtgcaag acatttctgg tccaagatct gtaaacctgt ccttaaagaa 660

ggtcaggtat gcaccaagca cagaaggaaa ggctcccacg ggctggagat attccagcgc 720

tgttactgtg gggaaggtct ggcttgcagg atacagaaag atcaccatca aaccagcaat 780

tcttccaggc tccacacctg ccagagacac 810

<210> 815
<211> 270
<212> PRT
<213> 玄鼠

<400> 815

Met Thr Val Val Arg Ala Val Ala Ala Val Arg Phe Leu Val Val Leu
1 5 10 15

Thr Thr Met Ala Leu Cys Ser Leu Pro Pro Leu Gly Val Ser Ala Thr
20 25 30

Leu Asn Ser Val Leu Ile Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro
35 40 45

Pro Leu Gly Gly Ala Gly Gly Gln Pro Gly Ser Ala Val Ser Val Ala
50 55 60

Pro Gly Val Leu Tyr Glu Gly Gly Asn Lys Tyr Gln Thr Leu Asp Asn
65 70 75 80

Tyr Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Thr Asp Glu
85 90 95

Tyr Cys Ser Ser Pro Ser Arg Gly Ala Ala Gly Val Gly Gly Val Gln
100 105 110

Ile Cys Leu Ala Cys Arg Lys Arg Arg Lys Arg Cys Met Arg His Ala
115 120 125

Met Cys Cys Pro Gly Asn Tyr Cys Lys Asn Gly Ile Cys Met Pro Ser
130 135 140

Asp His Ser His Leu Pro Arg Gly Glu Ile Glu Glu Gly Ile Ile Glu
145 150 155 160

Asn Leu Gly Asn Asp His Gly Ala Gly Asp Gly Tyr Pro Arg Arg Thr
165 170 175

Thr Leu Thr Ser Lys Ile Tyr His Thr Lys Gly Gln Glu Gly Ser Val
180 185 190

Cys Leu Arg Ser Ser Asp Cys Ala Thr Gly Leu Cys Cys Ala Arg His
195 200 205

Phe Trp Ser Lys Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys
210 215 220

Thr Lys His Arg Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg
225 230 235 240

Cys Tyr Cys Gly Glu Gly Leu Ala Cys Arg Ile Gln Lys Asp His His
245 250 255

Gln Thr Ser Asn Ser Ser Arg Leu His Thr Cys Gln Arg His
260 265 270

<210> 816
<211> 798
<212> DNA
<213> 人工序列

<220>
<223> 食蟹獼猴 DKK-1

<220>
<221> CDS
<222> (1)..(798)

<400> 816
atg atg gct ctg ggc gca gca gga gct gcc cgg gtc ttg gtc gcg ctg 48
Met Met Ala Leu Gly Ala Ala Gly Ala Ala Arg Val Leu Val Ala Leu
1 5 10 15

gta gcg gcg gct ctt ggc ggc cac cct ctg ctg gga gtg agc gcc acc 96
Val Ala Ala Ala Leu Gly Gly His Pro Leu Leu Gly Val Ser Ala Thr
20 25 30

ttg aac tcg gtt ctc aat tcc aac gcg atc aag aac ctg ccc cca ccg 144
Leu Asn Ser Val Leu Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro Pro
35 40 45

ctg ggc ggc gct gcg ggg cac cca ggc tct gca gtc agc gcc gcg cca 192
Leu Gly Gly Ala Ala Gly His Pro Gly Ser Ala Val Ser Ala Ala Pro
50 55 60

gga att ctg tac ccg ggc ggg aat aag tac cag acc att gac aac tac 240
Gly Ile Leu Tyr Pro Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn Tyr
65 70 75 80

cag ccg tac cct tgc gca gag gat gag gag tgc ggc act gat gag tac 288
Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Thr Asp Glu Tyr

85 90 95

tgc gct agt ccc acc cgc gga ggg gac gcg ggc gtg caa atc tgt ctc 336
Cys Ala Ser Pro Thr Arg Gly Gly Asp Ala Gly Val Gln Ile Cys Leu
100 105 110

gcc tgc agg aag cgc cga aaa cgc tgc atg cgt cac gct atg tgc tgc 384
Ala Cys Arg Lys Arg Arg Lys Arg Cys Met Arg His Ala Met Cys Cys
115 120 125

ccc ggg aat tac tgc aaa aat gga ata tgt gtg tct tct gat caa aat 432
Pro Gly Asn Tyr Cys Lys Asn Gly Ile Cys Val Ser Ser Asp Gln Asn
130 135 140

aat ttc cga ggg gaa att gag gaa acc att act gaa agc ttt ggt aat 480
Asn Phe Arg Gly Glu Ile Glu Glu Thr Ile Thr Glu Ser Phe Gly Asn
145 150 155 160

gat cat agc act ttg gat ggg tat tcc aga aga aca aca ttg tct tca 528
Asp His Ser Thr Leu Asp Gly Tyr Ser Arg Arg Thr Thr Leu Ser Ser
165 170 175

aaa atg tat cac agc aaa gga caa gaa ggt tct gtg tgt ctc cgg tca 576
Lys Met Tyr His Ser Lys Gly Gln Glu Gly Ser Val Cys Leu Arg Ser
180 185 190

tca gac tgt gcc aca gga ctg tgt tgt gct aga cac ttc tgg tcc aag 624
Ser Asp Cys Ala Thr Gly Leu Cys Cys Ala Arg His Phe Trp Ser Lys
195 200 205

atc tgt aaa cct gtc ctc aaa gaa ggt caa gtg tgt acc aag cat aga 672
Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys Thr Lys His Arg
210 215 220

aga aaa ggc tct cat ggg cta gaa ata ttc cag cgt tgt tac tgc gga 720
Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Tyr Cys Gly
225 230 235 240

gaa ggt ctg tct tgc cgg ata cag aaa gat cac cat caa gcc agt aat 768
Glu Gly Leu Ser Cys Arg Ile Gln Lys Asp His His Gln Ala Ser Asn
245 250 255

tct tct agg ctt cac act tgt cag aga cac 798
Ser Ser Arg Leu His Thr Cys Gln Arg His

260 265

<210> 817
<211> 266
<212> PRT
<213> 人工序列

<220>
<223> 合成構築體

<400> 817

Met Met Ala Leu Gly Ala Ala Gly Ala Ala Arg Val Leu Val Ala Leu
1 5 10 15

Val Ala Ala Ala Leu Gly Gly His Pro Leu Leu Gly Val Ser Ala Thr
20 25 30

Leu Asn Ser Val Leu Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro Pro
35 40 45

Leu Gly Gly Ala Ala Gly His Pro Gly Ser Ala Val Ser Ala Ala Pro
50 55 60

Gly Ile Leu Tyr Pro Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn Tyr
65 70 75 80

Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Thr Asp Glu Tyr
85 90 95

Cys Ala Ser Pro Thr Arg Gly Gly Asp Ala Gly Val Gln Ile Cys Leu
100 105 110

Ala Cys Arg Lys Arg Arg Lys Arg Cys Met Arg His Ala Met Cys Cys
115 120 125

Pro Gly Asn Tyr Cys Lys Asn Gly Ile Cys Val Ser Ser Asp Gln Asn
130 135 140

Asn Phe Arg Gly Glu Ile Glu Glu Thr Ile Thr Glu Ser Phe Gly Asn
145 150 155 160

Asp His Ser Thr Leu Asp Gly Tyr Ser Arg Arg Thr Thr Leu Ser Ser
165 170 175

Lys Met Tyr His Ser Lys Gly Gln Glu Gly Ser Val Cys Leu Arg Ser
180 185 190

Ser Asp Cys Ala Thr Gly Leu Cys Cys Ala Arg His Phe Trp Ser Lys
195 200 205

Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys Thr Lys His Arg
210 215 220

Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Tyr Cys Gly
225 230 235 240

Glu Gly Leu Ser Cys Arg Ile Gln Lys Asp His His Gln Ala Ser Asn
245 250 255

Ser Ser Arg Leu His Thr Cys Gln Arg His
260 265

<210> 818
<211> 103
<212> PRT
<213> 智人

<220>

<221> MISC_FEATURE
<223> DKK-1 mAb 11H10Hu VH

<400> 818

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Trp Val Ser Ser Tyr
20 25 30

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

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

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

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

Gly Thr Lys Leu Glu Ile Lys
100

<210> 819
<211> 120
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10Hu VL CDR1

<400> 819

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

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

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

Ser Gly Ile Asn Trp Asn Ser Gly Ser Arg Gly Tyr Ser Asp Ser Val
50 55 60

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

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

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

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 820
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10Hu VL CDR2

<400> 820

Arg Ala Ser Gln Trp Val Ser Ser Tyr Leu Ala
1 5 10

<210> 821
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10Hu VL CDR3

<400> 821

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 822
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10Hu VH CDR1

<400> 822

Ala Trp Gln Glu Phe
1 5

<210> 823
<211> 5
<212> PRT
<213> 智人

<400> 823

Asn His Trp Ile His
1 5

<210> 824
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10Hu VH CDR2

<400> 824

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

Gly

<210> 825
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10Hu VH CDR3

<400> 825

Glu Arg Pro Val Ala Thr Gly Ala Phe Asp Ile
1 5 10

<210> 826
<211> 107
<212> PRT
<213> 褐鼠

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10大鼠VL

<400> 826

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

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

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

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

Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
65 70 75 80

Glu Asp Val Ala Thr Tyr Phe Cys Gln Gln Tyr Asn Asn Tyr Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 827
<211> 120
<212> PRT
<213> 褐鼠

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 11H10 大鼠 VH

<400> 827

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

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

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

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

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

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

Gly Val Leu Val Thr Val Ser Ser
115 120

<210> 828
<211> 11
<212> PRT
<213> 褐鼠

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 11H10大鼠VL CDR1

<400> 828

Leu Ala Ser Glu Asp Ile Tyr Ser Asp Leu Ala
1 5 10

<210> 829
<211> 7
<212> PRT
<213> 褐鼠

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10大鼠VL CDR2

<400> 829

Asn Ala Asn Ser Leu Gln Asn
1 5

<210> 830
<211> 9
<212> PRT
<213> 褐鼠

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10大鼠VL CDR3

<400> 830

Gln Gln Tyr Asn Asn Tyr Pro Pro Thr
1 5

<210> 831
<211> 5
<212> PRT
<213> 褐鼠

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10 大鼠 VH CDR1

<400> 831

Asp Tyr Ala Met Ala
1 5

<210> 832
<211> 17
<212> PRT
<213> 褐鼠

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10 大鼠 VH CDR2

<400> 832

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

Gly

<210> 833
<211> 11
<212> PRT
<213> 褐鼠

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 11H10 大鼠 VH CDR3

<400> 833

Gly Leu Gly Ile Ala Thr Asp Tyr Phe Asp Tyr
1 5 10

<210> 834
<211> 107
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.4.1 VL

<400> 834

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

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

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

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

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

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

Ser Phe Gly Gln Gly Thr Lys Leu Glu Phe Lys
100 105

<210> 835
<211> 124
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.4.1 VH

<400> 835

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

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

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

Gly Trp Ile Ser Ala Asp Asn Gly His Thr Asn Tyr Ala Gln Lys Leu
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 Asp Gly Glu Leu Leu Asn Tyr Tyr Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 836
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.4.1 VL CDR1

<400> 836

Arg Ala Ser Gln Gly Ile Arg Asp Asp Leu Gly
1 5 10

<210> 837
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.4.1 VL CDR2

<400> 837

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 838
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.4.1 VL CDR3

<400> 838

Leu Gln His Asn Ser Tyr Pro Cys Ser
1 5

<210> 839
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.4.1 VH CDR1

<400> 839

Ser Tyr Gly Ile Ser
1 5

<210> 840
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.4.1 VH CDR2

<400> 840

Trp Ile Ser Ala Asp Asn Gly His Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> 841
<211> 15
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.4.1 VH CDR3

<400> 841

Asp Gly Glu Leu Leu Asn Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 842
<211> 112
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.20.1 VL

<400> 842

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

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

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

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

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

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

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

<210> 843
<211> 119
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.20.1 VH

<400> 843

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

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

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

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

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

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

Ala Arg Asp Gln Trp Gly Gly Ser Pro Ala Gly Pro Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 844
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.20.1 VL CDR1

<400> 844

Lys Ser Ser Gln Ser Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Tyr
1 5 10 15

<210> 845
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.20.1 VL CDR2

<400> 845

Glu Val Ser Asn Arg Phe Ser
1 5

<210> 846
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.20.1 VL CDR3

<400> 846

Met Gln Ser Ile Gln Val Pro Trp Thr
1 5

<210> 847
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.20.1 VH CDR1

<400> 847

Ser Tyr Gly Met His
1 5

<210> 848
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.20.1 VH CDR2

<400> 848

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

Gly

<210> 849
<211> 10
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.20.1 VH CDR3

<400> 849

Asp Gln Trp Gly Gly Ser Pro Ala Gly Pro
1 5 10

<210> 850
<211> 108
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.37.1 VL

<400> 850

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

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

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

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 851
<211> 119
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.37.1 VH

<400> 851

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

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

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

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

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

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

Ala Arg Glu Leu Gly Ile Ala Ala Ser Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 852
<211> 12
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.37.1 VL CDR1

<400> 852

Arg Ala Ser Gln Ser Val Ser Ser Asn Tyr Leu Ala
1 5 10

<210> 853
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.37.1 VL CDR2

<400> 853

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 854
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.37.1 VL CDR3

<400> 854

Gln Gln Tyr Gly Ser Ser Pro Ile Thr
1 5

<210> 855
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.37.1 VH CDR1

<400> 855

Ser Tyr Gly Met His
1 5

<210> 856
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 2.37.1 VH CDR2

<400> 856

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

Gly

<210> 857
<211> 10
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.37.1 VH CDR3

<400> 857

Glu Leu Gly Ile Ala Ala Ser Phe Asp Tyr
1 5 10

<210> 858
<211> 112
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.40.1 VL

<400> 858

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

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

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

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

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

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

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

<210> 859
<211> 117
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.40.1 VH

<400> 859

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

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

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

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

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

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

Ala Arg Asp Leu Val Asp Thr Ala Met Pro Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 860
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.40.1 VL CDR1

<400> 860

Lys Ser Ser Gln Ser Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Tyr
1 5 10 15

<210> 861
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.40.1 VL CDR2

<400> 861

Glu Val Ser Asn Arg Phe Ser
1 5

<210> 862
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.40.1 VL CDR3

<400> 862

Met Gln Ser Ile Gln Val Pro Trp Thr
1 5

<210> 863
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.40.1 VH CDR1

<400> 863

Ser Tyr Gly Met His
1 5

<210> 864
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.40.1 VH CDR2

<400> 864

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

Gly

<210> 865
<211> 8
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.40.1 VH CDR3

<400> 865

Asp Leu Val Asp Thr Ala Met Pro
1 5

<210> 866
<211> 112
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 2.41.1 VL

<400> 866

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

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

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

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

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

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

Lys Gln Leu Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105 110

<210> 867
<211> 122
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.41.1 VH

<400> 867

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

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

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

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

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

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

Ala Arg Ala Gly Tyr Ser Leu Tyr Tyr Tyr Tyr Gly Met Asp Val Trp
100 105 110

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

<210> 868
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.41.1 VL CDR1

<400> 868

Lys Ser Ser Gln Ser Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Tyr
1 5 10 15

<210> 869
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.41.1 VL CDR2

<400> 869

Glu Val Ser Asn Arg Phe Ser
1 5

<210> 870
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.41.1 VL CDR3

<400> 870

Met Gln Ser Lys Gln Leu Pro Phe Thr
1 5

<210> 871
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 2.41.1 VH CDR1

<400> 871

Ser Tyr Gly Met His
1 5

<210> 872
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.41.1 VH CDR2

<400> 872

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

Gly

<210> 873
<211> 13
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.41.1 VH CDR3

<400> 873

Ala Gly Tyr Ser Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 874
<211> 113
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.47.1 VL

<400> 874

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Asp Gly Asp Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

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

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

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

Lys

<210> 875
<211> 127
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.47.1 VH

<400> 875

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

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

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

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

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

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

Cys Ala Arg Asp Arg Ala Tyr Gly Asp Tyr Gly Gly Asp Tyr Tyr Tyr
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 876
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.47.1 VL CDR1

<400> 876

Arg Ser Ser Gln Ser Leu Leu Asp Ser Asp Asp Gly Asp Thr Tyr Leu
1 5 10 15

Asp

<210> 877
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.47.1 VL CDR2

<400> 877

Thr Leu Ser Tyr Arg Ala Ser
1 5

<210> 878
<211> 14
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 2.47.1 VL CDR3

<400> 878

Met Gln Arg Ile Glu Phe Pro Met Gln Arg Ile Glu Phe Pro
1 5 10

<210> 879
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.47.1 VH CDR1

<400> 879

Ser Gly Gly Tyr Tyr Trp Ser
1 5

<210> 880
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.47.1 VH CDR2

<400> 880

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

<210> 881
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 2.47.1 VH CDR3

<400> 881

Asp Arg Ala Tyr Gly Asp Tyr Gly Gly Asp Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> 882
<211> 107
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.17.1 VL

<400> 882

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

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

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Ala Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asp Phe Pro Leu
85 90 95

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

<210> 883
<211> 118
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.17.1 VH

<400> 883

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

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

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

Gly Tyr Ile Tyr Tyr Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

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

Leu Val Thr Val Ser Ser
115

<210> 884
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.17.1 VL CDR1

<400> 884

Gln Ala Ser Gln Asp Ile Asn Asn Tyr Leu Asn
1 5 10

<210> 885
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.17.1 VL CDR2

<400> 885

Asp Ala Ser Asn Leu Glu Thr
1 5

<210> 886
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.17.1 VL CDR3

<400> 886

Gln Gln Tyr Asp Asp Phe Pro Leu Thr
1 5

<210> 887
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.17.1 VH CDR1

<400> 887

Ser Tyr Tyr Trp Ser
1 5

<210> 888
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.17.1 VH CDR2

<400> 888

Tyr Ile Tyr Tyr Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 889
<211> 10
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.17.1 VH CDR3

<400> 889

Tyr Asn Trp Asn Asn Asp Leu Phe Asp Tyr
1 5 10

<210> 890
<211> 107
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.23.1 VL

<400> 890

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

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

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Leu
85 90 95

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

<210> 891
<211> 126
<212> PRT
<213> 智人

<220>
<221> MISC FEATURE
<223> DKK-1 mAb 5.23.1 VH

<400> 891

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

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

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

Ala Val Ile Trp Cys Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Gly Gly Tyr Gly Ser Gly Ser Tyr Glu Asp Tyr Tyr Tyr Gly
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 892
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.23.1 VL CDR1

<400> 892

Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 893
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.23.1 VL CDR2

<400> 893

Asp Ala Ser Asn Leu Glu Thr
1 5

<210> 894
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.23.1 VL CDR3

<400> 894

Gln Gln Tyr Asp Asn Leu Pro Leu Thr
1 5

<210> 895
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.23.1 VH CDR1

<400> 895

Ser Tyr Gly Met His
1 5

<210> 896
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 5.23.1 VH CDR2

<400> 896

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

Gly

<210> 897
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.23.1 VH CDR3

<400> 897

Gly Gly Tyr Gly Ser Gly Ser Tyr Glu Asp Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> 898
<211> 107
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.25.1 VL

<400> 898

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 Gln Ala Ser Gln Asp Ile Ser Lys Asp
20 25 30

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

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Ile Ala Thr Phe Tyr Cys Gln Gln Tyr Asp His Leu Pro Ile
85 90 95

Ala Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 899
<211> 119
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.25.1 VH

<400> 899

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

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

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asp Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Phe
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 Thr Asp Tyr Phe Tyr Phe Gly Met Asp Val Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser
115

<210> 900
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAps 5.25.1 VL CDR1

<400> 900

Gln Ala Ser Gln Asp Ile Ser Lys Asp Leu Asn
1 5 10

<210> 901
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.25.1 VL CDR2

<400> 901

Asp Ala Ser Asn Leu Glu Thr
1 5

<210> 902
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.25.1 VL CDR3

<400> 902

Gln Gln Tyr Asp Asn Leu Pro Leu Thr
1 5

<210> 903
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.25.1 VH CDR1

<400> 903

Ser Tyr Gly Met His
1 5

<210> 904
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.25.1 VH CDR2

<400> 904

Trp Met Asp Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 905
<211> 10
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb VH CDR3

<400> 905

Thr Asp Tyr Phe Tyr Phe Gly Met Asp Val
1 5 10

<210> 906
<211> 107
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.31.1 VL

<400> 906

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

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

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

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

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

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Leu
85 90 95

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

<210> 907
<211> 125
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 5.31.1 VH

<400> 907

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

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

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

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

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

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

Ala Arg Gly Gly Gly Ala Val Ala Asp Tyr Asn Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 908
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 5.31.1 VL CDR1

<400> 908

Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 909
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.31.1 VL CDR2

<400> 909

Asp Ala Ser Asn Leu Glu Ala
1 5

<210> 910
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.31.1 VL CDR3

<400> 910

Gln Gln Tyr Asp Asn Leu Pro Leu Thr
1 5

<210> 911
<211> 5
<212> PRT
<213> 智人

<220>
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<223> DKK-1 mAb 5.31.1 VH CDR1

<400> 911

Ser Tyr Gly Met His
1 5

<210> 912
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.31.1 VH CDR2

<400> 912

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

Gly

<210> 913
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.31.1 VH CDR3

<400> 913

Gly Gly Gly Ala Val Ala Asp Tyr Asn Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 914
<211> 107
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.32.1 VL

<400> 914

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 Gln Ala Ser Gln Asp Ile Ser Lys Asp
20 25 30

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

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asp Leu Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 915
<211> 119
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.32.1 VH

<400> 915

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

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

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

Gly Trp Met Asn Pro Ser Ser Gly Tyr Thr Gly Tyr Ala Gln Asn Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Trp Asn Thr Ser Ile Ser Thr Val Tyr
65 70 75 80

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

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

Thr Thr Val Thr Val Ser Ser
115

<210> 916
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.32.1 VL CDR1

<400> 916

Gln Ala Ser Gln Asp Ile Ser Lys Asp Leu Asn
1 5 10

<210> 917
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.32.1 VL CDR2

<400> 917

Asp Ala Ser Asn Leu Glu Thr
1 5

<210> 918
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.32.1 VL CDR3

<400> 918

Gln Gln Tyr Asp Asp Leu Pro Ile Thr
1 5

<210> 919
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.32.1 VH CDR1

<400> 919

Ser Tyr Asp Ile Ser
1 5

<210> 920
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.32.1 VH CDR2

<400> 920

Trp Met Asn Pro Ser Ser Gly Tyr Thr Gly Tyr Ala Gln Asn Phe Gln
1 5 10 15

Gly

<210> 921
<211> 10
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.32.1 VH CDR3

<400> 921

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

<210> 922
<211> 107
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.40.1 VL

<400> 922

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

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

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

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Phe Pro Leu
85 90 95

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

<210> 923
<211> 118
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.40.1 VH

<400> 923

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

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

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

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

Ser Arg Val Thr Ile Ser Met Tyr Thr Ser Lys Thr Glu Phe Ser Leu
65 70 75 80

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

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

Leu Val Thr Val Ser Ser
115

<210> 924
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.40.1 VL CDR1

<400> 924

Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 925
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.40.1 VL CDR2

<400> 925

Asp Ala Ser Asn Leu Glu Thr
1 5

<210> 926
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.40.1 VL CDR3

<400> 926

Gln Gln Tyr Asp Asn Phe Pro Leu Thr
1 5

<210> 927
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.40.1 VH CDR1

<400> 927

Ser Tyr Tyr Trp Ser
1 5

<210> 928
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.40.1 VH CDR2

<400> 928

Tyr Val Tyr Tyr Ser Gly Ser Thr Ser Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 929
<211> 10
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.40.1 VH CDR3

<400> 929

Tyr Asn Trp Asn Asn Asp Leu Phe Asp Tyr
1 5 10

<210> 930
<211> 108
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.65.1 VL

<400> 930

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

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

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

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

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

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

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

<210> 931
<211> 120
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.65.1 VH

<400> 931

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

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

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

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

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

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

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

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 932
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.65.1 VL CDR1

<400> 932

Gly Gly Asn Asn Ile Gly Ser Lys Ser Val His
1 5 10

<210> 933
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.65.1 VL CDR2

<400> 933

Asp Asp Ser Asp Arg Pro Ser
1 5

<210> 934
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.65.1 VL CDR3

<400> 934

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

<210> 935
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.65.1 VH CDR1

<400> 935

Asn Tyr Ala Met Ser
1 5

<210> 936
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.65.1 VH CDR2

<400> 936

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

Gly

<210> 937
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.65.1 VH CDR3

<400> 937

Glu Phe Gly Glu Leu Glu Pro Arg Phe Asp Tyr
1 5 10

<210> 938
<211> 108
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.76.1 VL

<400> 938

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

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

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

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

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

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Asn Asp His
85 90 95

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

<210> 939
<211> 124
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.76.1 VH

<400> 939

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

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

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

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

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

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

Cys Ala Arg Glu Arg Ala Ile Ala Val Ala Ala Ile Val Phe Phe Asp
100 105 110

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

<210> 940
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.76.1 VL CDR1

<400> 940

Gly Gly Asn Asn Ile Gly Ser Glu Ser Val His
1 5 10

<210> 941
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 5.76.1 VL CDR2

<400> 941

Asp Asp Ser Asp Arg Pro Ser
1 5

<210> 942
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.76.1 VL CDR3

<400> 942

Gln Val Trp Asp Ser Ser Asn Asp His Val Val
1 5 10

<210> 943
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.76.1 VH CDR1

<400> 943

Ser Ser Asn Tyr Tyr Trp Gly
1 5

<210> 944
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.76.1 VH CDR2

<400> 944

Thr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Thr Pro Ser Leu Lys Ser
1 5 10 15

<210> 945
<211> 14
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.76.1 VH CDR3

<400> 945

Glu Arg Ala Ile Ala Val Ala Ala Ile Val Phe Phe Asp Tyr
1 5 10

<210> 946
<211> 103
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.77.1 VL

<400> 946

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

Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val His Trp Tyr Gln Gln
20 25 30

Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asp Ser Asp Arg
35 40 45

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

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

Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His Trp Val Phe Gly Gly
85 90 95

Gly Thr Lys Leu Thr Val Leu
100

<210> 947
<211> 123
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.77.1 VH

<400> 947

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

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

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Leu Asn Ser Asp Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile 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 Ser Ile Ala Ala Arg Arg Asp Tyr Asn Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Lys Val Thr Val Ser Ser
115 120

<210> 948
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.77.1 VL CDR1

<400> 948

Gly Gly Asn Asn Ile Gly Ser Lys Ser Val His
1 5 10

<210> 949
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.77.1 VL CDR2

<400> 949

Asp Asp Ser Asp Arg Pro Ser
1 5

<210> 950
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.77.1 VL CDR3

<400> 950

Gln Val Trp Asp Ser Ser Ser Asp His Trp Val
1 5 10

<210> 951
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.77.1 VH CDR1

<400> 951

Ser Tyr Asp Ile Asn
1 5

<210> 952
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.77.1 VH CDR2

<400> 952

Trp Met Asn Leu Asn Ser Asp Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 953
<211> 14
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.77.1 VH CDR3

<400> 953

Ile Ala Ala Arg Arg Asp Tyr Asn Tyr Tyr Gly Met Asp Val
1 5 10

<210> 954
<211> 107
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 5.78.1 VL

<400> 954

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

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

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

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Phe
85 90 95

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

<210> 955
<211> 125
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.78.1 VH

<400> 955

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

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

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

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

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

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

Ala Arg Glu Gly Ile Ala Val Ala Gly Asp Tyr Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 956
<211> 12
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.78.1 VL CDR1

<400> 956

Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 957
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.78.1 VL CDR2

<400> 957

Gly Ala Ser Gly Arg Ala Thr
1 5

<210> 958
<211> 8
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.78.1 VL CDR3

<400> 958

Gln Gln Tyr Gly Ser Ser Phe Thr
1 5

<210> 959
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 5.78.1 VH CDR1

<400> 959

Ser Tyr Gly Met His
1 5

<210> 960
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.78.1 VH CDR2

<400> 960

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

Gly

<210> 961
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.78.1 VH CDR3

<400> 961

Glu Gly Ile Ala Val Ala Gly Asp Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 962
<211> 112
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.80.1 VL

<400> 962

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

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

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

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

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asn Ser
85 90 95

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

<210> 963
<211> 116
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.80.1 VH

<400> 963

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

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

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

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

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

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

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

Thr Val Ser Ser
115

<210> 964
<211> 14
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.80.1 VL CDR1

<400> 964

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

<210> 965
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.80.1 VL CDR2

<400> 965

Asp Tyr Ser Asn Arg Pro Ser
1 5

<210> 966
<211> 12
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.80.1 VL CDR3

<400> 966

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

<210> 967
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.80.1 VH CDR1

<400> 967

Ser Tyr Trp Ile Gly
1 5

<210> 968
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.80.1 VH CDR2

<400> 968

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

Gly

<210> 969
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 5.80.1 VH CDR3

<400> 969

Gln Gly Glu Ser Phe Asp Tyr
1 5

<210> 970
<211> 110
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.85.1 VL

<400> 970

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

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

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Arg Thr Ala Pro Lys Leu
35 40 45

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

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

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

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

<210> 971
<211> 116
<212> PRT
<213> 智人

<220>
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<223> DKK-1 mAb 5.85.1 VH

<400> 971

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

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

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

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

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

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

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

Thr Val Ser Ser
115

<210> 972
<211> 14
<212> PRT
<213> 智人

<220>
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<223> DKK-1 mAb 5.85.1 VL CDR1

<400> 972

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

<210> 973
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.85.1 VL CDR2

<400> 973

Gly Asn Ser Asn Arg Pro Ser
1 5

<210> 974
<211> 10
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 5.85.1 VL CDR3

<400> 974

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

<210> 975
<211> 5
<212> PRT
<213> 智人

<220>
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<223> DKK-1 mAb 5.85.1 VH CDR1

<400> 975

Thr Tyr Trp Ile Gly
1 5

<210> 976
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.85.1 VH CDR2

<400> 976

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

Gly

<210> 977
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 5.85.1 VH CDR3

<400> 977

Gln Gly Ile Ala Phe Asp Tyr
1 5

<210> 978
<211> 112
<212> PRT
<213> 智人

<220>
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<223> DKK-1 mAb 6.37.5 VL

<400> 978

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Gly Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

Pro Gln Phe Leu Ile Tyr Glu Val Ser Asn Arg Phe Ser Arg Val Pro
50 55 60

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

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

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

<210> 979
<211> 114
<212> PRT
<213> 智人

<220>
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<223> DKK-1 mAb 6.37.5 VH

<400> 979

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

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

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

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

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

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

Ala Arg Glu Leu Arg Val Leu Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 980
<211> 16
<212> PRT
<213> 智人

<220>
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<223> DKK-1 mAb 6.37.5 VL CDR1

<400> 980

Lys Ser Gly Gln Ser Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Tyr
1 5 10 15

<210> 981
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.37.5 VL CDR2

<400> 981

Glu Val Ser Asn Arg Phe Ser
1 5

<210> 982
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.37.5 VL CDR3

<400> 982

Met Gln Ser Ile Gln Leu Pro Trp Thr
1 5

<210> 983
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.37.5 VH CDR1

<400> 983

Gly Tyr Gly Met His
1 5

<210> 984
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.37.5 VH CDR2

<400> 984

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

Gly

<210> 985
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DDK-1 mAb 6.37.5 VH CDR3

<400> 985

Glu Leu Arg Val Leu
1 5

<210> 986
<211> 112
<212> PRT
<213> 智人

<220>
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<223> DDK-1 mAb 6.116.6 VL

<400> 986

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Gly Gln Ser Leu Leu His Asn
20 25 30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

Pro Gln Phe Leu Ile Tyr Glu Val Ser Asn Arg Phe Ser Arg Val Pro
50 55 60

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

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

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

<210> 987
<211> 114
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DDK-1 mAb 6.116.6 VH

<400> 987

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

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

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

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

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

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

Ala Arg Glu Leu Arg Val Leu Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 988
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.116.6 VL CDR1

<400> 988

Lys Ser Gly Gln Ser Leu Leu His Asn Asp Gly Lys Thr Tyr Leu Tyr
1 5 10 15

<210> 989
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 6.116.6 VL CDR2

<400> 989

Glu Val Ser Asn Arg Phe Ser
1 5

<210> 990
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.116.6 VL CDR3

<400> 990

Met Gln Ser Ile Gln Leu Pro Trp Thr
1 5

<210> 991
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.116.6 VH CDR1

<400> 991

Gly Tyr Gly Met His
1 5

<210> 992
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.116.6 VH CDR2

<400> 992

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

Gly

<210> 993
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.116.6 VH CDR3

<400> 993

Glu Leu Arg Val Leu
1 5

<210> 994
<211> 112
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.139.5 VL

<400> 994

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

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

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

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

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

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

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

<210> 995
<211> 114
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.139.5 VH

<400> 995

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

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

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

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

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

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

Ala Arg Glu Leu Arg Val Leu Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 996
<211> 13
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.139.5 VL CDR1

<400> 996

Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asp Met His
1 5 10

<210> 997
<211> 12
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.139.5 VL CDR2

<400> 997

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

<210> 998
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.139.5 VL CDR3

<400> 998

Ala Thr Leu Ala Ala Ala Phe Asp Tyr
1 5

<210> 999
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.139.5 VH CDR1

<400> 999

Ser Tyr Gly Met His
1 5

<210> 1000
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.139.5 VH CDR2

<400> 1000

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

Gly

<210> 1001
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.139.5 VH CDR3

<400> 1001

Glu Leu Arg Val Leu
1 5

<210> 1002
<211> 107
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.147.4 VL

<400> 1002

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

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

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

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

Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp
65 70 75 80

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

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

<210> 1003
<211> 116
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 6.147.4 VH

<400> 1003

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

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

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

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

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

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

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

Thr Val Ser Ser
115

<210> 1004
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE

<223> DKK-1 mAb 6.147.4 VL CDR1

<400> 1004

Gly Gly Asn Asn Ile Gly Ser Lys Ser Val His
1 5 10

<210> 1005
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.147.4 VL CDR2

<400> 1005

Asp Asp Ser Asp Arg Pro Ser
1 5

<210> 1006
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.147.4 VL CDR3

<400> 1006

Gln Val Trp Asp Ser Ser Ser Asp His Val Val
1 5 10

<210> 1007
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.147.4 VH CDR1

<400> 1007

Arg Tyr Asp Met His
1 5

<210> 1008
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.147.4 VH CDR2

<400> 1008

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

Gly

<210> 1009
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> DKK-1 mAb 6.147.4 VH CDR3

<400> 1009

Leu Ala Ala Ala Phe Asp Tyr
1 5

<210> 1010
<211> 110
<212> PRT
<213> 智人

<400> 1010

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

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

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

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

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

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

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

<210> 1011
<211> 123
<212> PRT
<213> 智人

<400> 1011

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

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

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

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

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

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

Arg Ser Trp Gly Glu Gly Asn Tyr Tyr Phe Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 1012
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 19D11 VL CDR1

<400> 1012

Gly Gly Asp Asn Ile Gly Ser Ile Ser Val His
1 5 10

<210> 1013
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 19D11 VL CDR2

<400> 1013

Asp Asp Ser Asp Arg Pro Ser
1 5

<210> 1014
<211> 12
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 19D11 VL CDR3

<400> 1014

Gln Val Trp Asp Ser Ser Ile Asp His Pro Val Leu
1 5 10

<210> 1015
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 19D11 VH CDR1

<400> 1015

Ser Tyr Asp Met His
1 5

<210> 1016
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 19D11 VH CDR2

<400> 1016

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

<210> 1017
<211> 15
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 19D11 VH CDR3

<400> 1017

Ser Trp Gly Glu Gly Asn Tyr Tyr Phe Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 1018
<211> 111

<212> PRT
<213> 智人

<400> 1018

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

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

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

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

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

Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ile Ser
85 90 95

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

<210> 1019
<211> 118
<212> PRT
<213> 智人

<400> 1019

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

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

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

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

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

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

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

Met Val Thr Val Ser Ser
115

<210> 1020
<211> 14
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 20C3 VL CDR1

<400> 1020

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

<210> 1021
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 20C3 VL CDR2

<400> 1021

Glu Val Ser Tyr Arg Pro Ser
1 5

<210> 1022
<211> 10
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 20C3 VL CDR3

<400> 1022

Ser Ser Tyr Ala Ile Ser Ser Thr Leu Val
1 5 10

<210> 1023
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 20C3 VH CDR1

<400> 1023

Ser Tyr Tyr Trp Ser
1 5

<210> 1024
<211> 16
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 20C3 VH CDR2

<400> 1024

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

<210> 1025
<211> 10
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 20C3 VH CDR3

<400> 1025

Trp Gln Leu Ala His Asp Ala Phe Asp Ile
1 5 10

<210> 1026
<211> 114
<212> PRT
<213> 智人

<400> 1026

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly

1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

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

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

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

Arg Ile Glu Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys Arg

<210> 1027
<211> 120
<212> PRT
<213> 智人

<400> 1027

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

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

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

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

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

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

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

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 1028
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 27H6 VL CDR1

<400> 1028

Arg Ser Ser Gln Ser Leu Leu Asn Ser Val Asp Gly Ser Thr Asn Leu
1 5 10 15

Asp

<210> 1029
<211> 7
<212> PRT
<213> 智人

<220>
<221> MISC FEATURE
<223> 27H6 VL CDR2

<400> 1029

Thr Leu Ser Tyr Arg Ala Ser
1 5

<210> 1030
<211> 9
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 27H6 VL CDR3

<400> 1030

Met Gln Arg Ile Glu Phe Pro Leu Thr
1 5

<210> 1031
<211> 5
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 27H6 VH CDR1

<400> 1031

Ser Tyr Ser Met Asn
1 5

<210> 1032
<211> 17
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 27H6 VH CDR2

<400> 1032

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

Gly

<210> 1033
<211> 11
<212> PRT
<213> 智人

<220>
<221> MISC_FEATURE
<223> 27H6 VH CDR3

<400> 1033

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

<210> 1034
<211> 442
<212> PRT

<213> 智人

<400> 1034

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

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

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

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

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

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

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

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

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

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

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

Gly Leu Tyr Ser Leu Lys Ser Val Val Thr Val Pro Ser Ser Asn Phe
180 185 190

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

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

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

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

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
290 295 300

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

Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380

Asn Tyr Asp Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400

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

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
420 425 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 1035
<211> 214
<212> PRT
<213> 智人

<400> 1035

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

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

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr

35 40 45

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

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

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

Val Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

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

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Glu Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

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

Ala Pro Thr Glu Cys Ser

210

<210> 1036
<211> 440
<212> PRT
<213> 智人

<400> 1036

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

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

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

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

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

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

Ala Arg Glu Leu Arg Val Leu Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

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

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
130 135 140

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
145 150 155 160

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

Tyr Ser Leu Lys Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr
180 185 190

Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
195 200 205

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

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

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

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
340 345 350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
355 360 365

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

Asp Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385 390 395 400

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

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 1037
<211> 219
<212> PRT
<213> 智人

<400> 1037

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Gly Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

Pro Gln Phe Leu Ile Tyr Glu Val Ser Asn Arg Phe Ser Arg Val Pro
50 55 60

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

Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Ser
85 90 95

Ile Gln Leu Pro Trp Thr Phe Gly Gln Gly Thr Gln Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Glu Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 1038
<211> 449
<212> PRT
<213> 智人

<400> 1038

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 Glu 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 Lys 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

Lys 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> 1039
<211> 214
<212> PRT
<213> 智人

<400> 1039

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 Lys
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> 1040
<211> 446
<212> PRT
<213> 智人

<400> 1040

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 Glu 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 Lys 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 Lys 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> 1041
<211> 213
<212> PRT
<213> 智人

<400> 1041

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 Lys 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> 1042
<211> 442
<212> PRT
<213> 智人

<400> 1042

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asp Met His Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ile Ile Phe Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Pro Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Leu Ala Ala Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Lys Ser Val Val Thr Val Pro Ser Ser Asn Phe
180 185 190

Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
210 215 220

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
225 230 235 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
290 295 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305 310 315 320

Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380

Asn Tyr Asp Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
405 410 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
420 425 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 1043
<211> 214
<212> PRT
<213> 智人

<400> 1043

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Glu Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Glu Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Val Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu Gly Gln Pro Lys

100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Glu Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 1044
<211> 440
<212> PRT
<213> 智人

<400> 1044

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr
20 25 30

Gly Met His Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Asn Asp Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Leu Arg Val Leu Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
115 120 125

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
130 135 140

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
145 150 155 160

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
165 170 175

Tyr Ser Leu Lys Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr
180 185 190

Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
195 200 205

Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
210 215 220

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
340 345 350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
355 360 365

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
370 375 380

Asp Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385 390 395 400

Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 1045
<211> 219
<212> PRT
<213> 智人

<400> 1045

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Gly Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Glu Lys Pro Gly Gln Pro
35 40 45

Pro Gln Phe Leu Ile Tyr Glu Val Ser Asn Arg Phe Ser Arg Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Ser
85 90 95

Ile Gln Leu Pro Trp Thr Phe Gly Gln Gly Thr Gln Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Glu Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

〈210〉 1046
〈211〉 449
〈212〉 PRT
〈213〉 智人

〈400〉 1046

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 Glu 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 Glu 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 Lys 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

Lys 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〉 1047
〈211〉 214
〈212〉 PRT
〈213〉 智人

〈400〉 1047

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 Lys 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 Lys
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> 1048
<211> 446
<212> PRT
<213> 智人

<400> 1048

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 Glu 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 Glu 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 Lys 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 Lys 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> 1049
<211> 214
<212> PRT
<213> 智人

<400> 1049

Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser
20 25 30

Tyr Leu Asn Trp Tyr Gln Lys Lys Pro Gly Lys Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Thr Ser Arg Leu Asn 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 Asp Ile Lys His Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Lys
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

申請專利範圍

1. 一種結合硬化蛋白及DKK-1之異二聚抗體，其包含

第一重鏈，該第一重鏈包含選自由SEQ ID NO: 378及366組成之群之可變區胺基酸序列且在該第一重鏈之EU位置S183E、E356K及D399K處包含胺基酸取代，

第二重鏈，該第二重鏈包含選自由SEQ ID NO: 1003及979組成之群之可變區胺基酸序列且在該第二重鏈之EU位置S183K、K392D及K409D處包含胺基酸取代，

第一輕鏈，該第一輕鏈包含選自由SEQ ID NO: 376及364組成之群之可變區胺基酸序列且在該第一輕鏈之EU位置S176K處包含胺基酸取代，及

第二輕鏈，該第二輕鏈包含選自由SEQ ID NO: 1002及978組成之群之可變區胺基酸序列且在該第二輕鏈之EU位置S176E處包含胺基酸取代。

2. 一種結合硬化蛋白之包含SEQ ID NO: 1之胺基酸86-111的區域之抗體，其中該抗體在以下各域中包含取代：第一CH_3域、第二CH_3域、CH_1域及C_L域，其中該抗體含有包含硬化蛋白結合部分之第一重鏈及第一輕鏈以及包含DKK1結合部分之第二重鏈及第二輕鏈，其中該第一重鏈在EU位置S183E、E356K及D399K處包含胺基酸取代，其中該第二重鏈在EU位置S183K、K392D及K409D處包含胺基酸取代，且其中該第一輕鏈在EU位置S176K處包含胺基酸取代，及該第二輕鏈在EU位置S176E處包含胺基酸取代，

其中該抗體之硬化蛋白結合部分包含選自由以下組成之群之6個CDR組：a)CDR序列SEQ ID NO: 54、55及56及CDR

序列SEQ ID NO: 51、52及53；b)CDR序列SEQ ID NO: 60、61及62及CDR序列SEQ ID NO: 57、58及59；c)CDR序列SEQ ID NO: 48、49及50及CDR序列SEQ ID NO: 45、46及47；d)CDR序列SEQ ID NO: 42、43及44及CDR序列SEQ ID NO: 39、40及41；e)CDR序列SEQ ID NO: 275、276及277及CDR序列SEQ ID NO: 287、288及289；f)CDR序列SEQ ID NO: 278、279及280及CDR序列SEQ ID NO: 290、291及292；g)CDR序列SEQ ID NO: 78、79及80及CDR序列SEQ ID NO: 245、246及247；h)CDR序列SEQ ID NO: 81、99及100及CDR序列SEQ ID NO: 248、249及250；i)CDR序列SEQ ID NO: 101、102及103及CDR序列SEQ ID NO: 251、252及253；j)CDR序列SEQ ID NO: 104、105及106及CDR序列SEQ ID NO: 254、255及256；k)CDR序列SEQ ID NO: 107、108及109及CDR序列SEQ ID NO: 257、258及259；l)CDR序列SEQ ID NO: 110、111及112及CDR序列SEQ ID NO: 260、261及262；m)CDR序列SEQ ID NO: 281、282及283及CDR序列SEQ ID NO: 293、294及295；n)CDR序列SEQ ID NO: 113、114及115及CDR序列SEQ ID NO: 263、264及265；o)CDR序列SEQ ID NO: 284、285及286及CDR序列SEQ ID NO: 296、297及298；p)CDR序列SEQ ID NO: 116、237及238及CDR序列SEQ ID NO: 266、267及268；q)CDR序列SEQ ID NO: 239、240及241及CDR序列SEQ ID NO: 269、270及271；r)CDR序列SEQ ID NO: 242、243及244及CDR序列SEQ ID NO: 272、273及274；及s)CDR序列SEQ ID NO: 351、352及353及CDR序列SEQ ID NO: 358、359及360；且

其中該DKK-1結合部分包含選自由以下組成之群之6個CDR組：(a)SEQ ID NO:820-825、(b)SEQ ID NO:828-833、

(c)SEQ ID NO:836-841、(d)SEQ ID NO:844-849、(e)SEQ ID NO:852-857、(f)SEQ ID NO:860-865、(g)SEQ ID NO:868-873、(h)SEQ ID NO:876-881、(i)SEQ ID NO:884-889、(j)SEQ ID NO:892-897、(k)SEQ ID NO:900-905、(l)SEQ ID NO:908-913、(m)SEQ ID NO:916-921、(n)SEQ ID NO:924-929、(o)SEQ ID NO:932-937、(p)SEQ ID NO:940-945、(q)SEQ ID NO:948-953、(r)SEQ ID NO:956-961、(s)SEQ ID NO:964-969、(t)SEQ ID NO:972-977、(u)SEQ ID NO:980-985、(v)SEQ ID NO:988-993、(w)SEQ ID NO:996-1001及(x)SEQ ID NO:1004-1009。

3. 如請求項2之抗體，其包含：

(a) 第一重鏈，該第一重鏈包含SEQ ID NO: 378中所述之可變區胺基酸序列且在該第一重鏈之EU位置S183E、E356K及D399K處包含胺基酸取代，

第二重鏈，該第二重鏈包含SEQ ID NO: 1003中所述之可變區胺基酸序列且在該第二重鏈之EU位置S183K、K392D及K409D處包含胺基酸取代，

第一輕鏈，該第一輕鏈包含SEQ ID NO: 376中所述之可變區胺基酸序列且在該第一輕鏈之EU位置S176K處包含胺基酸取代，及

第二輕鏈，該第二輕鏈包含SEQ ID NO: 1002中所述之可變區胺基酸序列且在該第二輕鏈之EU位置S176E處包含胺基酸取代；或

(b) 第一重鏈，該第一重鏈包含SEQ ID NO: 366中所述之可變

區胺基酸序列且在該第一重鏈之EU位置S183E、E356K及D399K處包含胺基酸取代，

第二重鏈，該第二重鏈包含SEQ ID NO: 979中所述之可變區胺基酸序列且在該第二重鏈之EU位置S183K、K392D及K409D處包含胺基酸取代，

第一輕鏈，該第一輕鏈包含SEQ ID NO: 364中所述之可變區胺基酸序列且在該第一輕鏈之EU位置S176K處包含胺基酸取代，及

第二輕鏈，該第二輕鏈包含SEQ ID NO: 978中所述之可變區胺基酸序列且在該第二輕鏈之EU位置S176E處包含胺基酸取代。

4. 如請求項2之抗體，其包含：

(a) 包含SEQ ID NO: 1038中所述之胺基酸序列之第一重鏈；包含SEQ ID NO: 1034中所述之胺基酸序列之第二重鏈；包含SEQ ID NO: 1039中所述之胺基酸序列之第一輕鏈及包含SEQ ID NO: 1035中所述之胺基酸序列之第二輕鏈；

(b) 包含SEQ ID NO: 1038中所述之胺基酸序列之第一重鏈；包含SEQ ID NO: 1036中所述之胺基酸序列之第二重鏈；包含SEQ ID NO: 1039中所述之胺基酸序列之第一輕鏈及包含SEQ ID NO: 1037中所述之胺基酸序列之第二輕鏈；

(c) 包含SEQ ID NO: 1040中所述之胺基酸序列之第一重鏈；包含SEQ ID NO: 1034中所述之胺基酸序列之第二重鏈；包含SEQ ID NO: 1041中所述之胺基酸序列之第一輕鏈及包含SEQ ID NO: 1035中所述之胺基酸序列之第二輕鏈；

(d) 包含SEQ ID NO: 1040中所述之胺基酸序列之第一重鏈；包含SEQ ID NO: 1036中所述之胺基酸序列之第二重鏈；包含SEQ ID NO: 1041中所述之胺基酸序列之第一輕鏈及包含SEQ ID NO: 1037中所述之胺基酸序列之第二輕鏈；

(e) 包含SEQ ID NO: 1046中所述之胺基酸序列之第一重鏈；包含SEQ ID NO: 1042中所述之胺基酸序列之第二重鏈；包含SEQ ID NO: 1047中所述之胺基酸序列之第一輕鏈及包含SEQ ID NO: 1043中所述之胺基酸序列之第二輕鏈；

(f) 包含SEQ ID NO: 1046中所述之胺基酸序列之第一重鏈；包含SEQ ID NO: 1044中所述之胺基酸序列之第二重鏈；包含SEQ ID NO: 1047中所述之胺基酸序列之第一輕鏈及包含SEQ ID NO: 1045中所述之胺基酸序列之第二輕鏈；

(g) 包含SEQ ID NO: 1048中所述之胺基酸序列之第一重鏈；包含SEQ ID NO: 1042中所述之胺基酸序列之第二重鏈；包含SEQ ID NO: 1049中所述之胺基酸序列之第一輕鏈及包含SEQ ID NO: 1043中所述之胺基酸序列之第二輕鏈；

(h) 包含SEQ ID NO: 1048中所述之胺基酸序列之第一重鏈；包含SEQ ID NO: 1044中所述之胺基酸序列之第二重鏈；包含SEQ ID NO: 1049中所述之胺基酸序列之第一輕鏈及包含SEQ ID NO: 1045中所述之胺基酸序列之第二輕鏈。

5. 如請求項1或2之抗體，其進一步包含位於AHo位置46之胺基酸取代。

6. 如請求項1至4中任一項之抗體，其為IgG免疫球蛋白。

7. 一種核酸，其包含編碼如請求項1至6中任一項之抗體之核苷酸序列。

8. 一種載體，其包含如請求項7之核苷酸序列。

9. 一種經分離宿主細胞，其包含如請求項7之核酸或如請求項8之載體。

10. 一種如請求項1至6中任一項之抗體之用途，其係用以製備用於增加哺乳動物個體中之骨礦物質密度之藥物。

11. 一種組合物，其包含如請求項1至6中任一項之抗體及醫藥學上可接受之載劑、稀釋劑或佐劑。

研究設計

組(n=6)

G1：媒劑(A5Su緩衝液)

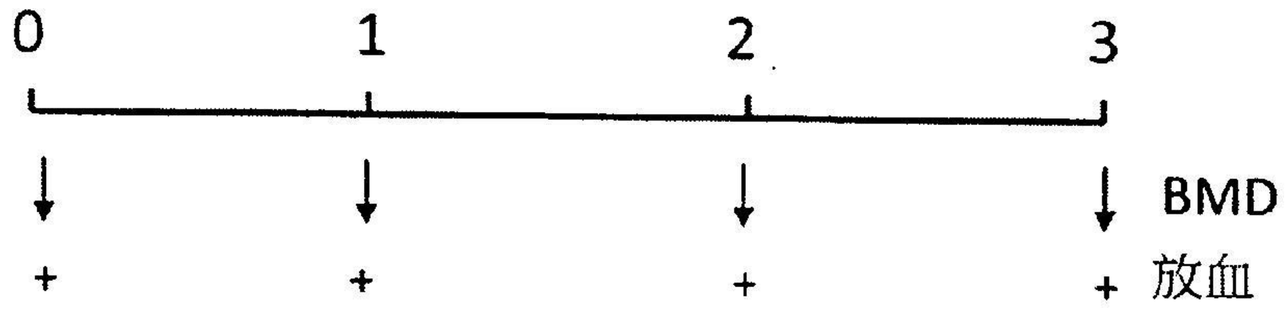
G2: huDVD Ig

G3：Ab5(硬化蛋白抗體)

G4：異Ig-1(Ab23-6.147)

G5：異Ig-2(Ab5-6.37.5)

G6：異Ig-3(7Ab5-6.147)



- 每週兩次皮下注射
- 劑量：12.5 mg/kg，一週2次

- 10週齡雄性B6D2F1小鼠
- 主要終點：在基線(BL)時活體內DXA掃描，接著每週進行該掃描

圖 1

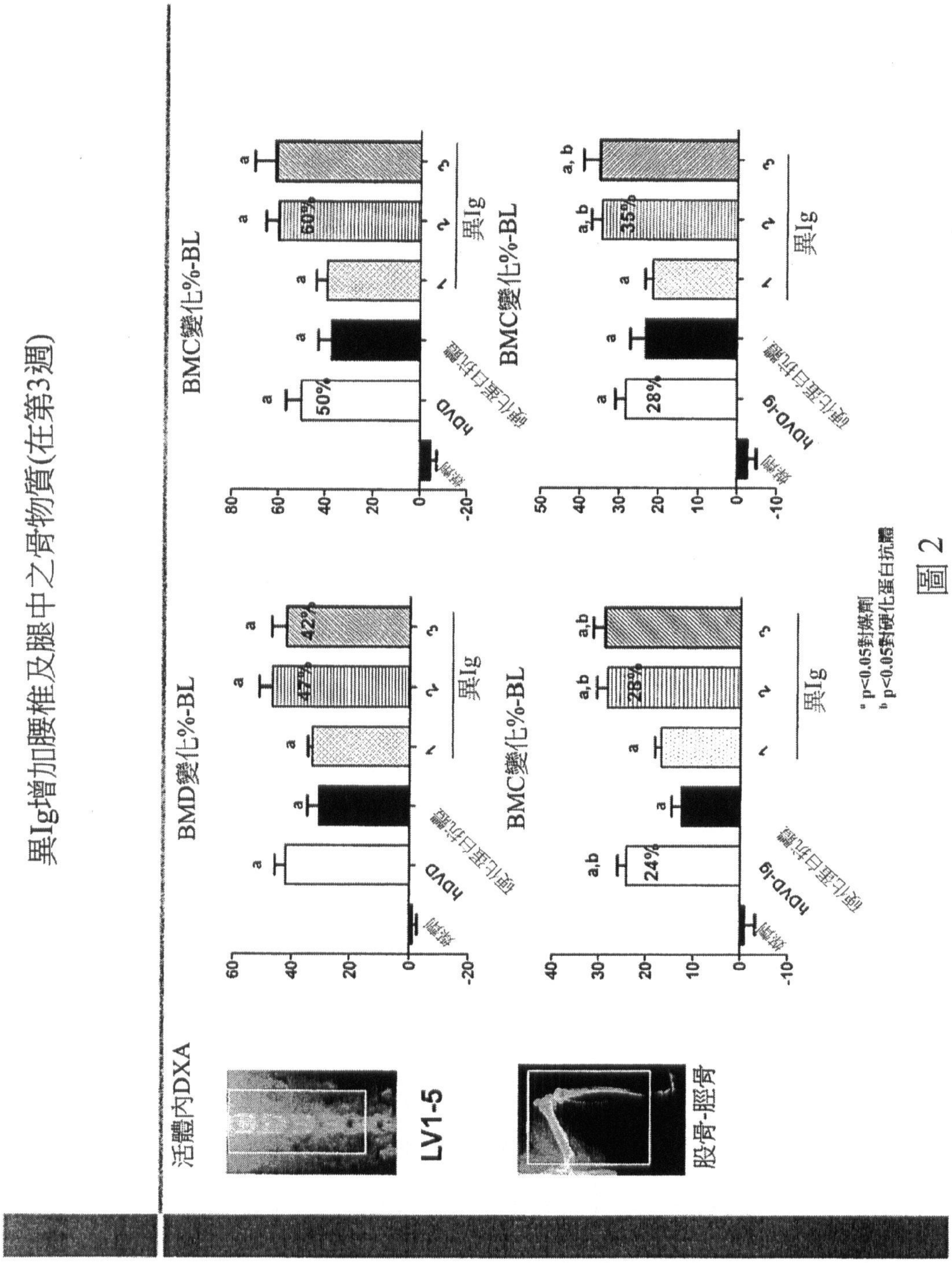

異Ig增加腰椎及腿中之骨物質(在第3週)
活體內DXA
LV1-5
股骨-脛骨
BMD變化%-BL
BMC變化%-BL
載劑
hDVD
hDVD-Ig
硬化蛋白抗體
異Ig
50%
60%
28%
35%
42%
47%
28%
24%
a
a,b
b
c
ᵃ p<0.05對媒劑
ᵇ p<0.05對硬化蛋白抗體

圖 2

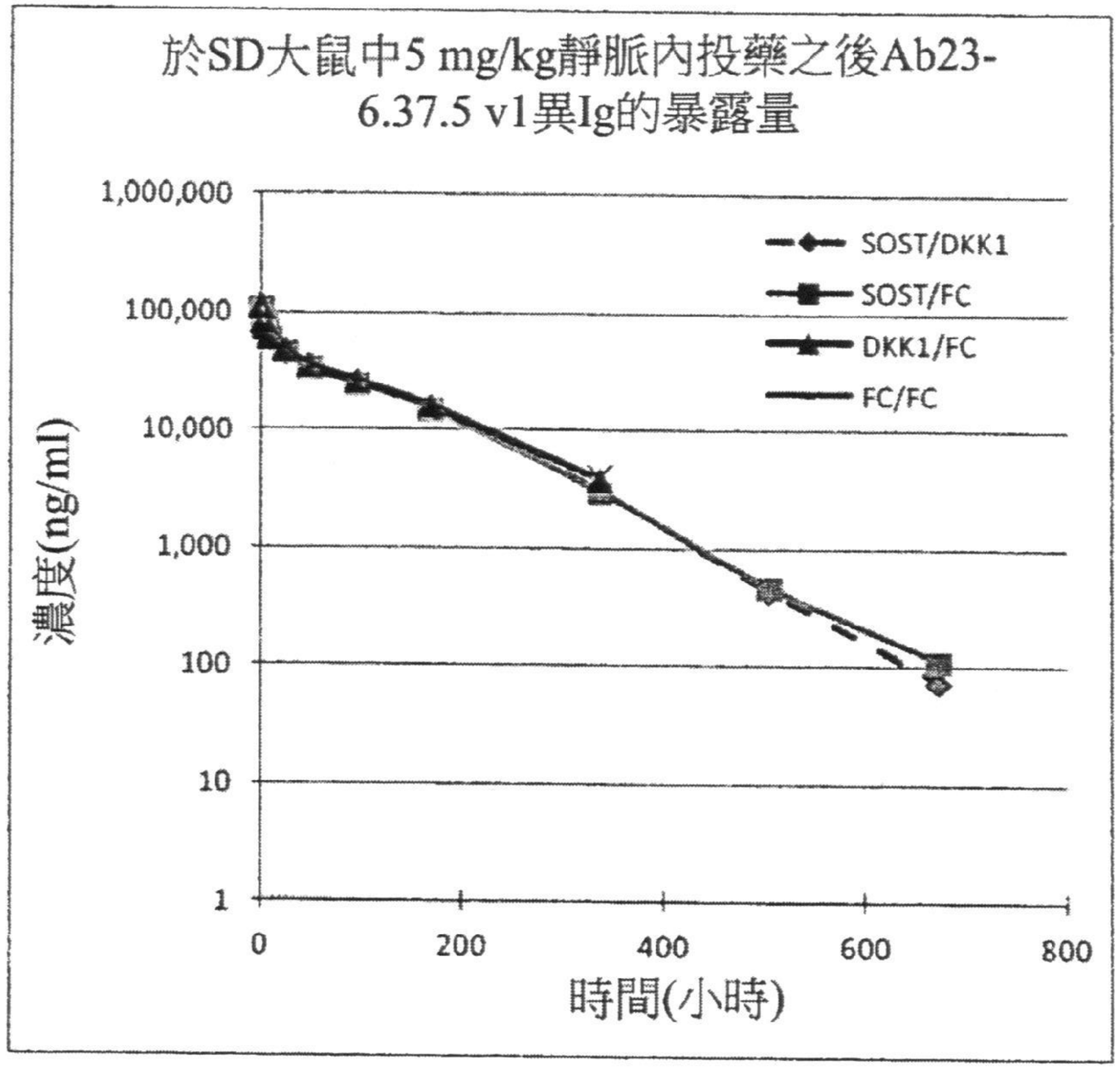

於SD大鼠中5 mg/kg靜脈內投藥之後Ab23-6.37.5 v1異Ig的暴露量
濃度(ng/ml)
1,000,000
100,000
10,000
1,000
100
10
1
0
200
400
600
800
時間(小時)
SOST/DKK1
SOST/FC
DKK1/FC
FC/FC

圖 3A

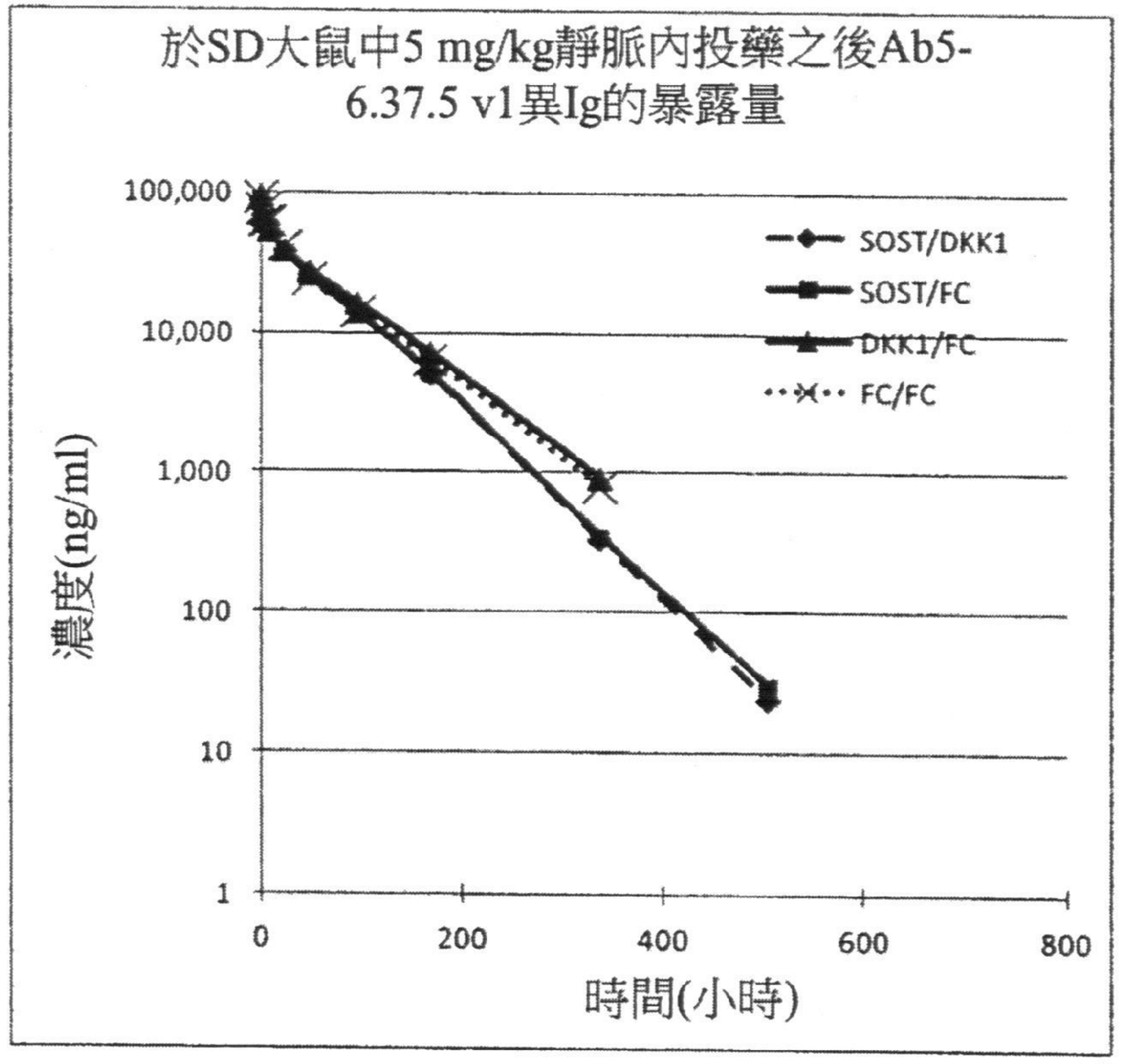

於SD大鼠中5 mg/kg靜脈內投藥之後Ab5-6.37.5 v1異Ig的暴露量
濃度(ng/ml)
100,000
10,000
1,000
100
10
1
0
200
400
600
800
時間(小時)
SOST/DKK1
SOST/FC
DKK1/FC
FC/FC

圖 3B

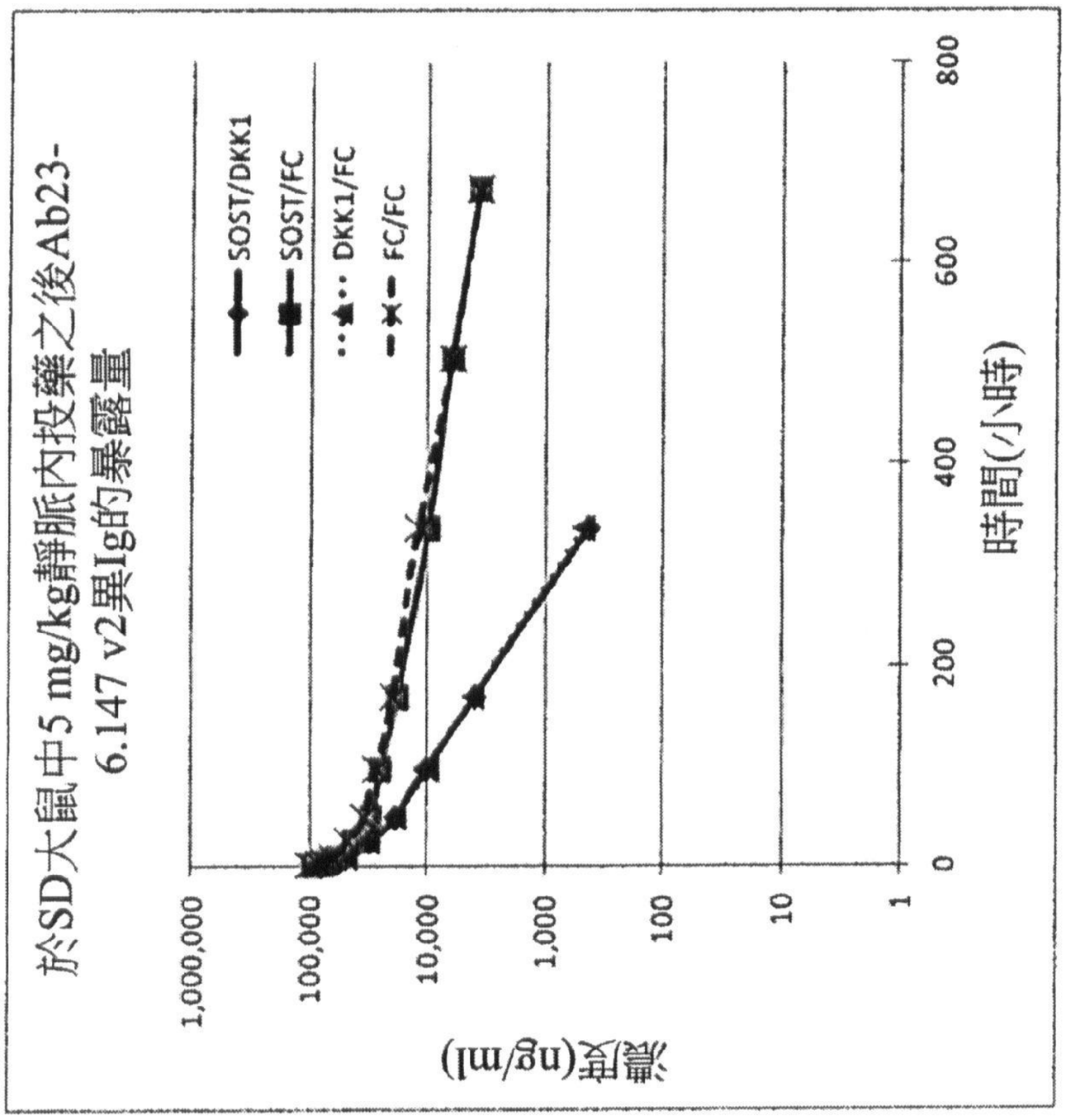

於SD大鼠中5 mg/kg靜脈內投藥之後Ab23-
6.147 v2異Ig的暴露量
SOST/DKK1
SOST/FC
DKK1/FC
FC/FC
濃度(ng/ml)
1,000,000
100,000
10,000
1,000
100
10
1
0
200
400
600
800
時間(小時)

圖 3D

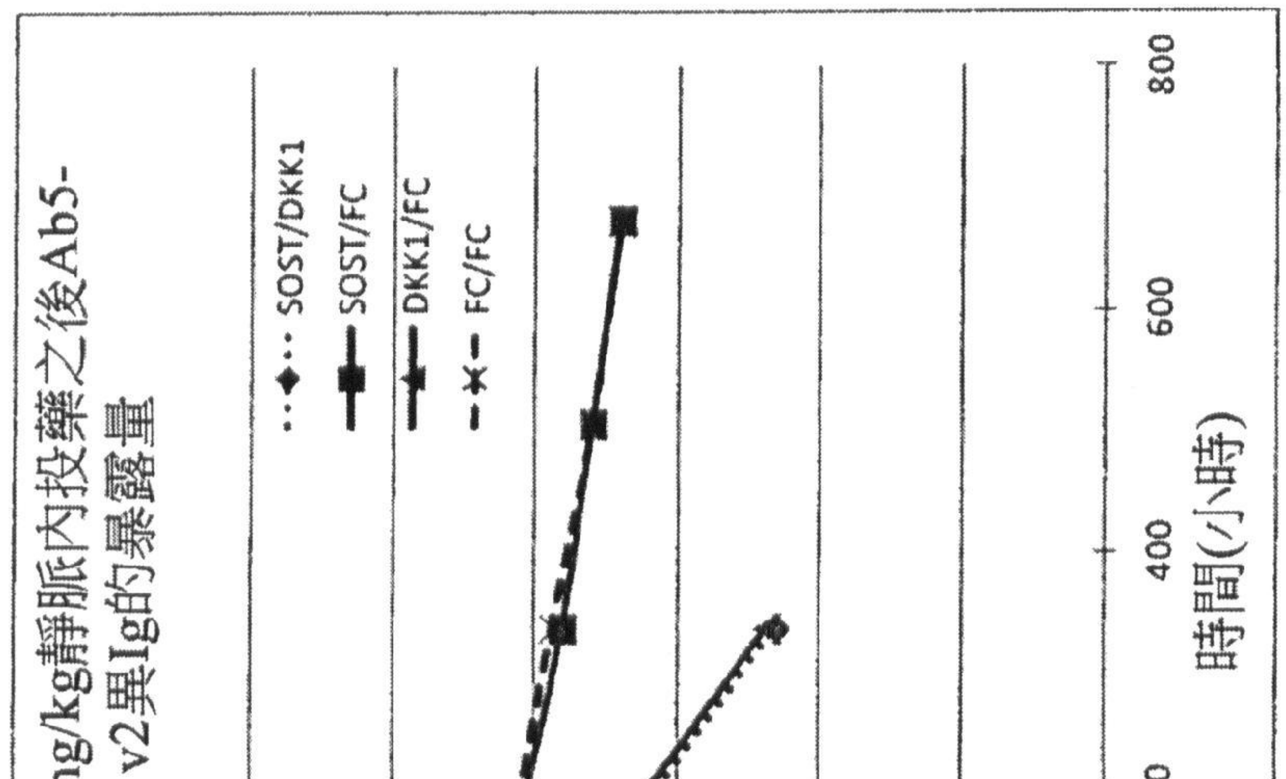

於SD大鼠中5 mg/kg靜脈內投藥之後Ab5-
6.147 v2異Ig的暴露量
SOST/DKK1
SOST/FC
DKK1/FC
FC/FC
濃度(ng/ml)
1,000,000
100,000
10,000
1,000
100
10
1
0
200
400
600
800
時間(小時)

圖 3C

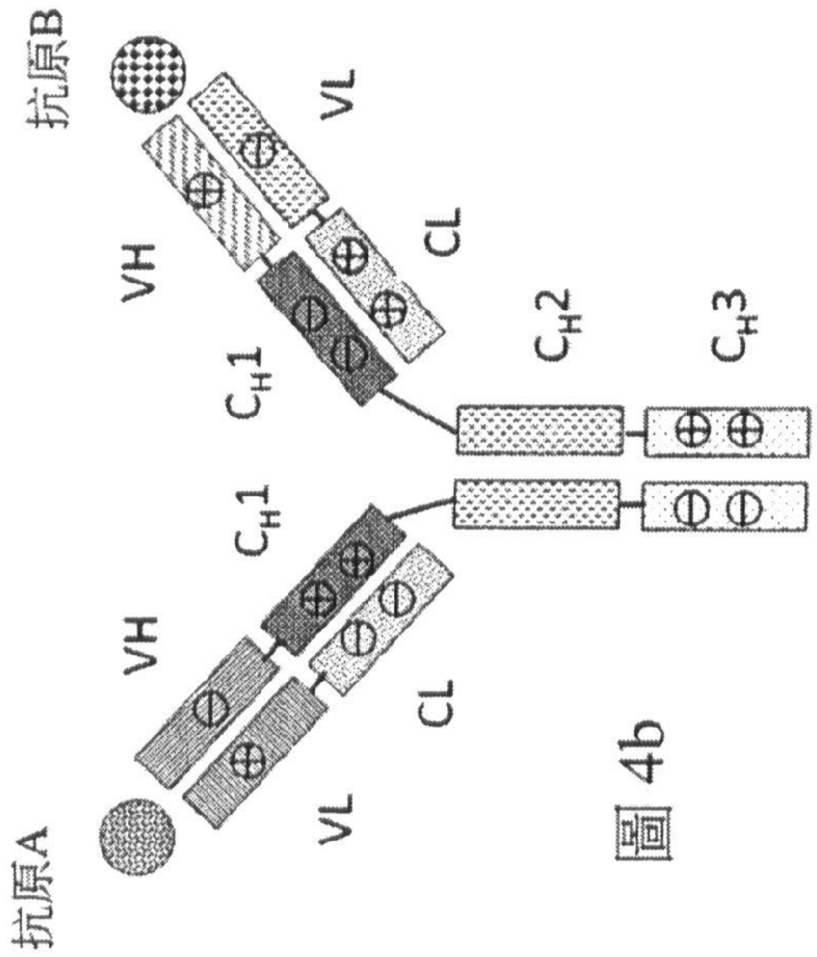


圖 4a

圖 4b

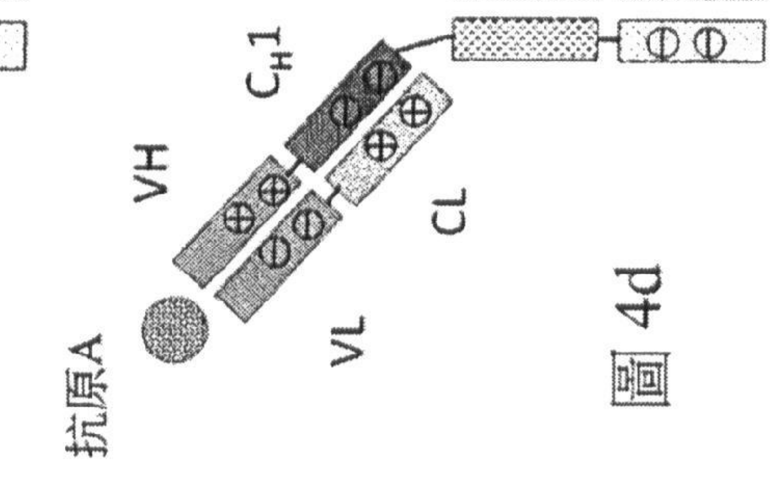


圖 4c

圖 4d

圖 4

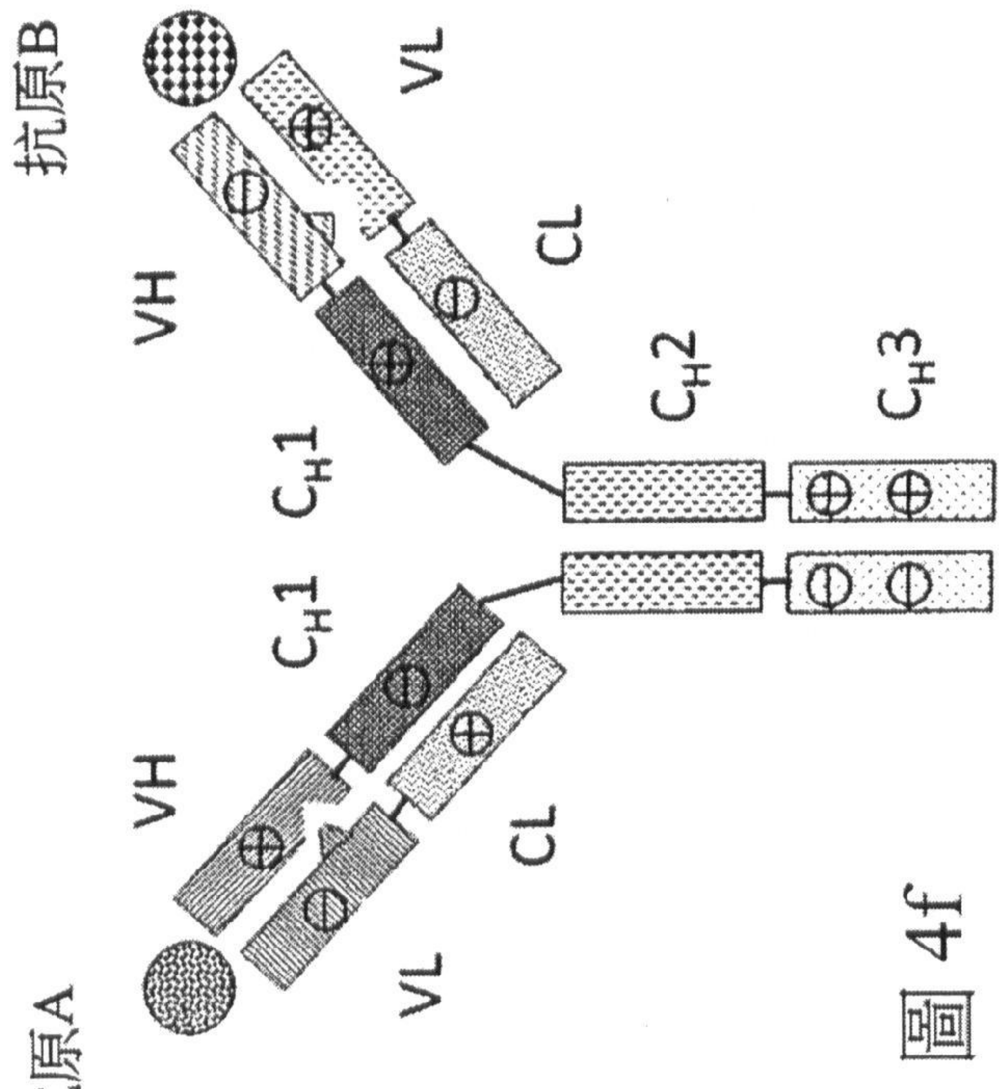

抗原B
VL
VH
CL
C_H1
C_H2
C_H3
抗原A
VH
C_H1
VL
CL

圖 4f

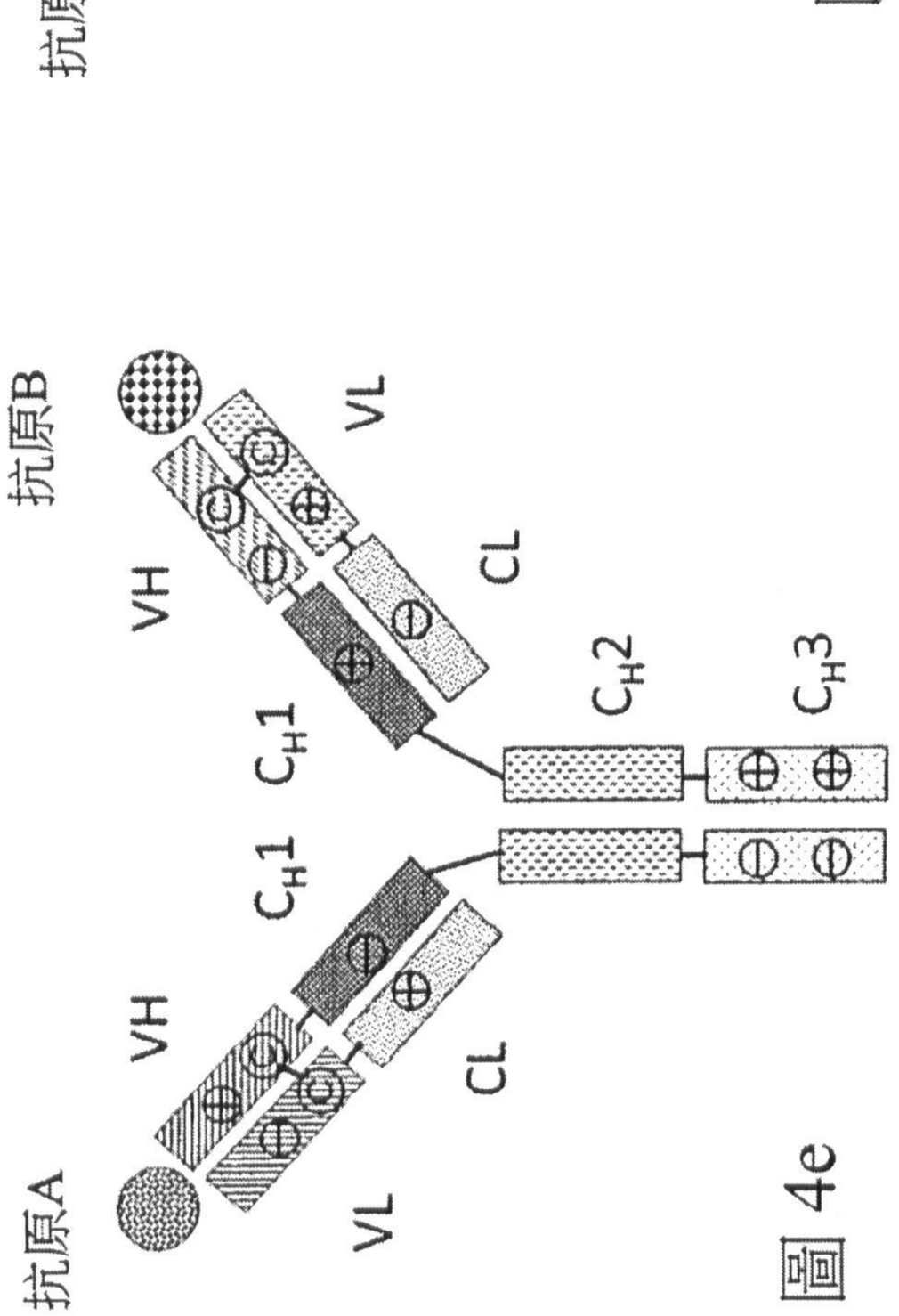

抗原B
VL
VH
CL
C_H1
C_H2
C_H3
C_H1
VH
CL
抗原A
VL

圖 4e

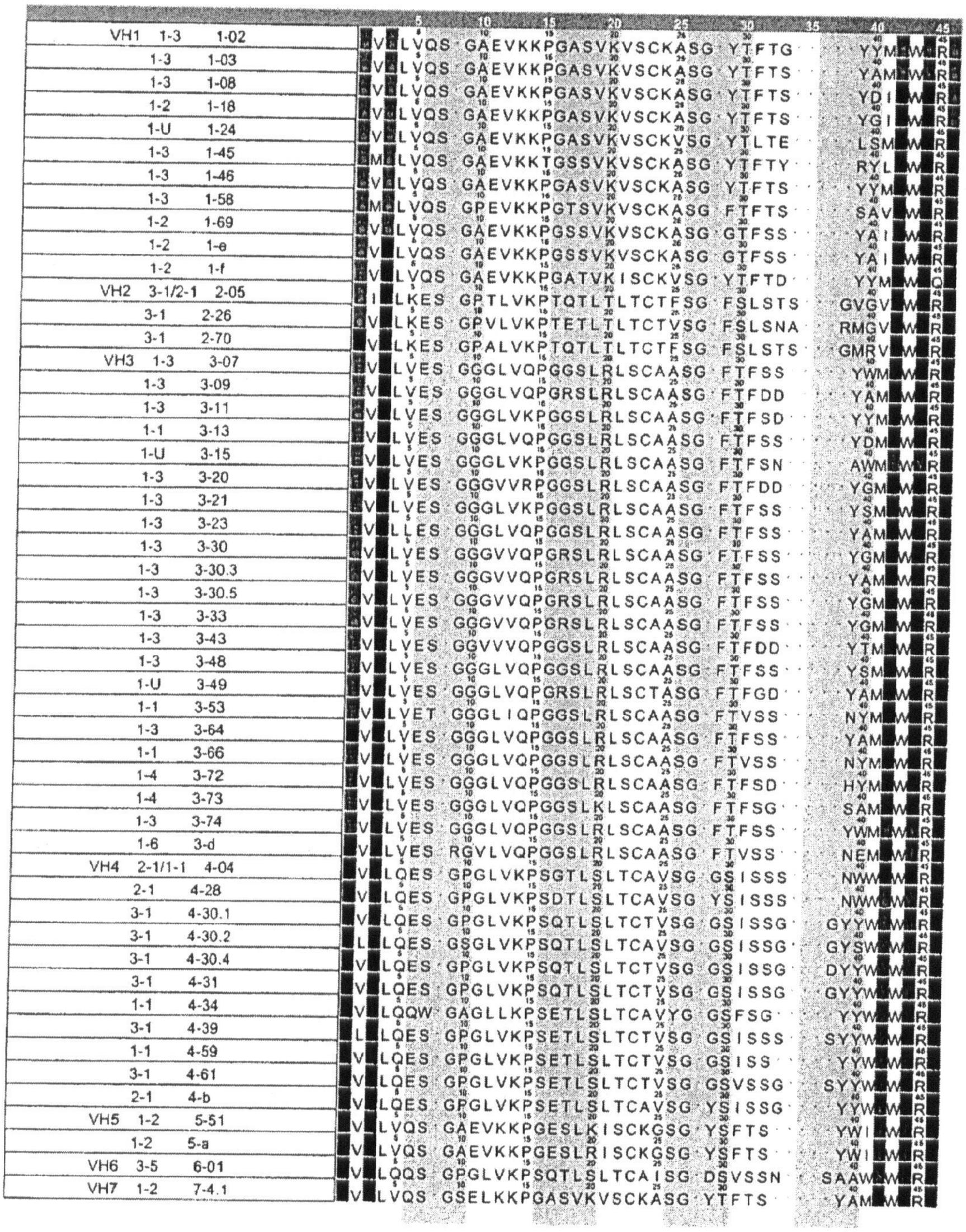

VH1 1-3 1-02
1-3 1-03
1-3 1-08
1-2 1-18
1-U 1-24
1-3 1-45
1-3 1-46
1-3 1-58
1-2 1-69
1-2 1-e
1-2 1-f
VH2 3-1/2-1 2-05
3-1 2-26
3-1 2-70
VH3 1-3 3-07
1-3 3-09
1-3 3-11
1-1 3-13
1-U 3-15
1-3 3-20
1-3 3-21
1-3 3-23
1-3 3-30
1-3 3-30.3
1-3 3-30.5
1-3 3-33
1-3 3-43
1-3 3-48
1-U 3-49
1-1 3-53
1-3 3-64
1-1 3-66
1-4 3-72
1-4 3-73
1-3 3-74
1-6 3-d
VH4 2-1/1-1 4-04
2-1 4-28
3-1 4-30.1
3-1 4-30.2
3-1 4-30.4
3-1 4-31
1-1 4-34
3-1 4-39
1-1 4-59
3-1 4-61
2-1 4-b
VH5 1-2 5-51
1-2 5-a
VH6 3-5 6-01
VH7 1-2 7-4.1

圖 5A

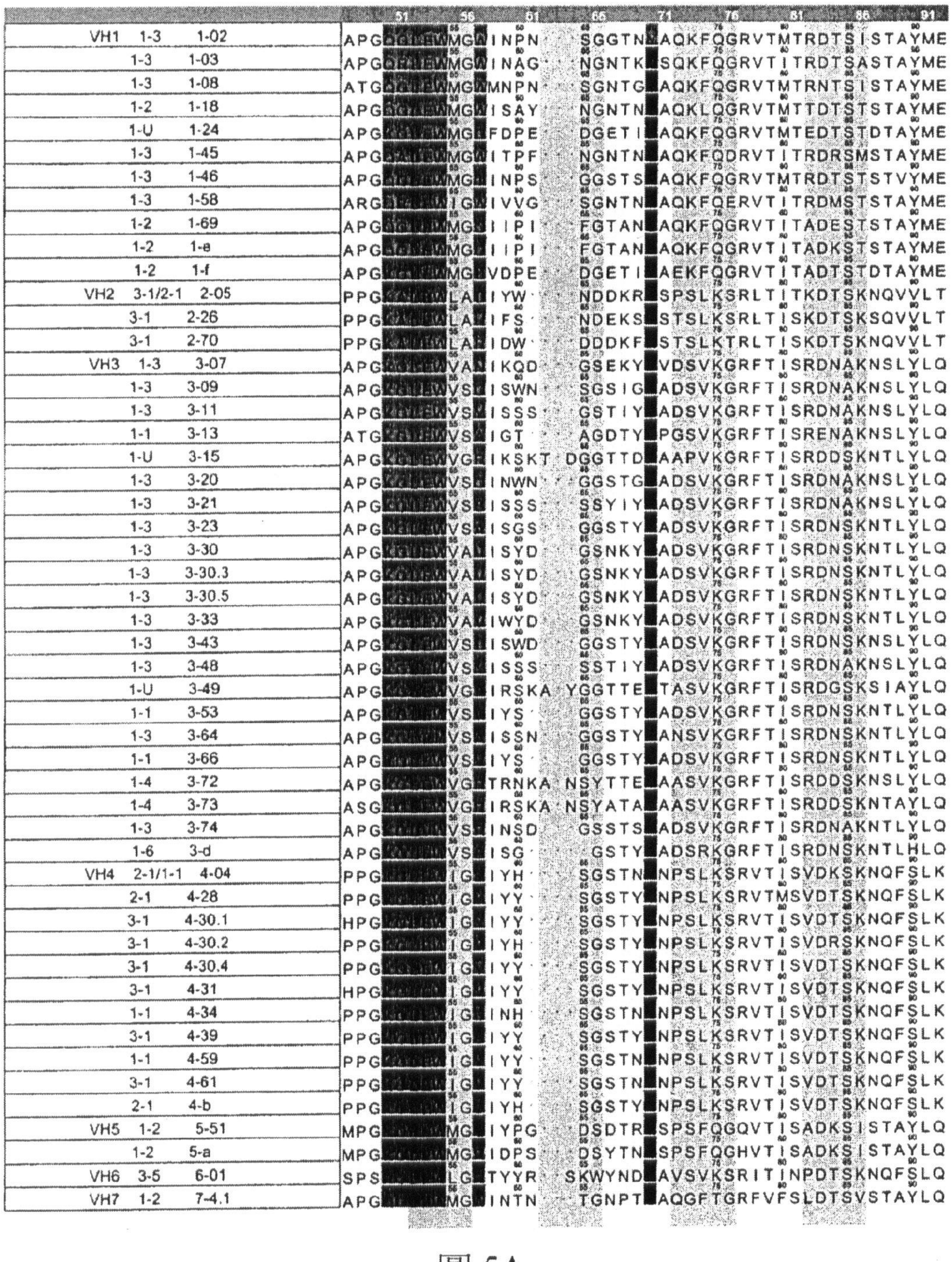

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1-3 1-03 APGQRLEWMGWINAGNGNTKLSQKFQGRVTITRDTSASTAYME
1-3 1-08 ATGQGLEWMGWMNPNSGNTGLAQKFQGRVTMTRNTSISTAYME
1-2 1-18 APGQGLEWMGWISAYNGNTNLAQKLQGRVTMTTDTSTSTAYME
1-U 1-24 APGKGLEWMGLFDPEDGETILAQKFQGRVTMTEDTSTDTAYME
1-3 1-45 APGQGLEWMGWITPFNGNTNLAQKFQDRVTITRDRSMSTAYME
1-3 1-46 APGQGLEWMGWINPSGGSTSLAQKFQGRVTMTRDTSTSTVYME
1-3 1-58 ARGTGLKWIGWIVVGSGNTNLAQKFQERVTITRDMSTSTAYME
1-2 1-69 APGQGLEWMGSIIPIFGTANLAQKFQGRVTITADESTSTAYME
1-2 1-e APGQGLEWMGIIPIFGTANLAQKFQGRVTITADKSTSTAYME
1-2 1-f APGQGLEWMGLVDPEDGETILAEKFQGRVTITADTSTDTAYME
VH2 3-1/2-1 2-05 PPGKALEWLALIYWNDDKRLSPSLKSRLTITKDTSKNQVVLT
3-1 2-26 PPGKALEWLALIFSNDEKSLSTSLKSRLTISKDTSKSQVVLT
3-1 2-70 PPGKALEWLALIDWDDDKFLSTSLKTRLTISKDTSKNQVVLT
VH3 1-3 3-07 APGKGLEWVANIKQDGSEKYLVDSVKGRFTISRDNAKNSLYLQ
1-3 3-09 APGKGLEWVSLISWNSGSIGLADSVKGRFTISRDNAKNSLYLQ
1-3 3-11 APGKGLEWVSYISSSGSTIYLADSVKGRFTISRDNAKNSLYLQ
1-1 3-13 ATGKGLEWVSSIGTAGDTYLPGSVKGRFTISRENAKNSLYLQ
1-U 3-15 APGKGLEWVGRIKSKTDGGTTDLAAPVKGRFTISRDDSKNTLYLQ
1-3 3-20 APGKGLEWVSDINWNGGSTGLADSVKGRFTISRDNAKNSLYLQ
1-3 3-21 APGKGLEWVSSISSSSSYIYLADSVKGRFTISRDNAKNSLYLQ
1-3 3-23 APGKGLEWVSRISGSGGSTYLADSVKGRFTISRDNSKNTLYLQ
1-3 3-30 APGKGLEWVALISYDGSNKYLADSVKGRFTISRDNSKNTLYLQ
1-3 3-30.3 APGKGLEWVALISYDGSNKYLADSVKGRFTISRDNSKNTLYLQ
1-3 3-30.5 APGKGLEWVALISYDGSNKYLADSVKGRFTISRDNSKNTLYLQ
1-3 3-33 APGKGLEWVALIWYDGSNKYLADSVKGRFTISRDNSKNTLYLQ
1-3 3-43 APGKGLEWVSLISWDGGSTYLADSVKGRFTISRDNSKNSLYLQ
1-3 3-48 APGKGLEWVSSISSSSSTIYLADSVKGRFTISRDNAKNSLYLQ
1-U 3-49 APGKGLEWVGFIRSKAYGGTTELTASVKGRFTISRDGSKSIAYLQ
1-1 3-53 APGKGLEWVSVIYSGGSTYLADSVKGRFTISRDNSKNTLYLQ
1-3 3-64 APGKGLEWVSSISSNGGSTYLANSVKGRFTISRDNSKNTLYLQ
1-1 3-66 APGKGLEWVSVIYSGGSTYLADSVKGRFTISRDNSKNTLYLQ
1-4 3-72 APGKGLEWVGFTRNKANSYTTEYAASVKGRFTISRDDSKNSLYLQ
1-4 3-73 ASGKGLEWVGFIRSKANSYATAYAASVKGRFTISRDDSKNTAYLQ
1-3 3-74 APGKGLEWVSVINSDGSSTSYADSVKGRFTISRDNAKNTLYLQ
1-6 3-d APGKGLEWVSVISGGSTYLADSRKGRFTISRDNSKNTLHLQ
VH4 2-1/1-1 4-04 PPGKGLEWIGYIYHSGSTNNPSLKSRVTISVDKSKNQFSLK
2-1 4-28 PPGKGLEWIGYIYYSGSTYNPSLKSRVTMSVDTSKNQFSLK
3-1 4-30.1 HPGKGLEWIGYIYYSGSTYNPSLKSRVTISVDTSKNQFSLK
3-1 4-30.2 PPGKGLEWIGYIYHSGSTYNPSLKSRVTISVDRSKNQFSLK
3-1 4-30.4 PPGKGLEWIGYIYYSGSTYNPSLKSRVTISVDTSKNQFSLK
3-1 4-31 HPGKGLEWIGYIYYSGSTYNPSLKSRVTISVDTSKNQFSLK
1-1 4-34 PPGKGLEWIGYINHSGSTNNPSLKSRVTISVDTSKNQFSLK
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1-1 4-59 PPGKGLEWIGYIYYSGSTNNPSLKSRVTISVDTSKNQFSLK
3-1 4-61 PPGKGLEWIGYIYYSGSTNNPSLKSRVTISVDTSKNQFSLK
2-1 4-b PPGKGLEWIGYIYHSGSTYNPSLKSRVTISVDTSKNQFSLK
VH5 1-2 5-51 MPGKGLEWMGIIYPGDSDTRLSPSFQGQVTISADKSISTAYLQ
1-2 5-a MPGKGLEWMGIIDPSDSYTNLSPSFQGHVTISADKSISTAYLQ
VH6 3-5 6-01 SPSKGLEWLGRTYYRSKWYNDLAVSVKSRITINPDTSKNQFSLQ
VH7 1-2 7-4.1 APGQGLEWMGWINTNTGNPTLAQGFTGRFVFSLDTSVSTAYLQ

圖 5A

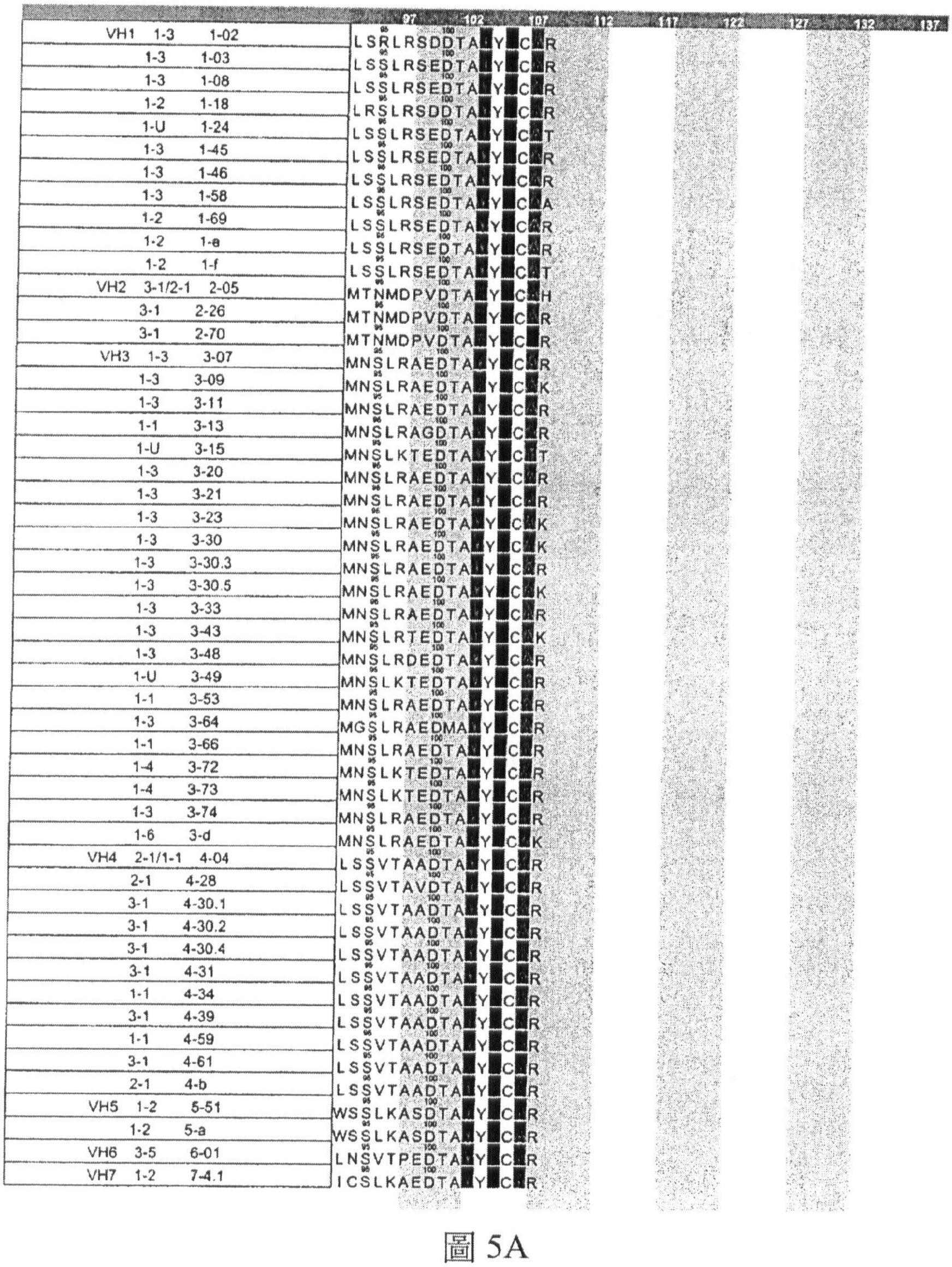

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1-3 1-03
1-3 1-08
1-2 1-18
1-U 1-24
1-3 1-45
1-3 1-46
1-3 1-58
1-2 1-69
1-2 1-a
1-2 1-f
VH2 3-1/2-1 2-05
3-1 2-26
3-1 2-70
VH3 1-3 3-07
1-3 3-09
1-3 3-11
1-1 3-13
1-U 3-15
1-3 3-20
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1-3 3-30.3
1-3 3-30.5
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1-U 3-49
1-1 3-53
1-3 3-64
1-1 3-66
1-4 3-72
1-4 3-73
1-3 3-74
1-6 3-d
VH4 2-1/1-1 4-04
2-1 4-28
3-1 4-30.1
3-1 4-30.2
3-1 4-30.4
3-1 4-31
1-1 4-34
3-1 4-39
1-1 4-59
3-1 4-61
2-1 4-b
VH5 1-2 5-51
1-2 5-a
VH6 3-5 6-01
VH7 1-2 7-4.1

圖 5A

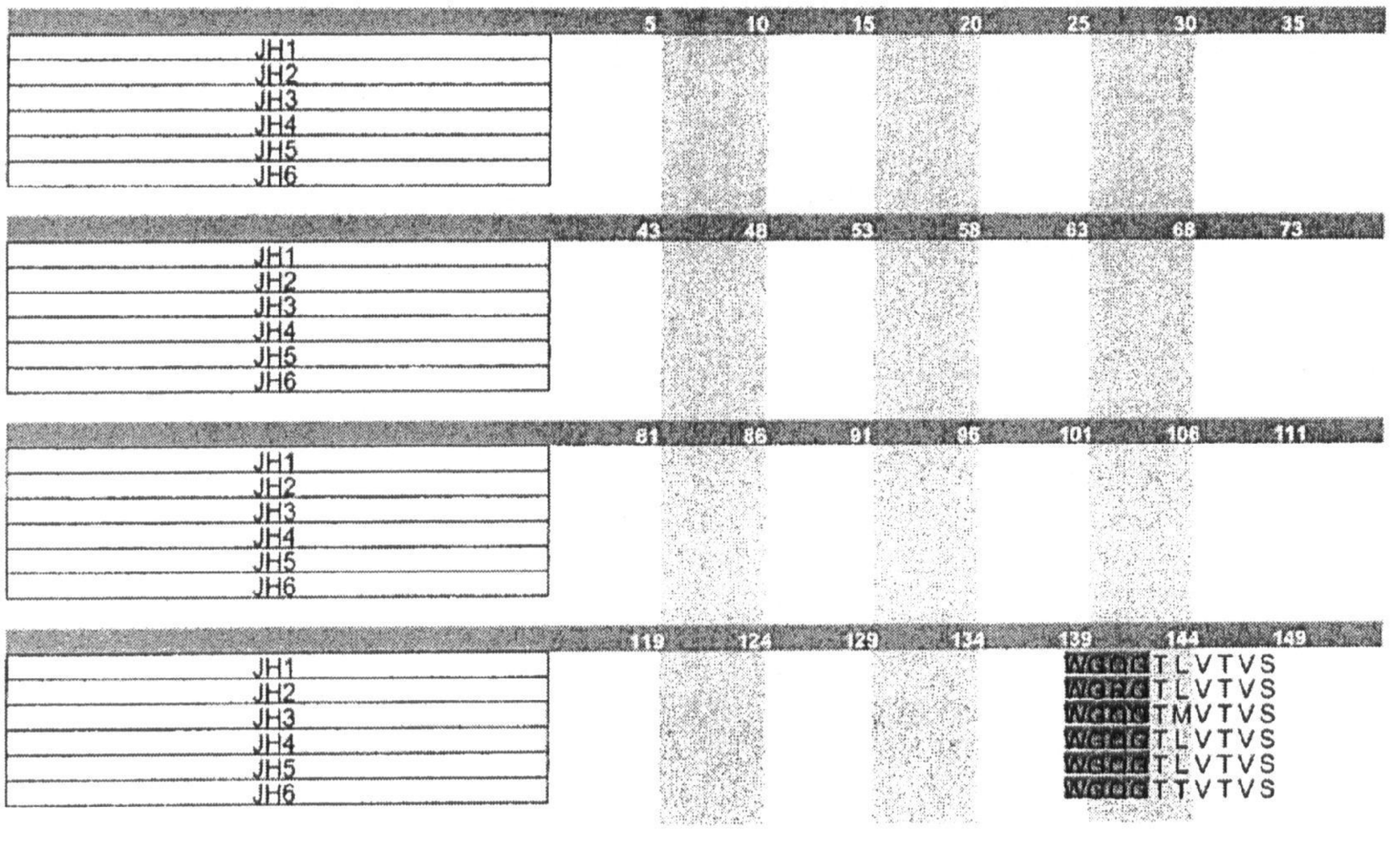

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JH1
JH2
JH3
JH4
JH5
JH6
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JH1
JH2
JH3
JH4
JH5
JH6
81 86 91 95 101 106 111
JH1
JH2
JH3
JH4
JH5
JH6
119 124 129 134 139 144 149
JH1
JH2
JH3
JH4
JH5
JH6
WGQG TLVTVS
WGRG TLVTVS
WGAG TMVTVS
WGLG TLVTVS
WGPG TLVTVS
WGDG TTVTVS

圖 5B

	5 10 15 20 25 30 35
VKI 2-1-(1) O12	DIQMTQSPSSLSASVGDRVTITCRASQSIS
2-1-(1) O2	DIQMTQSPSSLSASVGDRVTITCRASQSIS
2-1-(1) O18	DIQMTQSPSSLSASVGDRVTITCQASQDIS
2-1-(1) O8	DIQMTQSPSSLSASVGDRVTITCQASQDIS
2-1-(U) A20	DIQMTQSPSSLSASVGDRVTITCRASQGIS
2-1-(1) A30	DIQMTQSPSSLSASVGDRVTITCRASQGIR
2-1-(1) L14	NIQMTQSPSAMSASVGDRVTITCRARQGIS
2-1-(1) L1	DIQMTQSPSSLSASVGDRVTITCRASQGIS
2-1-(1) L15	DIQMTQSPSSLSASVGDRVTITCRASQGIS
2-1-(1) L4	AIQLTQSPSSLSASVGDRVTITCRASQGIS
2-1-(1) L18	AIQLTQSPSSLSASVGDRVTITCRASQGIS
2-1-(1) L5	DIQMTQSPSSVSASVGDRVTITCRASQGIS
2-1-(1) L19	DIQMTQSPSSVSASVGDRVTITCRASQGIS
2-1-(1) L8	DIQLTQSPSFLSASVGDRVTITCRASQGIS
2-1-(1) L23	AIRMTQSPFSLSASVGDRVTITCWASQGIS
2-1-(1) L9	AIRMTQSPSSFSASTGDRVTITCRASQGIS
U-1-(1) L24	VIWMTQSPSLLSASTGDRVTISCRMSQGIS
2-1-(1) L11	AIQMTQSPSSLSASVGDRVTITCRASQGIR
2-1-(U) L12	DIQMTQSPSTLSASVGDRVTITCRASQSIS
VKII 3-1-(1) O11	DIVMTQTPLSLPVTPGEPASISCRSSQSLLDSDDGN
3-1-(1) O1	DIVMTQTPLSLPVTPGEPASISCRSSQSLLDSDDGN
4-1-(1) A17	DVVMTQSPLSLPVTLGQPASISCRSSQSLVYSDGN
4-1-(1) A1	DVVMTQSPLSLPVTLGQPASISCRSSQSLVYSDGN
4-1-(1) A18	DIVMTQTPLSLSVTPGQPASISCKSSQSLLHSDGK
4-1-(1) A2	DIVMTQTPLSLSVTPGQPASISCKSSQSLLHSDGK
4-1-(1) A19	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGY
4-1-(1) A3	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGY
4-1-(1) A23	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGN
VKIII 6-1-(1) A27	EIVLTQSPGTLSLSPGERATLSCRASQSVSS
6-1-(1) A11	EIVLTQSPATLSLSPGERATLSCGASQSVSS
2-1-(1) L2	EIVMTQSPATLSVSPGERATLSCRASQSVS
2-1-(1) L16	EIVMTQSPATLSVSPGERATLSCRASQSVS
2-1-(1) L6	EIVLTQSPATLSLSPGERATLSCRASQSVS
2-1-(U) L20	EIVLTQSPATLSLSPGERATLSCRASQGVS
6-1-(1) L25	EIVMTQSPATLSLSPGERATLSCRASQSVSS
VKIV 3-1-(1) B3	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNK
VKV 2-1-(1) B2	ETTLTQSPAFMSATPGDKVNISCKASQDID
VKVI 2-1-(1) A26	EIVLTQSPDFQSVTPKEKVTITCRASQSIG
2-1-(1) A10	EIVLTQSPDFQSVTPKEKVTITCRASQSIG
2-1-(1) A14	DVVMTQSPAFLSVTPGEKVTITCQASEGIG

圖 6A

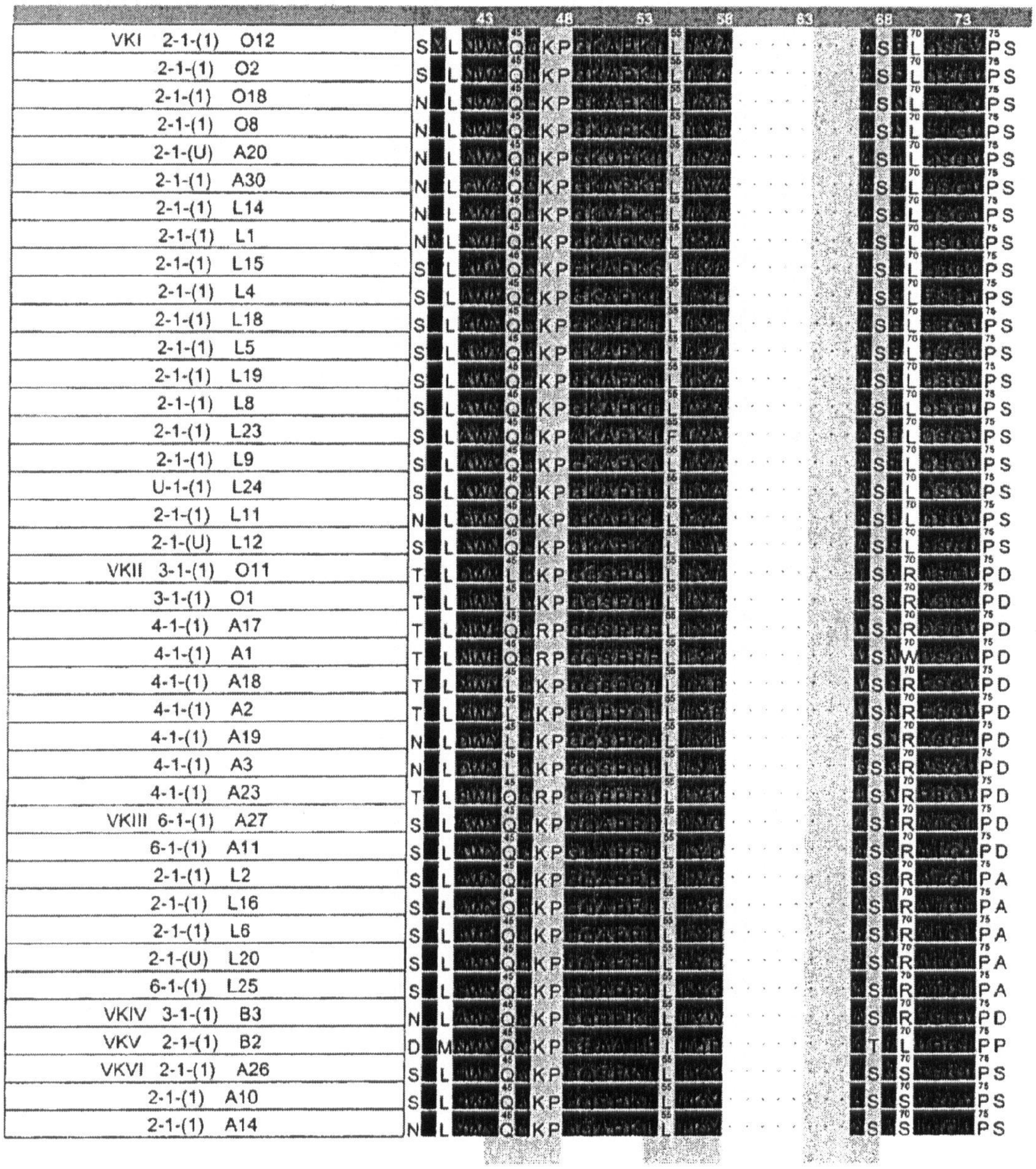

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VKI 2-1-(1) O12
2-1-(1) O2
2-1-(1) O18
2-1-(1) O8
2-1-(U) A20
2-1-(1) A30
2-1-(1) L14
2-1-(1) L1
2-1-(1) L15
2-1-(1) L4
2-1-(1) L18
2-1-(1) L5
2-1-(1) L19
2-1-(1) L8
2-1-(1) L23
2-1-(1) L9
U-1-(1) L24
2-1-(1) L11
2-1-(U) L12
VKII 3-1-(1) O11
3-1-(1) O1
4-1-(1) A17
4-1-(1) A1
4-1-(1) A18
4-1-(1) A2
4-1-(1) A19
4-1-(1) A3
4-1-(1) A23
VKIII 6-1-(1) A27
6-1-(1) A11
2-1-(1) L2
2-1-(1) L16
2-1-(1) L6
2-1-(U) L20
6-1-(1) L25
VKIV 3-1-(1) B3
VKV 2-1-(1) B2
VKVI 2-1-(1) A26
2-1-(1) A10
2-1-(1) A14

圖 6A

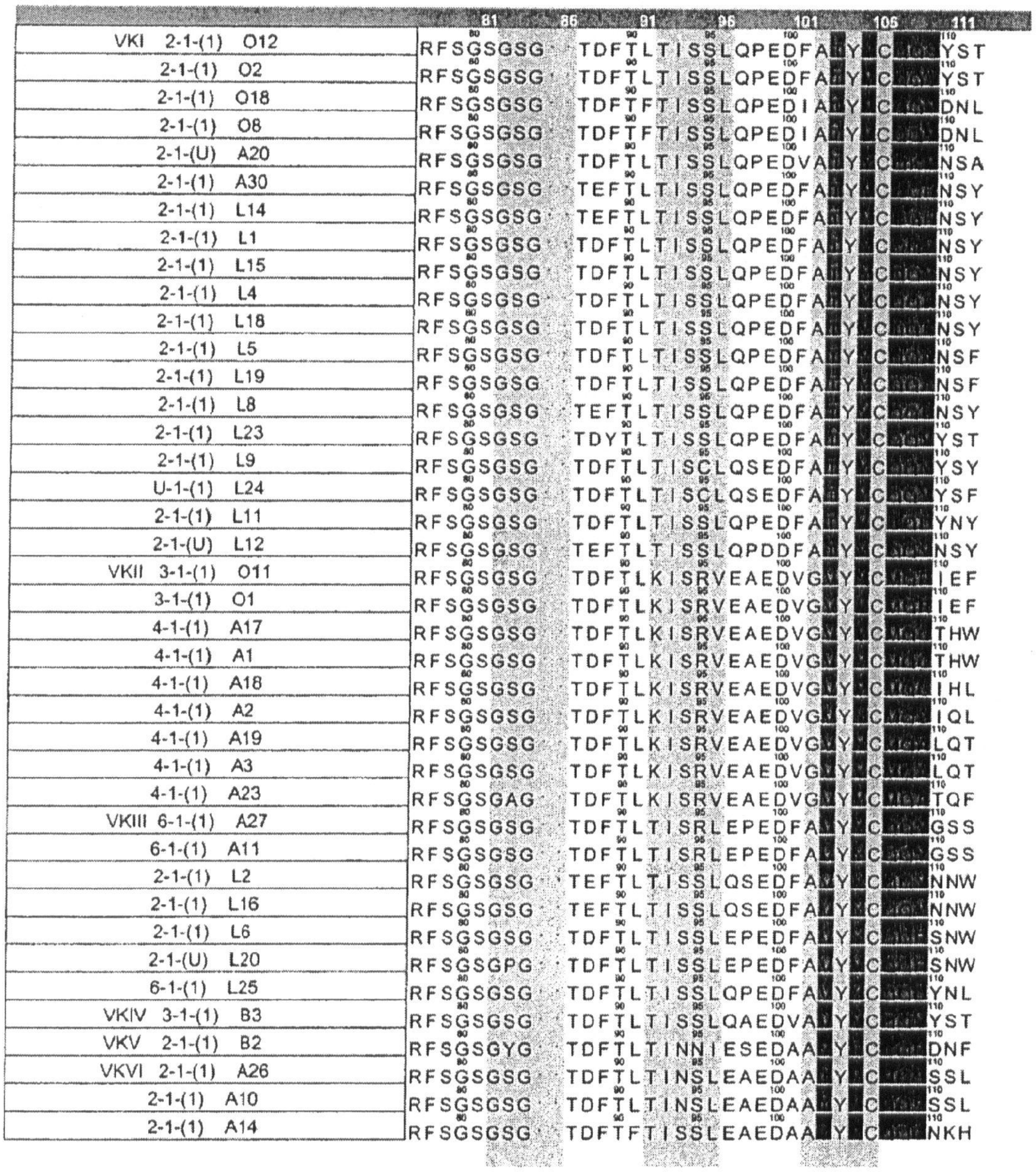

81 86 91 96 101 105 111
VKI 2-1-(1) O12 RFSGSGSG TDFTLTISSLQPEDFATYYC YST
2-1-(1) O2 RFSGSGSG TDFTLTISSLQPEDFATYYC YST
2-1-(1) O18 RFSGSGSG TDFTFTISSLQPEDIATYYC DNL
2-1-(1) O8 RFSGSGSG TDFTFTISSLQPEDIATYYC DNL
2-1-(U) A20 RFSGSGSG TDFTLTISSLQPEDVATYYC NSA
2-1-(1) A30 RFSGSGSG TEFTLTISSLQPEDFATYYC NSY
2-1-(1) L14 RFSGSGSG TEFTLTISSLQPEDFATYYC NSY
2-1-(1) L1 RFSGSGSG TDFTLTISSLQPEDFATYYC NSY
2-1-(1) L15 RFSGSGSG TDFTLTISSLQPEDFATYYC NSY
2-1-(1) L4 RFSGSGSG TDFTLTISSLQPEDFATYYC NSY
2-1-(1) L18 RFSGSGSG TDFTLTISSLQPEDFATYYC NSY
2-1-(1) L5 RFSGSGSG TDFTLTISSLQPEDFATYYC NSF
2-1-(1) L19 RFSGSGSG TDFTLTISSLQPEDFATYYC NSF
2-1-(1) L8 RFSGSGSG TEFTLTISSLQPEDFATYYC NSY
2-1-(1) L23 RFSGSGSG TDYTLTISSLQPEDFATYYC YST
2-1-(1) L9 RFSGSGSG TDFTLTISCLQSEDFATYYC YSY
U-1-(1) L24 RFSGSGSG TDFTLTISCLQSEDFATYYC YSF
2-1-(1) L11 RFSGSGSG TDFTLTISSLQPEDFATYYC YNY
2-1-(U) L12 RFSGSGSG TEFTLTISSLQPDDFATYYC NSY
VKII 3-1-(1) O11 RFSGSGSG TDFTLKISRVEAEDVGMYYC IEF
3-1-(1) O1 RFSGSGSG TDFTLKISRVEAEDVGMYYC IEF
4-1-(1) A17 RFSGSGSG TDFTLKISRVEAEDVGMYYC THW
4-1-(1) A1 RFSGSGSG TDFTLKISRVEAEDVGMYYC THW
4-1-(1) A18 RFSGSGSG TDFTLKISRVEAEDVGMYYC IHL
4-1-(1) A2 RFSGSGSG TDFTLKISRVEAEDVGMYYC IQL
4-1-(1) A19 RFSGSGSG TDFTLKISRVEAEDVGMYYC LQT
4-1-(1) A3 RFSGSGSG TDFTLKISRVEAEDVGMYYC LQT
4-1-(1) A23 RFSGSGAG TDFTLKISRVEAEDVGMYYC TQF
VKIII 6-1-(1) A27 RFSGSGSG TDFTLTISRLEPEDFAMYYC GSS
6-1-(1) A11 RFSGSGSG TDFTLTISRLEPEDFAMYYC GSS
2-1-(1) L2 RFSGSGSG TEFTLTISSLQSEDFAMYYC NNW
2-1-(1) L16 RFSGSGSG TEFTLTISSLQSEDFAMYYC NNW
2-1-(1) L6 RFSGSGSG TDFTLTISSLEPEDFAMYYC SNW
2-1-(U) L20 RFSGSGPG TDFTLTISSLEPEDFAMYYC SNW
6-1-(1) L25 RFSGSGSG TDFTLTISSLQPEDFAMYYC YNL
VKIV 3-1-(1) B3 RFSGSGSG TDFTLTISSLQAEDVAMYYC YST
VKV 2-1-(1) B2 RFSGSGYG TDFTLTINNIESEDAAMYYC DNF
VKVI 2-1-(1) A26 RFSGSGSG TDFTLTINSLEAEDAAMYYC SSL
2-1-(1) A10 RFSGSGSG TDFTLTINSLEAEDAAMYYC SSL
2-1-(1) A14 RFSGSGSG TDFTFTISSLEAEDAAMYYC NKH

圖 6A

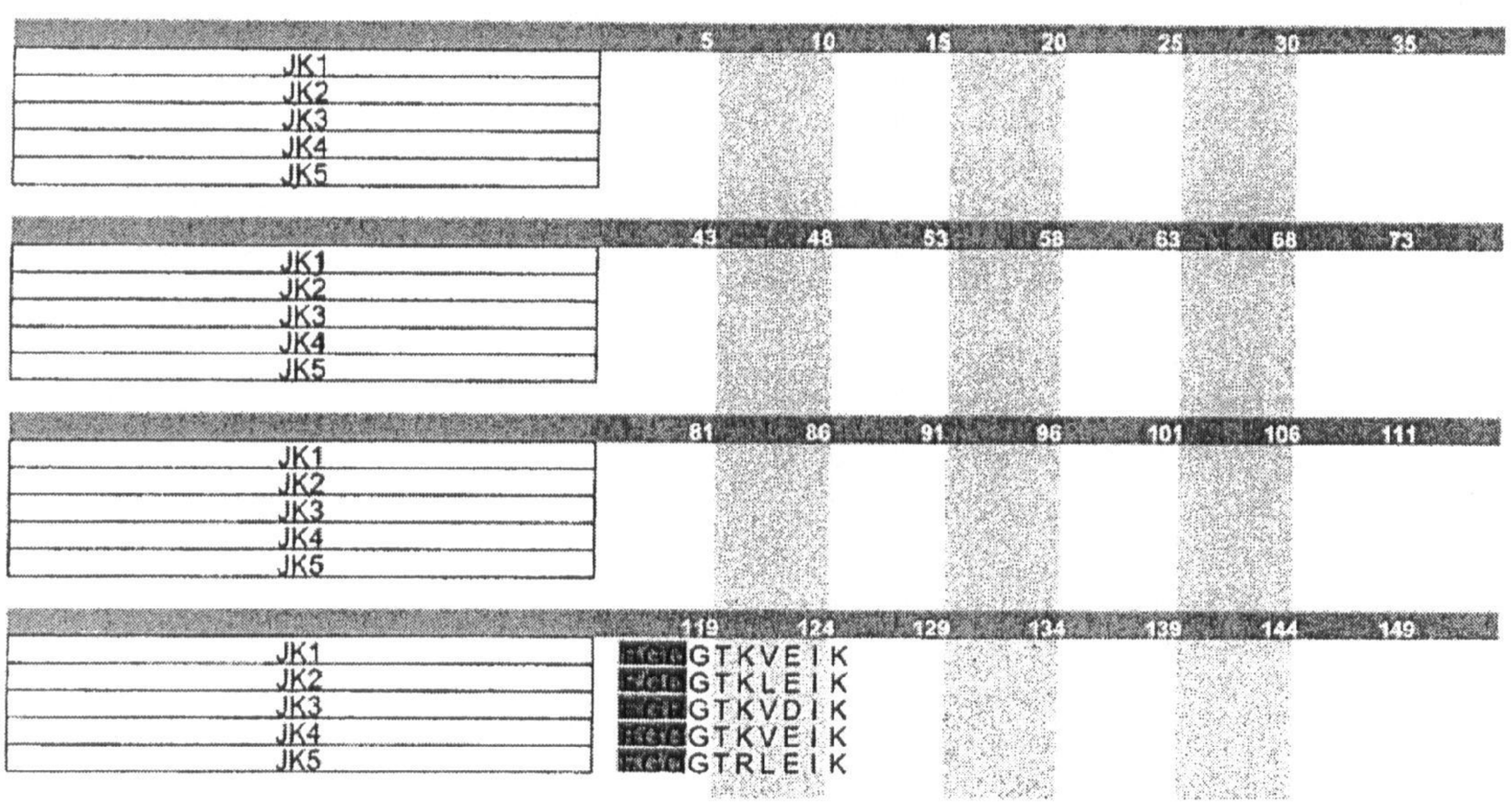

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JK1
JK2
JK3
JK4
JK5
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JK1
JK2
JK3
JK4
JK5
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JK1
JK2
JK3
JK4
JK5
119 124 129 134 139 144 149
JK1 GTKVEIK
JK2 GTKLEIK
JK3 GTKVDIK
JK4 GTKVEIK
JK5 GTRLEIK

圖 6B

	5 10 15 20 25 30 35
VL1 13-7(A) 1a	QSVLTQP PSVSEAPRQRVTISCSGSS SNIGN
14-7(A) 1e	QSVLTQP PSVSGAPGQRVTISCTGSS SNIGAG
13-7(A) 1c	QSVLTQP PSASGTPGQRVTISCSGSS SNIGS
13-7(A) 1g	QSVLTQP PSASGTPGQRVTISCSGSS SNIGS
13-7(A) 1b	QSVLTQP PSVSAAPGQKVTISCSGSS SNIGN
VL2 14-7(A) 2c	QSALTQP PSASGSPGQSVTISCTGTS SDVGGY
14-7(A) 2e	QSALTQP RSVSGSPGQSVTISCTGTS SDVGGY
14-7(A) 2a2	QSALTQP ASVSGSPGQSITISCTGTS SDVGGY
14-7(A) 2d	QSALTQP PSVSGSPGQSVTISCTGTS SDVGSY
14-7(A) 2b2	QSALTQP ASVSGSPGQSITISCTGTS SDVGSY
VL3 11-7 3r	SYELTQP PSVSVSPGQTASITCSGD KLGD
11-7 3j	SYELTQP LSVSVALGQTARITCGGN NIGS
11-7 3p	SYELTQP PSVSVSPGQTARITCSGD ALPK
11-7 3a	SYELTQP PSVSVSLGQMARITCSGE ALPK
11-7 3l	SSELTQD PAVSVALGQTVRITCQGD SLRS
11-7 3h	SYVLTQP PSVSVAPGKTARITCGGN NIGS
11-7 3e	SYELTQL PSVSVSPGQTARITCSGD VLGE
11-7 3m	SYELMQP PSVSVSPGQTARITCSGD ALPK
11-7 2-19	SYELTQP SSVSVSPGQTARITCSGD VLAK
VL4 12-11 4c	LPVLTQP PSASALLGASIKLTCTLSS EHSTY
12-11 4a	QPVLTQS SSASASLGSSVKLTCTLSS GHSSY
12-11 4b	QLVLTQS PSASASLGASVKLTCTLSS GHSSY
VL5 14-11 5e	QPVLTQP PSSSASPGESARLTCTLPS DINVGS
14-11 5c	QAVLTQP ASLSASPGASASLTCTLRS GINVGT
14-11 5b	QPVLTQP SSHSASSGASVRLTCMLSS GFSVGD
VL6 13-7(B) 6a	NFMLTQP HSVSESPGKTVTISCTRSS GSIAS
VL7 14-7(B) 7a	QTVVTQE PSLTVSPGGTVTLTCASST GAVTSG
14-7(B) 7b	QAVVTQE PSLTVSPGGTVTLTCGSST GAVTSG
VL8 14-7(B) 8a	QTVVTQE PSFSVSPGGTVTLTCGLSS GSVSTS
VL9 12-12 9a	QPVLTQP PSASASLGASVTLTCTLSS GYSNY
VL10 13-7(C) 10a	QAGLTQP PSVSKGLRQTATLTCTGNS NNVGN

圖 7A

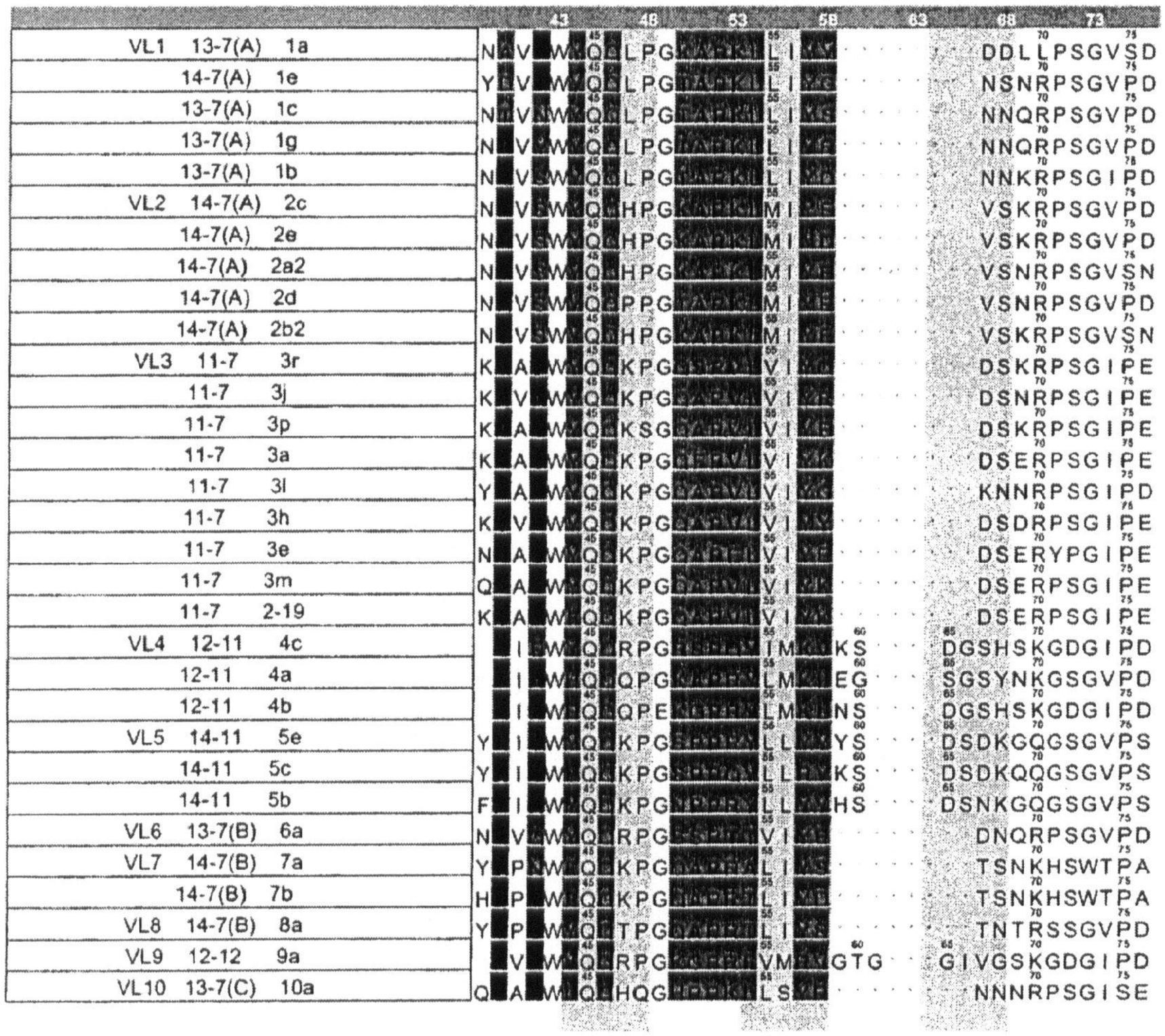

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VL1 13-7(A) 1a
14-7(A) 1e
13-7(A) 1c
13-7(A) 1g
13-7(A) 1b
VL2 14-7(A) 2c
14-7(A) 2e
14-7(A) 2a2
14-7(A) 2d
14-7(A) 2b2
VL3 11-7 3r
11-7 3j
11-7 3p
11-7 3a
11-7 3l
11-7 3h
11-7 3e
11-7 3m
11-7 2-19
VL4 12-11 4c
12-11 4a
12-11 4b
VL5 14-11 5e
14-11 5c
14-11 5b
VL6 13-7(B) 6a
VL7 14-7(B) 7a
14-7(B) 7b
VL8 14-7(B) 8a
VL9 12-12 9a
VL10 13-7(C) 10a

圖 7A

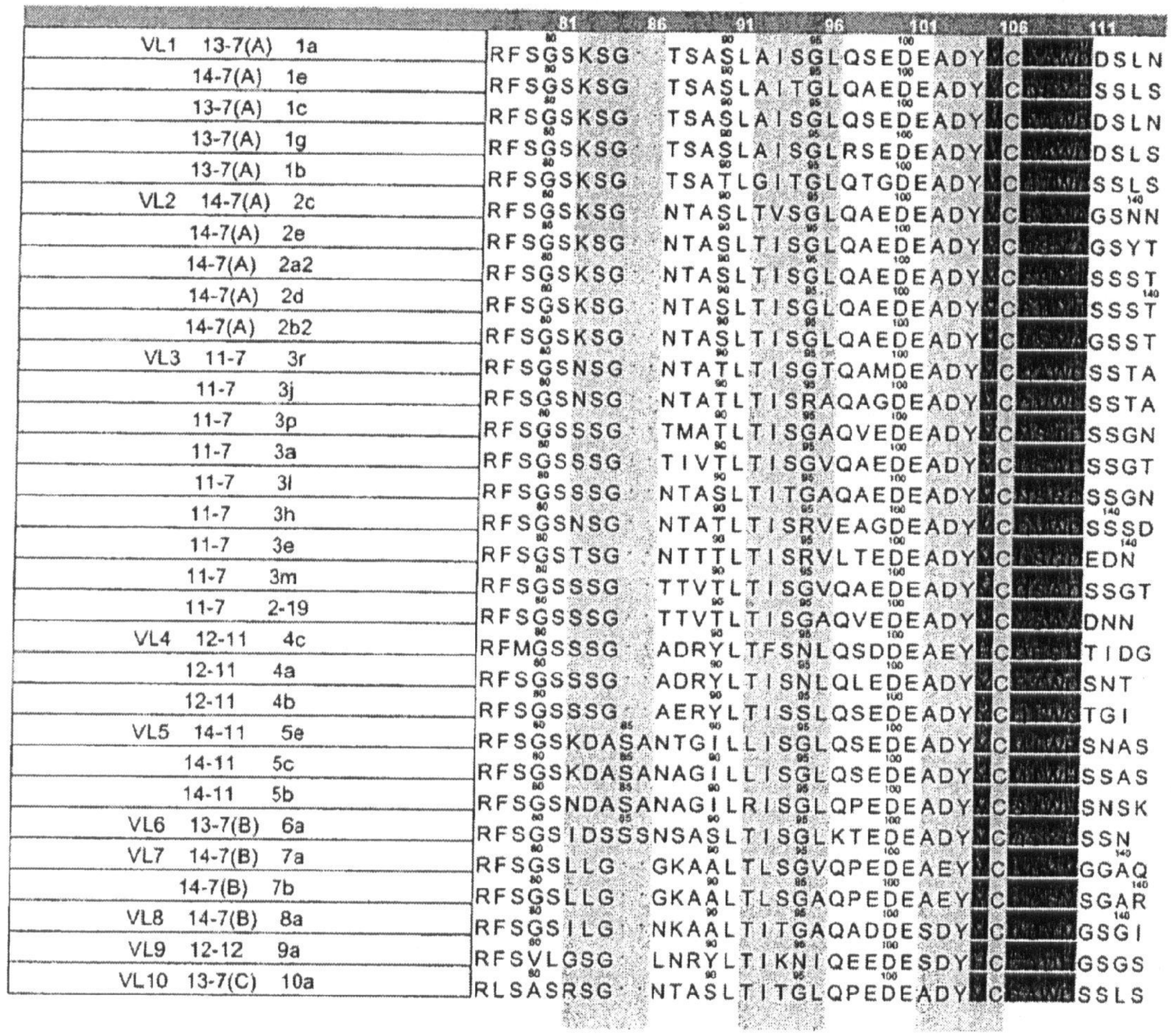

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14-7(A) 1e RFSGSKSG TSASLAITGLQAEDEADY C SSLS
13-7(A) 1c RFSGSKSG TSASLAISGLQSEDEADY C DSLN
13-7(A) 1g RFSGSKSG TSASLAISGLRSEDEADY C DSLS
13-7(A) 1b RFSGSKSG TSATLGITGLQTGDEADY C SSLS
VL2 14-7(A) 2c RFSGSKSG NTASLTVSGLQAEDEADY C GSNN
14-7(A) 2e RFSGSKSG NTASLTISGLQAEDEADY C GSYT
14-7(A) 2a2 RFSGSKSG NTASLTISGLQAEDEADY C SSST
14-7(A) 2d RFSGSKSG NTASLTISGLQAEDEADY C SSST
14-7(A) 2b2 RFSGSKSG NTASLTISGLQAEDEADY C GSST
VL3 11-7 3r RFSGSNSG NTATLTISGTQAMDEADY C SSTA
11-7 3j RFSGSNSG NTATLTISRAQAGDEADY C SSTA
11-7 3p RFSGSSSG TMATLTISGAQVEDEADY C SSGN
11-7 3a RFSGSSSG TIVTLTISGVQAEDEADY C SSGT
11-7 3l RFSGSSSG NTASLTITGAQAEDEADY C SSGN
11-7 3h RFSGSNSG NTATLTISRVEAGDEADY C SSSD
11-7 3e RFSGSTSG NTTTLTISRVLTEDEADY C EDN
11-7 3m RFSGSSSG TTVTLTISGVQAEDEADY C SSGT
11-7 2-19 RFSGSSSG TTVTLTISGAQVEDEADY C DNN
VL4 12-11 4c RFMGSSSG ADRYLTFSNLQSDDEAEY C TIDG
12-11 4a RFSGSSSG ADRYLTISNLQLEDEADY C SNT
12-11 4b RFSGSSSG AERYLTISSLQSEDEADY C TGI
VL5 14-11 5e RFSGSKDASANTGILLISGLQSEDEADY C SNAS
14-11 5c RFSGSKDASANAGILLISGLQSEDEADY C SSAS
14-11 5b RFSGSNDASANAGILRISGLQPEDEADY C SNSK
VL6 13-7(B) 6a RFSGSIDSSSNSASLTISGLKTEDEADY C SSN
VL7 14-7(B) 7a RFSGSLLG GKAALTLSGVQPEDEAEY C GGAQ
14-7(B) 7b RFSGSLLG GKAALTLSGAQPEDEAEY C SGAR
VL8 14-7(B) 8a RFSGSILG NKAALTITGAQADDESDY C GSGI
VL9 12-12 9a RFSVLGSG LNRYLTIKNIQEEDESDY C GSGS
VL10 13-7(C) 10a RLSASRSG NTASLTITGLQPEDEADY C SSLS

圖 7A

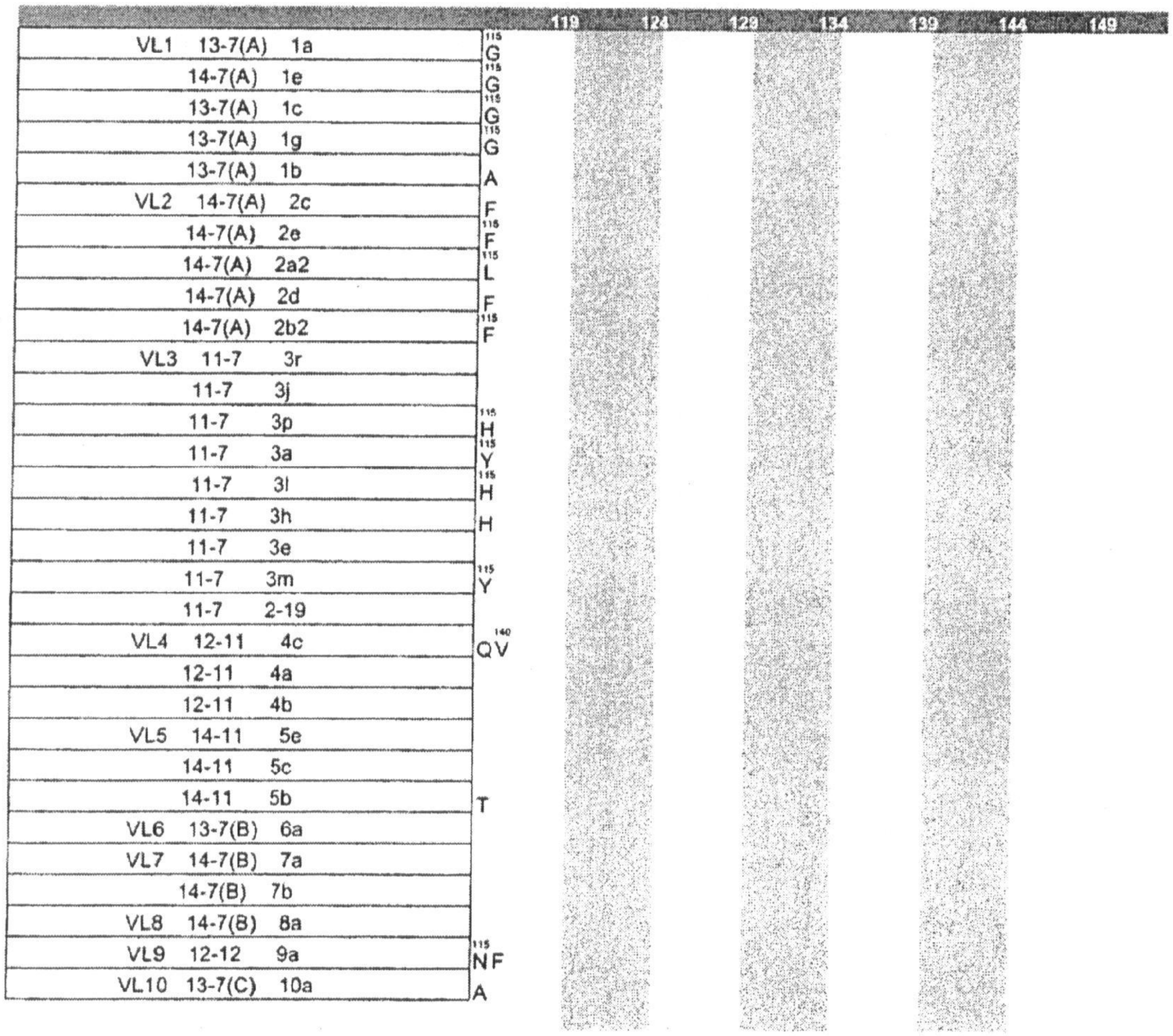

119 124 129 134 139 144 149
VL1 13-7(A) 1a
14-7(A) 1e
13-7(A) 1c
13-7(A) 1g
13-7(A) 1b
VL2 14-7(A) 2c
14-7(A) 2e
14-7(A) 2a2
14-7(A) 2d
14-7(A) 2b2
VL3 11-7 3r
11-7 3j
11-7 3p
11-7 3a
11-7 3l
11-7 3h
11-7 3e
11-7 3m
11-7 2-19
VL4 12-11 4c
12-11 4a
12-11 4b
VL5 14-11 5e
14-11 5c
14-11 5b
VL6 13-7(B) 6a
VL7 14-7(B) 7a
14-7(B) 7b
VL8 14-7(B) 8a
VL9 12-12 9a
VL10 13-7(C) 10a
115 G
115 G
115 G
115 G
A
F
115 F
115 L
F
115 F
115 H
115 Y
115 H
H
115 Y
140 QV
T
115 NF
A

圖 7A

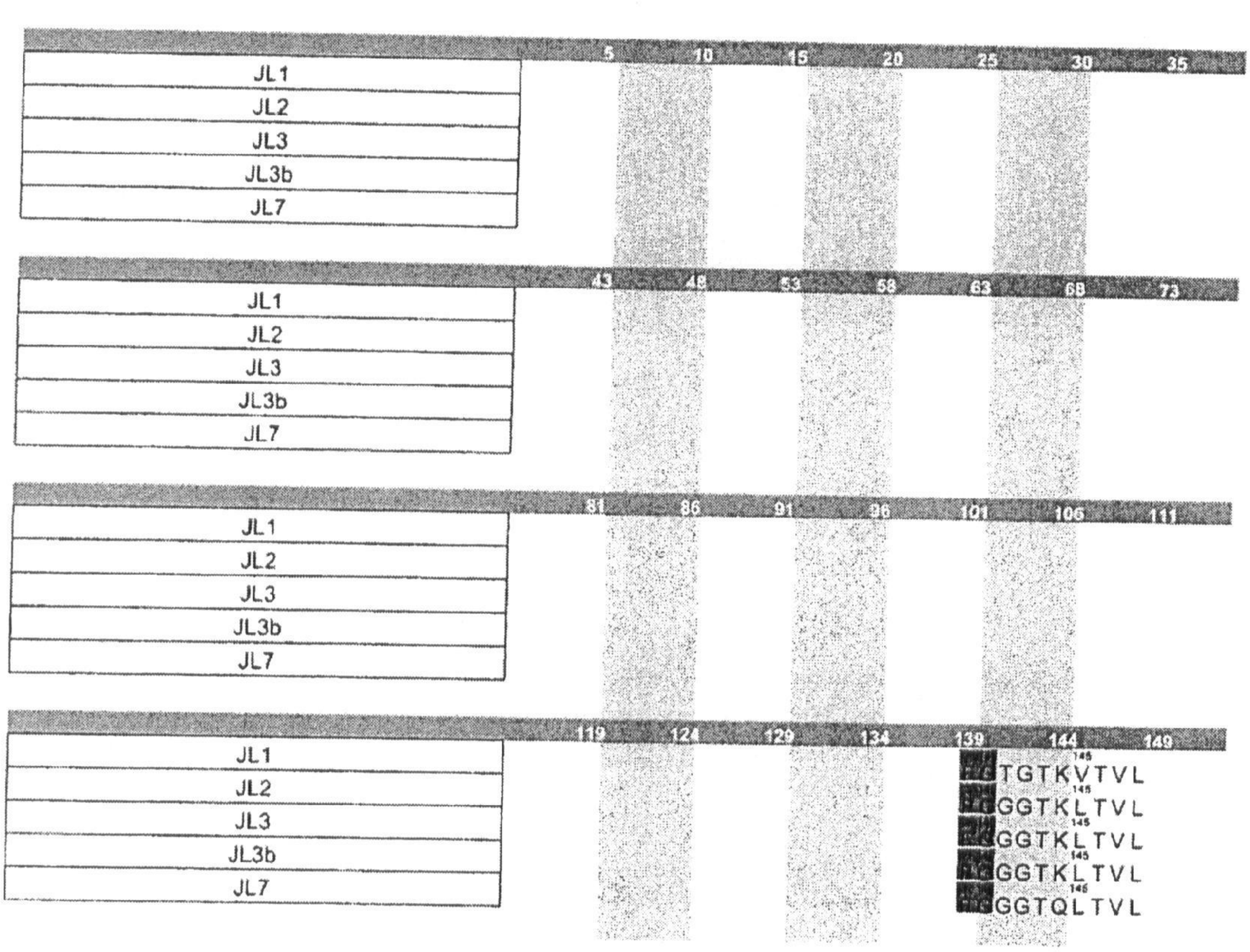

JL1
JL2
JL3
JL3b
JL7
5
10
15
20
25
30
35
43
48
53
58
63
68
73
81
86
91
96
101
106
111
119
124
129
134
139
144
149
TGTKVTVL
GGTKLTVL
GGTKLTVL
GGTKLTVL
GGTQLTVL

圖 7B

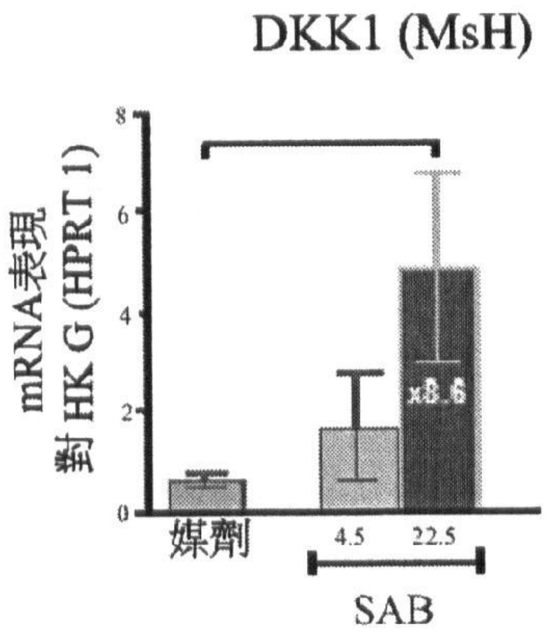

DKK1 (MsH)
mRNA表現
對 HK G (HPRT 1)
8
6
4
2
0
x8.6
媒劑
4.5
22.5
SAB

圖 8

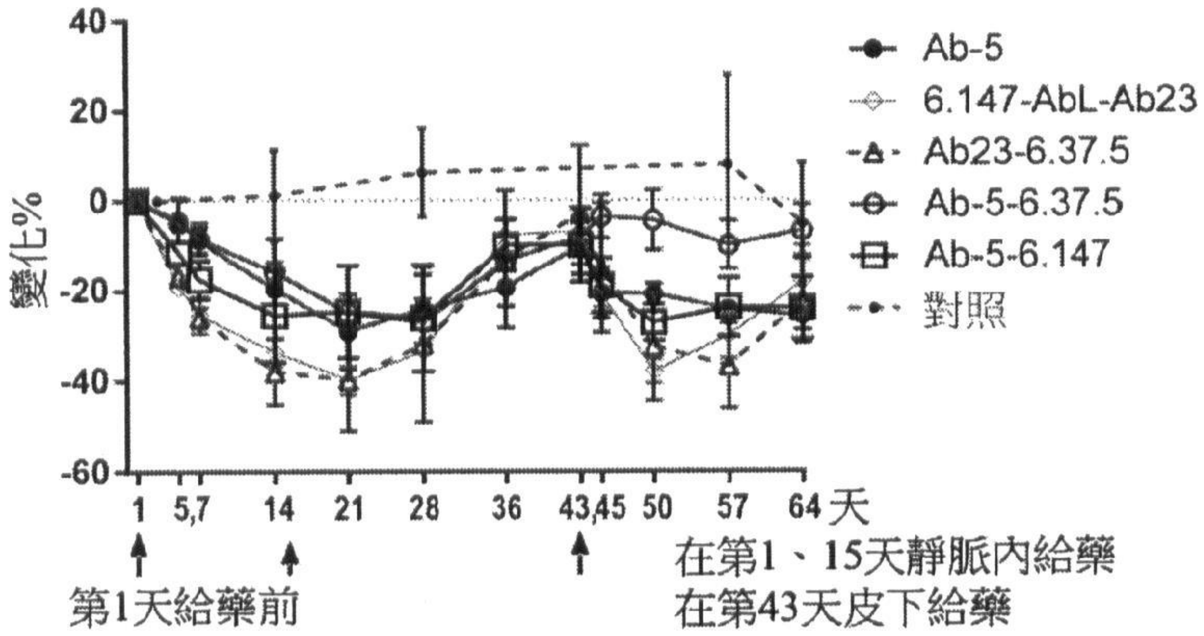
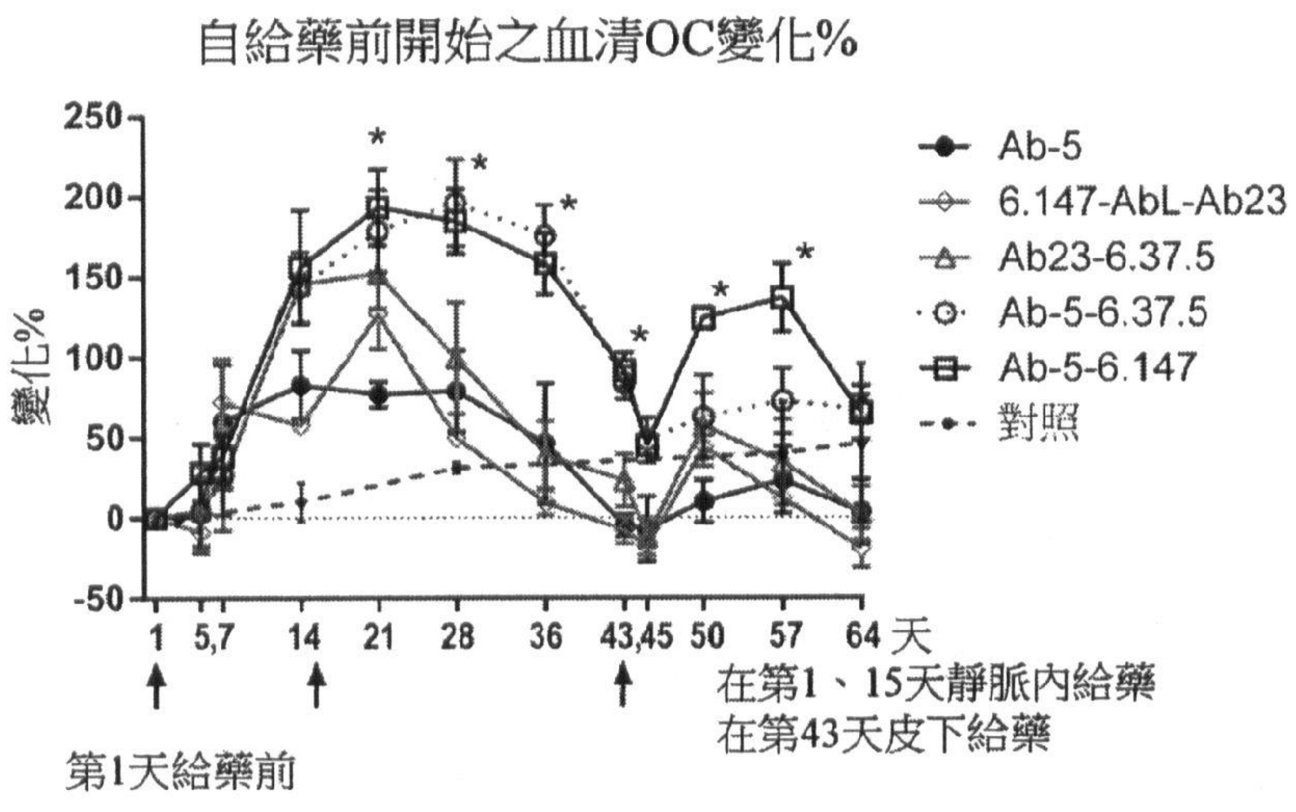
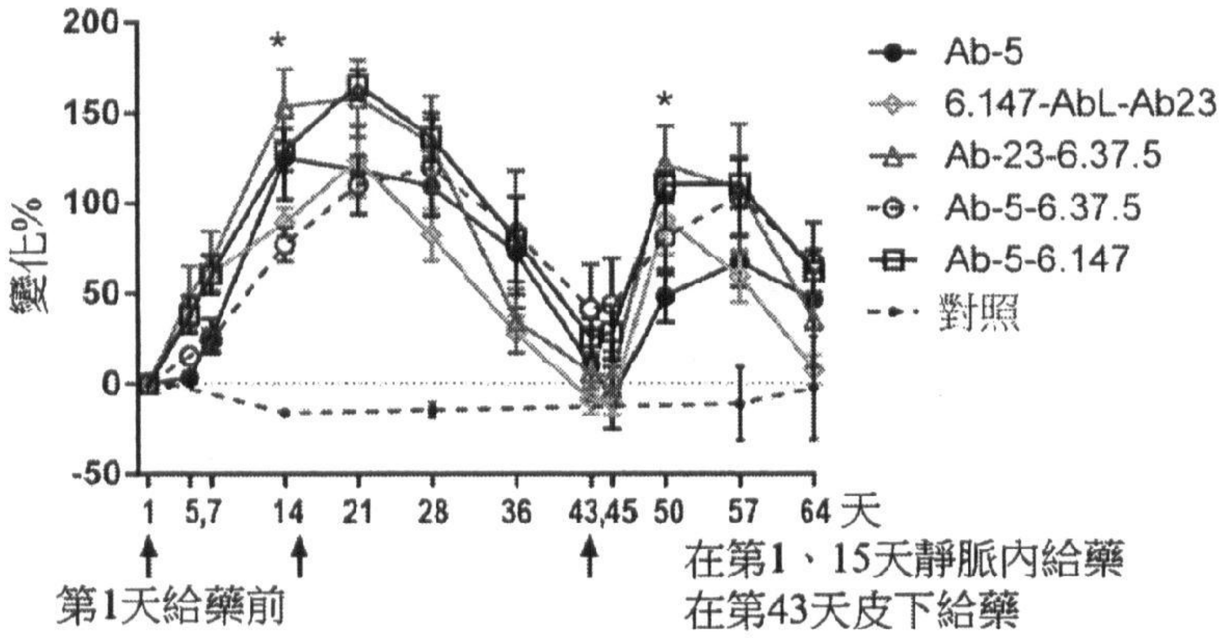

自給藥前開始之血清TRACP 5b變化%
40
20
0
-20
-40
-60
變化%
1
5,7
14
21
28
36
43,45
50
57
64 天
Ab-5
6.147-AbL-Ab23
Ab23-6.37.5
Ab-5-6.37.5
Ab-5-6.147
對照
第1天給藥前
在第1、15天靜脈內給藥
在第43天皮下給藥

圖 9



*p<0.05對Ab-5(單因子ANOVA)

圖 10



*p<0.05對Ab-5(單因子ANOVA)

圖 11

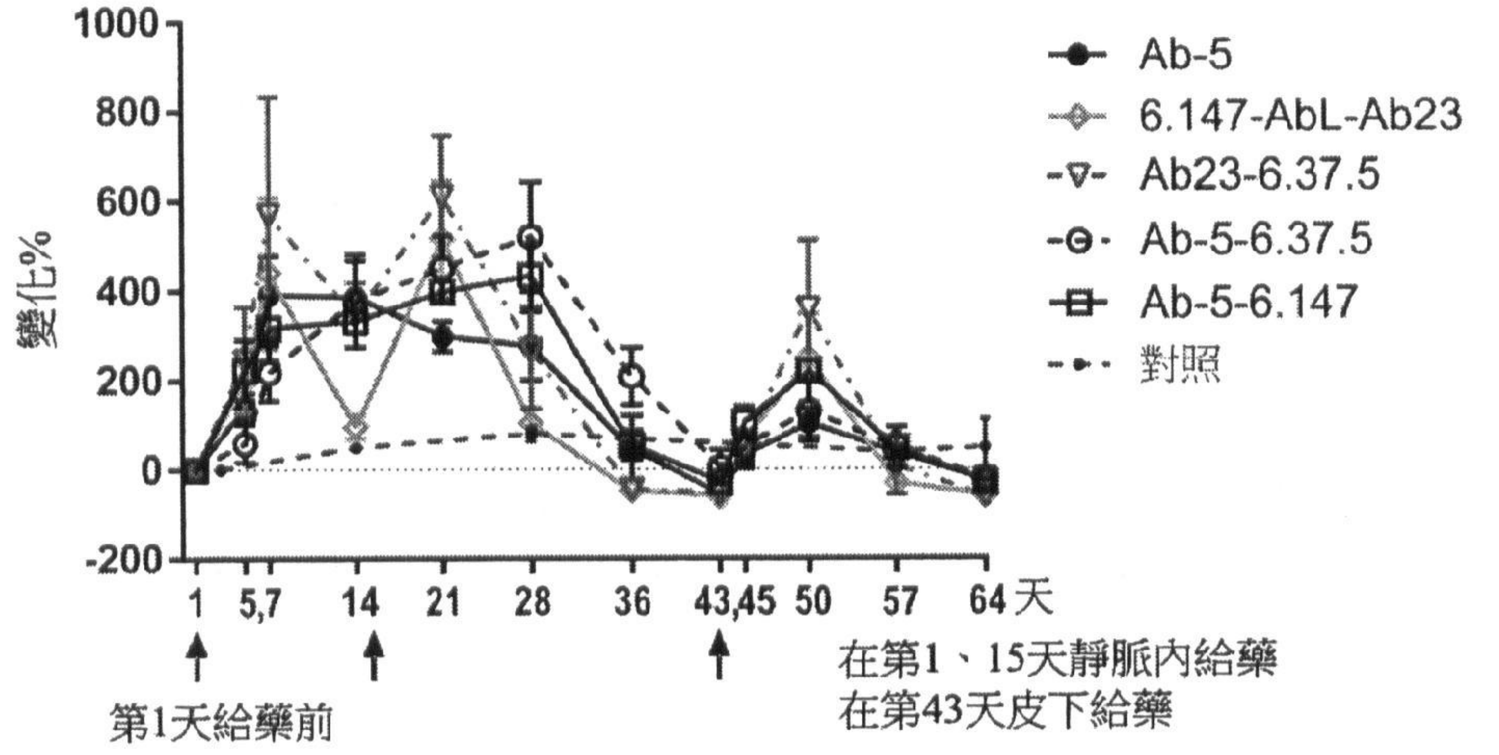

自給藥前開始之血清CICP變化%
變化%
1000
800
600
400
200
0
-200
1
5,7
14
21
28
36
43,45
50
57
64天
Ab-5
6.147-AbL-Ab23
Ab23-6.37.5
Ab-5-6.37.5
Ab-5-6.147
對照
第1天給藥前
在第1、15天靜脈內給藥
在第43天皮下給藥

圖 12

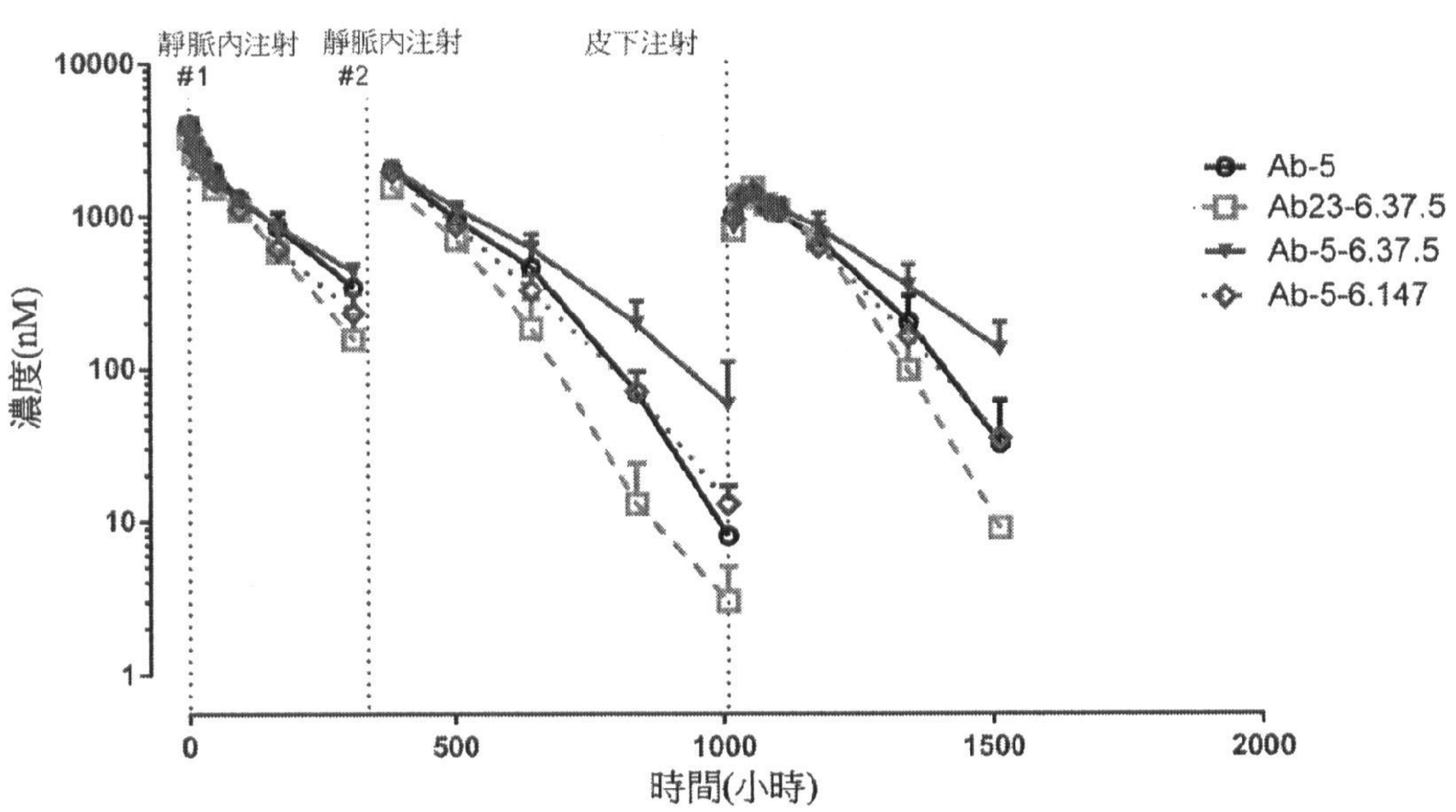
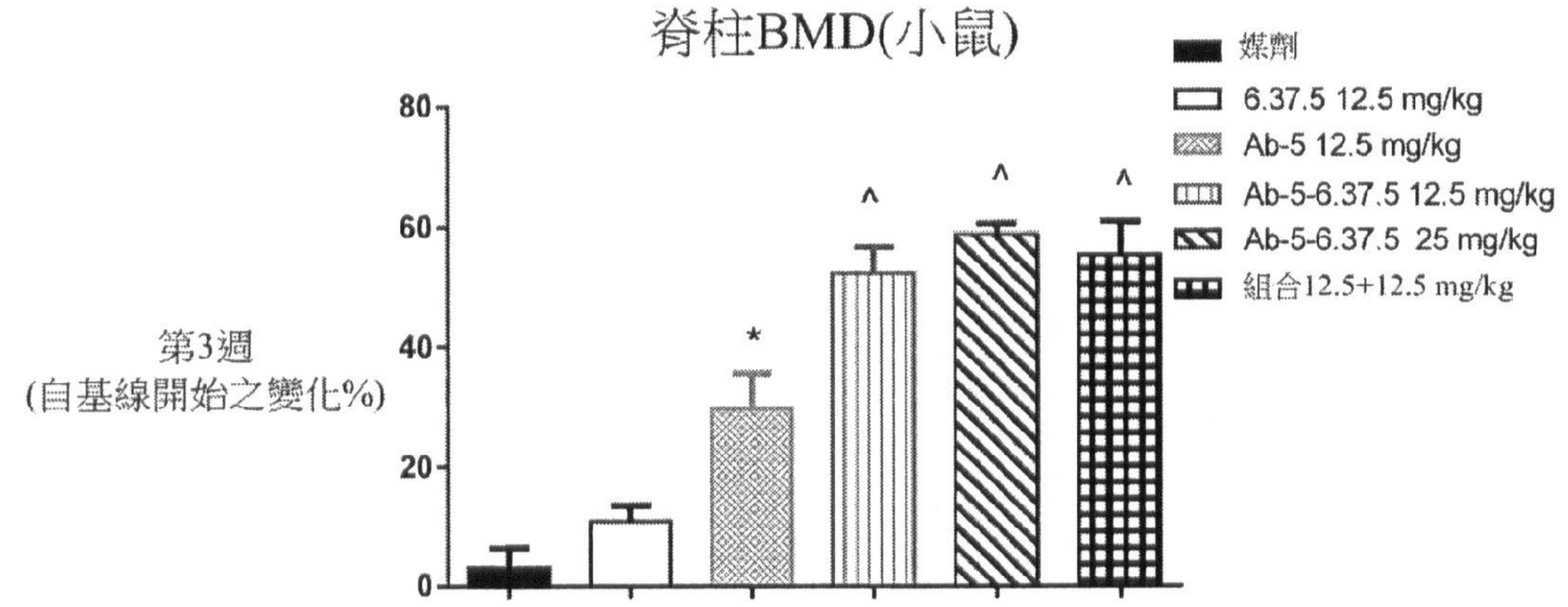

靜脈內注射 #1
靜脈內注射 #2
皮下注射
濃度(nM)
10000
1000
100
10
1
0
500
1000
1500
2000
時間(小時)
Ab-5
Ab23-6.37.5
Ab-5-6.37.5
Ab-5-6.147

圖 13



* p<0.05對媒劑或6.37.5; ^ p<0 .01對Ab-5或6.37.5(單因子ANOVA)

圖 14