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可活化的基質降解酵素之活體內暫時性控制

IN VIVO TEMPORAL CONTROL OF ACTIVATABLE MATRIX-DEGRADING ENZYMES

(57)摘要

本發明提供用於控制基質降解酵素之活體內作用之持續時間的方法及組合。該等方法及組合容許在向細胞外基質(或「ECM」)投藥之後暫時性活體內活化基質降解酵素。具有受控作用持續時間之基質降解酵素可用於治療特徵在於一或多種 ECM 組份之沈積或積累增加的 ECM 介導之疾病或病症。

Methods and combinations are provided for controlling the duration of action,in vivo , of matrix-degrading enzymes. The methods and combinations permit temporary in-vivo activation of matrix-degrading enzymes upon administration to the extra cellular matrix (or “ECM”). Matrix-degrading enzymes having a controlled duration of action can be used to treat ECM-mediated diseases or disorders characterized by increased deposition or accumulation of one or more ECM components.

六、發明說明：

相關申請案

本發明主張2008年3月6日申請之Gilbert Keller及Gregory Frost之標題為「In Vivo Temporal Control of Activatable Matrix-Degrading Enzymes」的美國臨時申請案第61/068,667號，及2008年5月14日申請之Gilbert Keller及Gregory Frost之標題為「In Vivo Temporal Control of Activatable Matrix-Degrading Enzyme」的美國臨時申請案第61/127,725號之優先權。容許時，上述申請案之要點以全文引用的方式併入本文中。

【發明所屬之技術領域】

本發明提供用於控制基質降解酵素之活體內作用之持續時間的方法及組合。該等方法及組合容許在向細胞外基質（或「ECM」）投藥之後暫時性活體內活化基質降解酵素。具有受控作用持續時間之基質降解酵素可用於治療特徵在於一或多種ECM組份之沈積或積累增加的ECM介導之疾病或病症。

【先前技術】

細胞外基質（extracellular matrix，ECM）對細胞及組織提供重要結構支撐。由ECM組份之過量沈積或積累引起之細胞外基質的缺陷或變化會導致ECM介導之疾病或病狀。此等疾病中包含膠原蛋白（collagen）介導之疾病或病狀，其特徵在於存在豐富的膠原蛋白纖維中隔（fibrous septae）。對於該等疾病或病狀之唯一批准治療方法通常為

會具有高度侵襲性之手術。諸如用於治療杜普宜特朗氏症候群（Dupuytren's syndrome）（亦稱為杜普宜特朗氏攣縮（Dupuytren's contracture））之刺穿腱膜切開術（needle aponeurotomy）或用於脂肪團之吸脂術的其他治療亦具有高度侵襲性。

降解膠原蛋白之於中性 pH 值下具活性的酵素膠原酶（collagenase）已用於治療 ECM 介導之病狀，諸如脂肪團（參見例如，公開美國申請案第 US20070224184 號）；杜普宜特朗氏症候群（參見例如，美國專利第 USRE39941 號；第 5589171 號；第 6086872 號）；及帕榮雷氏病（Peyronie's disease）（參見例如，美國專利 6022539）。然而，膠原酶能夠不可逆地裂解 I 型、II 型及 III 型膠原蛋白。延長之膠原酶活性限制可投予之劑量且亦冒與延長活化相關之副作用的危險。因此，對 ECM 介導之疾病及病狀的替代性治療存在需要。因此，本文之目的在於提供用於治療 ECM 介導之疾病及病狀之可活化的基質降解酵素的方法及組合。

【發明內容】

本發明提供藉由投予可活化的基質降解酵素（activatable matrix-degrading enzyme，AMDE）及活化劑來治療細胞外基質（ECM）之疾病或病狀的方法。通常投予治療有效量之 AMDE。該量與所治療之疾病或病狀有關且可憑經驗確定。所選之 AMDE 為在活體內投藥位點無活性之 AMDE（諸如 ECM）。AMDE 包括天然存在之基質降解（matrix-degrading，MD）酵素，其物種及對偶基因及其他

變異體，諸如經修飾以改變活性（諸如受質特異性）或性質（諸如穩定性）之酵素。AMDE 可藉由製程及方法來修飾以具有諸如增加之對裂解特定類型之膠原蛋白的特異性之性質，或具有改變之 pH 值曲線或對於本文之方法最佳。與活化劑或活化劑組合（不存在於投藥位點處）結合投藥產生當該活化劑耗散或以其他方式自該位點移除時在有限時期內具活性之 AMDE。AMDE 及活化劑可以同一或分開的組成物形式依次、同時投予，或間歇投予。病狀可經選擇從而使活性之時期得以預先確定。AMDE 可需要活性或全部活性之一種以上活化劑。AMDE 可以酵素原（zymogen）形式、以全長成熟多肽（諸如單鏈或雙鏈多肽）形式或以前軀多肽形式投予。AMDE 可以組成物（諸如溶液或懸浮液）形式提供，或以結晶或凍乾形式提供。例示性 AMDE 包括（但不限於）組織蛋白酶（cathepsin）、鈣激活中性蛋白酶（calpain）及肝素酶（heparanase）。

通常，AMDE 係經表皮下投予。當向其他位點投予（包括局部投予）時，選擇 AMDE 以使 AMDE 於 pH 5.5 下實質上具活性（典型地與於其最大 pH 值下相比保留活性之至少約 10%、11%、12%、13%或 15%）。另外，對於該投藥而言，AMDE 典型地於中性 pH 值下無活性（保留活性之小於約 10%、11%、12%、13%或 15%）。ECM 之疾病及病狀包括（例如）膠原蛋白介導之疾病及病狀。該等疾病及病狀包括（但不限於）：脂肪團；杜普宜特朗氏病（Dupuytren's disease）手術黏連、瘢痕瘤、肥厚性瘢痕及凹陷性瘢痕；帕榮雷氏

病（Peyronie's disease）；萊德豪斯纖維化（Ledderhose fibrosis）；關節僵硬；包括凍肩；現有瘢痕，包括手術黏連、瘢痕瘤、肥厚性瘢痕及凹陷性瘢痕；硬皮病；淋巴水腫及膠原性結腸炎。表皮下投藥包括（但不限於）皮下投藥、肌肉內投藥、病灶內投藥及皮內投藥。

因此，本發明提供藉由向細胞外基質（ECM）經表皮下投予可活化的基質降解酵素（AMDE）及活化劑來治療ECM之疾病或病狀的方法。AMDE在該活化劑不存在之情況下在該ECM中無活性或部分無活性；該活化劑在向ECM投予時提供該酵素活化條件，藉此AMDE具活性，且在投予該活化劑之前該活化條件通常不存在於ECM中。在一些具體實例中，選擇AMDE為實質上於中性pH值下無活性之酵素。

本發明亦提供藉由投予可活化的基質降解酵素（AMDE）及活化劑來治療細胞外基質（ECM）之疾病或病狀的方法，其中該AMDE於中性pH值下無活性，該活化劑提供該酵素之酸性pH值活化條件以使得AMDE在投予之後具活性，且在投予活化劑之前該活化條件不存在於投藥位點；且AMDE實質上於pH 5.5下具活性。AMDE及活化劑可藉由任何合適之途徑投予，包括（但不限於）皮下、肌肉內、病灶內、皮內、表面（topical）、經皮、靜脈內、經口及經直腸投藥。舉例而言，投藥可為表皮下投藥。

本發明亦提供藉由投予可活化的基質降解酵素（AMDE）及活化劑來治療細胞外基質（ECM）之疾病或病

狀的方法，其中該 AMDE 在該活化劑不存在之情況下在該 ECM 中無活性以使得該活化劑在投予時提供該酵素活化條件以使 AMDE 具活性，在投予活化劑之前該活化條件不存在於 ECM 中，且活化劑係選自金屬離子、溫度及賦形劑或還原劑或氧化劑之離子強度。AMDE 及活化劑或活化劑組合可藉由任何合適之途徑投予，包括（但不限於）皮下、肌肉內、病灶內、皮內、表面、經皮、靜脈內、經口及經直腸投藥。舉例而言，投藥可為表皮下投藥。

在一例示性具體實例中，提供藉由向細胞外基質（ECM）投予可活化的基質降解酵素（AMDE）及活化劑來治療 ECM 之疾病或病狀的方法，其中 AMDE 在該活化劑不存在之情況下在 ECM 中無活性以使得活化劑在向 ECM 投予時提供該酵素活化條件以使 AMDE 具活性，在投予活化劑之前該活化條件不存在於 ECM 中；且活化劑係選自金屬離子、溫度及離子強度。AMDE 及活化劑可藉由任何合適之途徑投予，包括（但不限於）皮下、肌肉內、病灶內、皮內、表面、經皮、靜脈內、經口及經直腸投藥。舉例而言，投藥可為表皮下投藥。

在其他例示性具體實例中，提供藉由向 ECM 經表皮下投予治療有效量之可活化的組織蛋白酶 L 及活化劑來治療膠原蛋白介導之疾病或病狀的方法，其中該可活化的組織蛋白酶 L 在該活化劑不存在之情況下在該 ECM 中無活性，活化劑在向 ECM 投予時提供酵素活化條件以使可活化的組織蛋白酶 L 具活性，在投予活化劑之前該活化條件不存在

於 ECM 中；且活化條件為酸性 pH 值。例示性組織蛋白酶 L 多肽為包括 SEQ ID NO:1 中所闡明之胺基酸序列者，或其對偶基因、物種或其他變異體，其中該等變異體經修飾以具有改變之性質或活性且典型地與 SEQ ID NO:1 中之任一者中所闡明之胺基酸序列相比具有至少或具有 60%、65%、70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%或 99%序列一致性。

一般而言，隨時間，在本文之方法中，活化劑將由局部環境移除或耗散或中和以致 AMDE 不再具活性。可選擇或製備活化條件及/或活化劑以使 AMDE 在有限或預定時間內具活性。活化劑可與 AMDE 在同一組成物中或以分開的組成物形式提供或投予，且其可依次、同時或間歇投予。舉例而言，在投藥之前或投藥之後使 AMDE 暴露於活化劑，藉此酵素在投藥之後具活性。活化條件包括（但不限於）pH 值、離子強度、溫度及金屬離子。活化條件中之一者為 pH 值，諸如酸性 pH 值，例如在或約在 3 至 6.5、或 3.5 至 6、或 3 至 5.5、或 3 至 4.5、或 4 至 6、或 4 至 5.5、或 4.5 至 5、或 5 至 6 範圍內，諸如 3、3.5、4、4.5、5、5.5、6 或 6.5。pH 值可藉由使 AMDE 與具有所需 pH 值之緩衝溶液接觸來獲得。緩衝液可包括含有選自 2-(N-嗎啉基)乙烷磺酸（2-(N-morpholino)ethanesulfonic acid，MES）、乙酸、檸檬酸、順丁烯二酸鹽、丁二酸鹽、乳酸鹽、甘胺酸鹽、檸檬酸磷酸鹽及組胺酸之酸者。其他例示性活性條件包括（但不限於）金屬離子及溫度。舉例而言，活化條件可為金屬

離子，諸如 Ca^{2+}、Zn^{2+}或 Mg^{2+}。溫度可為低溫或高溫，其中酵素實質上於投藥位點之溫度（典型地為 37℃）下無活性。因此，活化條件為溫度且該溫度為或約為 20℃、21℃、22℃、23℃、24℃、25℃、26℃、27℃、28℃、29℃、30℃或 37℃以上，諸如 40℃、41℃、42℃、43℃、44℃、45℃、46℃、47℃、48℃、49℃、50℃、55℃、60℃、65℃、70℃、80℃且更高至不活體內損害組織或細胞之任何耐受溫度。

對活性之暫時性控制可例如藉由選擇緩衝液之緩衝能力及/或其離子強度來達成。活性之預定時間可藉由選擇該等條件來實現，其可憑經驗確定或藉由熟習此項技術者已知之任何方法來確定。預定時間可在少於或約一分鐘至數小時之範圍內，諸如約為或為 1 分鐘、2 分鐘、3 分鐘、4 分鐘、5 分鐘、6 分鐘、7 分鐘、8 分鐘、9 分鐘、10 分鐘、20 分鐘、30 分鐘、40 分鐘、50 分鐘、1 小時、2 小時、3 小時及 4 小時。

應注意，AMDE 可為可活化或經修飾以使其可藉由特定活化劑或活化條件活化的任何基質降解酵素。供本文之方法中所用的 AMDE 為溶酶體酵素。AMDE 包括（例如）組織蛋白酶，諸如為半胱胺酸蛋白酶（cysteine protease）或天冬胺酸蛋白酶（aspartic protease）之組織蛋白酶。此等組織蛋白酶包括（例如）組織蛋白酶 S、組織蛋白酶 K、組織蛋白酶 L、組織蛋白酶 B、組織蛋白酶 C、組織蛋白酶 H、組織蛋白酶 F、組織蛋白酶 O、組織蛋白酶 R、組織蛋白酶 V、組織蛋白酶 W、組織蛋白酶 D 及組織蛋白酶 E。

該等組織蛋白酶之實例為選自具有 SEQ ID NO: 57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93 及 96 中之任一者中所闡明之胺基酸序列，或為 SEQ ID NO: 57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93 及 96 中之任一者的對偶基因或物種變異體或其他變異體之組織蛋白酶的任何組織蛋白酶。其他變異體包括（例如）經修飾以具有改變之性質（諸如穩定性）或活性（諸如受質特異性）之酵素。變異體可與胺基酸序闡明於 SEQ ID NO: 57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93 及 96 中之任一者的多肽中之任一者具有（例如）60%、65%、70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或更高之序列一致性。

在本文之方法中，AMDE 在投藥之後可裂解任一或多種細胞外基質（ECM）組份。該裂解可進行可預定之有限時間。所裂解之 ECM 組份包括（但不限於）例如膠原蛋白、彈性蛋白（elastin）、纖維結合蛋白（fibronectin）及蛋白聚糖（proteoglycan），諸如 I 型、II 型、III 型或 IV 型膠原蛋白。AMDE 可諸如藉由直接演化方法或其他方法來修飾，以具有改變之性質或活性，諸如相對於 IV 型膠原蛋白具有增加之對 I 型膠原蛋白之受質特異性。

可將其他藥劑與活化劑及酵素一起投予。投藥可與活化劑及/或酵素在同一組成物中或以分開的組成物進行。投藥可同時、分開或間歇執行。例示性藥劑包括（但不限於）

例如選自其他生物製劑、小分子化合物、分散劑、麻醉劑及血管收縮劑及/或其組合之藥理劑。分散劑之實例為玻尿酸降解酵素（hyaluronan degrading enzyme），例如玻尿酸酶（hyaluronidase），諸如 PH20，諸如其可溶形式，尤其 rHuPH20。該玻尿酸酶典型地在投予酵素及活化劑之前投予。可溶性玻尿酸酶之實例為稱作 rHuPH20 之產物，其由編碼具有 SEQ ID NO:226 中所闡明之胺基酸序列或為其對偶基因或物種變異體或其他變異體的多肽或與 SEQ ID NO:226 中所闡明之胺基酸序列具有至少約 60%、65%、70%、75%、80%、85%、90%、95%、96%、97%、98%、99% 或更高序列一致性之該多肽的變異體之核酸編碼。

其他藥劑包括麻醉劑，諸如利多卡因（lidocaine）；及血管收縮劑，諸如 α 腎上腺素能受體促效劑（alpha adrenergic receptor agonist），包括（例如）可巴君（levonordefrin）、腎上腺素（epinephrine）及去甲腎上腺素（norepinephrine）。典型地該等藥劑與 AMDE 及活化劑一起或在其之前投予。因此，提供藉由經表皮下投予如上文所述之可活化的基質降解酵素（AMDE）、活化劑、玻尿酸酶、利多卡因及腎上腺素來治療細胞外基質（ECM）之疾病或病狀的方法。該 AMDE 在該活化劑不存在之情況下在該 ECM 中無活性。該酵素、玻尿酸酶、利多卡因及腎上腺素可同時、依次或間歇投予，其限制條件為利多卡因在酵素之前投予。舉例而言，玻尿酸酶、利多卡因及腎上腺素在投予酵素之前投予，或玻尿酸酶、利多卡因及腎上腺

素同時投予，或玻尿酸酶、利多卡因及腎上腺素可在單一組成物中投予。AMDE 及活化劑及其他藥劑可藉由任何合適之途徑投予，包括（但不限於）皮下、肌肉內、病灶內、皮內、表面、經皮、靜脈內、經口及經直腸投藥。舉例而言，投藥可為表皮下投藥。

本發明亦提供可用於實現方法之產品，包括組成物、容器、組合及套組。舉例而言，提供含有兩個隔室之容器。第一隔室含有治療有效量之可活化的基質降解酵素（AMDE），其中該量係用於單一劑量或複數個劑量且單一劑量有效治療 ECM 之疾病或病狀；且第二隔室含有活化劑，其中該活化劑為活化該酵素之活化劑。AMDE 包括（例如）溶酶體酵素，諸如組織蛋白酶、鈣激活中性蛋白酶及肝素酶，包括上述供方法中所用者。該等容器中之 AMDE 為如上文所述者，包括（例如）於 pH 5.5 下實質上具活性且視情況於中性 pH 值下實質上無活性之 AMDE。活化劑提供諸如上述者之活化條件。因此，該第二隔室可含有實現變化或維持 pH 值（諸如緩衝液）或離子強度或提供金屬離子（諸如 Ca^{2+}、Zn^{2+}、Mg^{2+}）之組成物。例示性緩衝液可包括含有選自 2-(N-嗎啉基)乙烷磺酸（MES）、乙酸、檸檬酸、順丁烯二酸鹽、丁二酸鹽、乳酸鹽、甘胺酸鹽、檸檬酸磷酸鹽及組胺酸之酸的彼等緩衝液。該等疾病及病狀包括上述彼等疾病及病狀。容器亦可包括用於實現第一及第二隔室中之組份之混合的混合隔室。例示性容器包括管及瓶、無菌容器，諸如有或無注射用針之注射器。

AMDE 及活化劑係以用於單劑量或多劑量投藥之量提供。容器中之 AMDE 可以為或約為 10 μg 至 100 mg、50 μg 至 75 mg、100 μg 至 50 mg、250 μg 至 25 mg、500 μg 至 10 mg、1 mg 至 5 mg 或 2 mg 至 4 mg 之量提供。其可以固體形式，諸如以結晶形式或凍乾形式提供，或以液體形式，諸如溶液或懸浮液、凝膠或其他合適之形式提供。容器中之液體的總體積例如可為或約為 1-100 ml、1-50 ml、10-50 ml、10-30 ml、1-20 ml 及 1-10 ml。

在一例示性具體實例中，提供具有至少兩個隔室之容器，其中第一隔室含有治療有效量之可活化的組織蛋白酶 L 且該量有效治療細胞外基質（ECM）之疾病或病狀；且第二隔室含有活化該組織蛋白酶 L 之酸性緩衝液。該等疾病及病狀為上文對於治療方法所述者。活化劑可為由緩衝液、尤其具有為或約為 pH 4.0-5.0、尤其 4.5 至 6、更尤其 4.0、4.5、5、5.5 或 6 之範圍的酸性緩衝液提供之 pH 值。例示性緩衝液為含有諸如 2-(N-嗎啉基)乙烷磺酸（MES）、乙酸、檸檬酸、丁二酸、乳酸、順丁烯二酸、甘胺酸-鹽酸、檸檬酸磷酸鹽及組胺酸之酸的酸性緩衝液。例示性組織蛋白酶 L 多肽為包括 SEQ ID NO:1 中所闡明之胺基酸序列的彼等多肽，或其對偶基因、物種或其他變異體，其中該等變異體經修飾以具有改變之性質或活性且典型地與 SEQ ID NO: 1 中之任一者中所闡明之胺基酸序列相比具有至少或具有 60%、65%、70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%或 99%序列一致性。可

活化的組織蛋白酶 L 可以凍乾粉末形式，尤其以呈雙鏈或單鏈形式之活化成熟形式的凍乾粉末形式提供。容器中之可活化的組織蛋白酶 L 之量對於特定疾病或病狀在治療上有效，且可例如在約為或為 10 μg 至 100 mg、50 μg 至 75 mg、100 μg 至 50 mg、250 μg 至 25 mg、500 μg 至 10 mg、1 mg 至 5 mg 及 2 mg 至 4 mg 之範圍內。特定量可取決於特定疾病或病狀，且必要時可憑經驗確定。組織蛋白酶 L 可以固體（諸如凍乾粉末）、糊狀物或液體（諸如懸浮液、分散液或溶液）形式提供。容器中之體積對於組織蛋白酶 L 之量及預定投藥途徑及/或位點而言適合。舉例而言，容器中之典型體積為或約為 1-100 ml、1-50 ml、10-50 ml、10-30 ml、1-20 ml 或 1-10 ml。

亦提供包括上述容器及一或多個含有另一藥理學有效藥劑之其他容器之組合。該等藥劑可選自生物製劑、小分子化合物、分散劑、麻醉劑及血管收縮劑及其組合。此等藥劑包括如上文關於方法所述之藥劑及量。舉例而言，另一容器可含有玻尿酸酶，諸如 rHuPH20。量可例如為或約為：10 單位至 500,000 單位、100 單位至 100,000 單位、500 單位至 50,000 單位、1000 單位至 10,000 單位、5000 單位至 7500 單位、5000 單位至 50,000 單位或 1,000 單位至 10,000 單位。其他容器可含有例如為或約為 10 mg 至 1000 mg、100 mg 至 500 mg、200 mg 至 400 mg、20 mg 至 60 mg 或 30 mg 至 50 mg 之麻醉劑，諸如利多卡因；及/或於投藥位點及區域實現血管收縮之量的血管收縮劑，諸如 α 腎上腺素能受

體促效劑，包括可巴君、腎上腺素或去甲腎上腺素。該量例如可為或約為 10 μg 至 5 mg、50 μg 至 1 mg、50 μg 至 500 μg、50 μg 至 250 μg、100 μg 至 500 μg、200 μg 至 400 μg、1 mg 至 5 mg 或 2 mg 至 4 mg 之（例如）腎上腺素或其他血管收縮劑。其他藥理學有效藥劑中之每一者可以任何組合混合於一個容器中或可提供於單一容器中。其可以如上文對於組織蛋白酶 L 所例示及所述之液體或固體形式提供。

在例示性具體實例中，該等組合可含有 AMDE 及活化劑，且該容器可含有至少兩種藥理學有效藥劑，其中該等藥理劑係以彼此分開之分開的組成物形式提供或以同一組成物形式提供於同一容器中。舉例而言，其他容器可含有玻尿酸酶、利多卡因及腎上腺素中之一或多者。其他容器可呈有或無針之注射器的形式。該一或多個其他容器中之總體積為或約為 1-100 ml、1-50 ml、10-50 ml、10-30 ml、1-20 ml 或 1-10 ml。

在例示性具體實例中，組合包括組織蛋白酶 L 及玻尿酸酶（諸如 rHuPH20）。其可以分開的組成物形式提供或以單一組成物形式處於一個容器中。組合可包括活化組織蛋白酶 L 之酸性緩衝液。該緩衝液可提供於分開的容器中或與組織蛋白酶 L 與玻尿酸酶中之一或兩者混合。

亦提供含有在與酸性緩衝液同時或依次投予之後有效治療 ECM 介導之疾病或病狀的量之組織蛋白酶 L 的醫藥組成物，其中該組成物經調配以供單劑量投藥；且該緩衝液具有活化組織蛋白酶 L 之 pH 值。組織蛋白酶 L 之量對於特

定疾病或病狀有效，且例如為或約為 10 μg 至 100 mg、50 μg 至 75 mg、100 μg 至 50 mg、250 μg 至 25 mg、500 μg 至 10 mg、1 mg 至 5 mg 或 2 mg 至 4 mg。該組成物可進一步含有利多卡因、腎上腺素及玻尿酸酶中之一或多者。

容器及/或組合及組成物可以套組形式包裝。該等套組含有容器及/或組合及視情況供本文提供之方法中使用的其他試劑、本文提供之投藥裝置（諸如小瓶、管、注射器及針）及/或關於該用途之說明書。

【實施方式】

概述

A. 定義

B. 細胞外基質

1. ECM 之組份

a. 膠原蛋白

b. 彈性蛋白

c. 纖維結合蛋白

d. 葡糖胺聚糖（Glycosaminoglycan，GAG）

i. 蛋白聚糖

ii. 玻尿酸（Hyaluronic Acid）

2. 皮膚組織學

a. 表皮

b. 真皮

c. 下皮

3. ECM 之疾病

C. 基質降解酵素

1. 酵素活化

a. 絲胺酸蛋白酶（Serine Protease）

b. 半胱胺酸蛋白酶

i. 組織蛋白酶

組織蛋白酶 L

ii. 鈣激活中性蛋白酶

c. 天冬胺酸蛋白酶

d. 金屬蛋白酶（Metalloprotease）

e. 肝素酶

D. 可活化的基質降解酵素（AMDE）

1. 活化可活化的基質降解酵素之活化條件及方法

a. 活化條件-酸性 pH 值

b. 活化條件-金屬陽離子濃度

2. 基質降解酵素與活化劑之組合

E. 產生編碼基質降解酵素之核酸及其多肽的方法

1. 載體及細胞

2. 表現

a. 原核細胞

b. 酵母細胞

c. 蟲細胞

d. 哺乳動物細胞

e. 植物

3. 純化技術

F. 可活化的基質降解酵素之製備、調配及投藥

1. 可注射劑、溶液及乳液

凍乾粉末

2. 表面投藥

3. 用於其他投藥途徑之組成物

4. 組合療法

a. 玻尿酸降解酵素

i. 玻尿酸酶

1） 哺乳動物型玻尿酸酶

2） 細菌玻尿酸酶

3） 來自水蛭、其他寄生蟲及甲殼動物之玻尿酸酶

ii. 其他玻尿酸降解酵素

iii. 可溶性玻尿酸降解酵素

1） 可溶性人類 PH20

2） rHuPH20

iv. 修飾玻尿酸降解酵素以改良其藥物動力學性質

G. 可活化的基質降解酵素之包裝及製品

1. 單腔室設備

2. 雙腔室設備

3. 套組

H. 評估基質降解酵素之活性的方法

1. 評估酵素活性之方法

2. 評估 ECM 降解之方法

a. 試管內檢定

b. 活體內檢定

c. 非人類動物模型

I. 治療 ECM 之疾病或缺陷的例示性方法

膠原蛋白介導之疾病或病狀

a. 脂肪團

b. 杜普宜特朗氏病

c. 帕榮雷氏病

d. 萊德豪斯纖維化

e. 關節僵硬

f. 現有瘢痕

i. 手術黏連

ii. 瘢痕瘤

iii. 肥厚性瘢痕

iv. 凹陷性瘢痕

g. 硬皮病

h. 淋巴水腫

i. 膠原性結腸炎

J. 實施例

A. 定義

除非另作定義，否則本文中所用之所有技術及科學術語具有與熟習本發明所屬技術者通常所理解相同之含義。

除非另有註釋，否則本文整個揭示案中通篇所提及之所有專利、專利申請案、公開申請案及公開案、Genbank序列、資料庫、網站及其他公開材料係以整體引用的方式併入。在關於本文之術語存在複數個定義之情況下，以本部分中之彼等定義為主。當提及URL或其他此類識別符或位址時，應瞭解該等識別符可變化且關於網際網路之特定資訊可來往，但等效資訊可藉由檢索網際網路而找到。對其之提及證明該資訊之可用性及公開傳播。

如本文中所使用，細胞外基質（ECM）係指包圍特化組織及器官之細胞且對特化組織及器官之細胞提供結構支撐的複雜網狀結構。該ECM由以下蛋白質組成：結構蛋白，諸如膠原蛋白及彈性蛋白；特化蛋白，諸如纖維結合蛋白；及蛋白聚糖。確切生物化學組成在組織之間不同。舉例而言，在皮膚中，其為含有ECM之真皮層。對「間質」之提及在本文中可互換使用以指ECM。

如本文中所使用，ECM之組份（components of the ECM）係指由結締組織之細胞產生且分泌至間質中的任何物質。出於本文之目的，對ECM組份之提及係指蛋白質及糖蛋白，而非其他細胞組份或ECM之其他組份。例示性ECM組份包括（但不限於）膠原蛋白、纖維結合蛋白、彈性蛋白及蛋白聚糖。

如本文中所使用，基質降解酵素（matrix degrading enzyme）係指降解ECM之一或多種組份的任何酵素。基質降解酵素包括蛋白酶，其為催化共價肽鍵之水解的酵素。

基質降解酵素包括熟習此項技術者已知之任何酵素，諸如本文所述之任何酵素（參見例如表 3），其對偶基因或物種變異體或其他變異體。

如本文中所使用，經修飾之基質降解酵素（modified matrix-degrading enzyme）（或基質降解酵素之變異體（variant of a matrix-degrading enzyme））係指與野生型酵素相比在一級序列中具有一或多個修飾之酵素。一或多個突變可為一或多個胺基酸置換（取代）、插入、缺失及其任何組合。經修飾之酵素包括具有 1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20 處或更多處經修飾位置者。經修飾之酵素保留野生型酵素之活性，但可具有改變之受質特異性或穩定性。經修飾之酵素典型地與野生型酵素之相應胺基酸序列具有 60%、70%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或更高序列一致性。

如本文中所使用，溶酶體酵素（lysosomal enzyme）係指降解功能於酸性 pH 值下最佳之酵素。由於需要低 pH 值，該等酵素通常存在於細胞之溶酶體中。溶酶體酵素包括（但不限於）組織蛋白酶 S、K、L、B、C、H、F、O、R、V、D 及 E。溶酶體酵素之實例包括 SEQ ID NO:56、59、62、64、179、67、70、73、76、182、185、188、79、194、89、92 及 95 中之任一者中所闡明之前軀體形式及 SEQ ID NO:57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93 及 96 中所闡明之其成熟形式，或其對偶

基因變異體或物種變異體或其他變異體。其他溶酶體酵素包括（但不限於）溶酶體酸性脂肪酶、胃脂肪酶、溶酶體磷脂酶及膽汁鹽活化脂肪酶（編碼包括其成熟形式之胺基酸序列之核酸序列闡明於 SEQ ID NO: 196-207 中之任一者中）。

如本文中所使用，「酵素原（zymogen）」係指為無活性前軀體且需要一些變化（諸如多肽之蛋白水解）以變為具活性之酵素。一些酵素原亦需要添加用於活化之輔助因素，諸如（但不限於）pH 值、離子強度、金屬離子或溫度。酵素原包括酵素之酵素原（proenzyme）形式。因此，酵素原通常無活性且可藉由在其他輔助因素存在或不存在之情況下自酵素原催化或自體催化裂解前區來轉化為成熟多肽。

如本文中所使用，前區段（prosegment）或前區（proregion）係指經裂解以產生成熟蛋白之區域或區段。其可包括起作用以藉由遮蔽催化機構來抑制酵素活性之區段。前區為位於成熟多肽之胺基末端處的胺基酸序列且可少至數個胺基酸或可為多域結構。

如本文中所使用，活化序列（activation sequence）係指酵素原中為活化裂解或成熟裂解形成活性蛋白酶所需之位點的胺基酸序列。活化序列之裂解可以自體催化方式或藉由活化搭配物來催化。

活化裂解為一種類型之成熟裂解，其中出現活性所需之構形變化。活化會導致產生蛋白酶之多鏈形式（例如雙

鏈形式）。在一些情況下，蛋白酶之單鏈形式可展現如單鏈之蛋白水解活性。

如本文中所使用，輔助因素（cofactor）係指酵素活性所需之條件或因素。輔助因素包括酵素活性所需之任何因素。輔助因素之實例包括（但不限於）pH值、離子強度、金屬離子或溫度。當提及酵素之活體內投藥時，輔助因素包括內源性存在之因素及外源性提供之因素。

如本文中所使用，活化條件（activating condition）係指酵素活性所需之任何物理條件或條件組合。出於本文之目的，用於可活化的基質降解酵素（AMDE）之活化條件包括不以活化酵素所需之量（亦即數量、程度、含量或其他物理度量）存在於投藥位點處（例如不存在於細胞外基質中）者。活化條件之實例包括（但不限於）pH值、金屬離子、還原劑或氧化劑、溫度及離子強度。舉例而言，在於低pH值之條件下具活性、但於中性pH值下無活性之溶酶體基質降解酵素的情況下，使無活性酵素暴露於酸性pH值之活化條件使得酵素活化。由於活化條件不存在於酵素之投藥位點處、而必須外源性添加的事實，活化條件將隨時間耗散及/或中和，以致活化條件不再存在來活化酵素。因此，酵素將在投藥之後的有限或預定時間內具活性。

如本文中所使用，活化劑（activator）係指提供可活化的基質降解酵素活化條件的任何組成物。活化劑之實例包括（但不限於）酸性pH值緩衝液、冷緩衝液或鈣緩衝液。

如本文中所使用，「可活化的基質降解酵素（AMDE）」

係指需要活化條件以便具活性之基質降解酵素。舉例而言，出於本文之目的，除非在投予 AMDE 之前、同時或之後暴露於活化劑，藉此提供酵素活化條件，否則 AMDE 在 ECM 中實質上無活性。因此，可活化的酵素之活化受外來條件控制以便活體內位置或位點處之時期（在此期間酵素具活性）可因活化條件之耗散及/或中和而得以預先確定及/或受到控制（亦即時間上可控制或受時間控制）。因此，藉助於暴露於活化條件，酵素在 ECM 中在有限時間內及/或在有限程度上具活性（亦即條件性地具活性）。活化之程度及時間可藉由選擇活化劑或活化條件來控制，且可持續預定時間。舉例而言，諸如組織蛋白酶 L 之溶酶體酵素為可活化的，因為其可藉由暴露於 pH 值之活化條件（諸如由酸性緩衝溶液提供）而活化。在向 ECM 之中性 pH 值環境中投予經活化酵素之後，該 pH 值環境將在可基於酸性緩衝液之緩衝能力預先確定的時期內恢復至中性，以致酵素將變為無活性。

如本文中所使用，「活化劑之量（amount of an activator）」係指活化劑之數量、程度或含量。活化劑之量可為濃度或絕對量，或特定溫度或 pH 值。出於本文之目的，活化劑之量典型地為足以使得酵素條件性活化的量。可調整該量以改變活化之持續時間以使活化可持續有限或預定時間。

如本文中所使用，「治療有效量（therapeutically effective amount）」或「治療有效劑量（therapeutically

effective dose)」係指含有至少足以產生治療作用之化合物的藥劑、化合物、物質或組成物。

如本文中所使用，在有限時間內或在有限持續時間內具活性之酵素（an enzyme that is active for a limited time or for limited duration）係指具有隨時間耗散及/或中和之活性的活性酵素。因此，藉助於不存在活化條件，使酵素無活性。

如本文中所使用，預定時間（predetermined time）意謂先前已知且可控制之有限時間。可滴定酵素活性所需之活化條件之耗散及/或中和以使活性酵素變為無活性所需之時間為已知的。舉例而言，將隨時間使投入酸性培養基中且暴露於具有中性 pH 值之活體內環境（亦即 ECM）之經酸活化酵素暴露於逐漸增加之 pH 值以使該酵素將僅在有限時間內保持活性。pH 值增加之速率可例如藉由改變酸性緩衝液之緩衝能力來控制以使得可預先確定活性酵素變為無活性所需之時期。出於本文之目的，酵素可在為或約為 1 分鐘、2 分鐘、3 分鐘、4 分鐘、5 分鐘、15 分鐘、7 分鐘、8 分鐘、9 分鐘、10 分鐘、15 分鐘、20 分鐘、30 分鐘、1 小時、2 小時、3 小時或 4 小時之預定時間內具活性。

如本文中所使用，於中性 pH 值下實質上無活性（substantially inactive at neutral pH）意謂酵素在處於中性 pH 值時展現小於酵素於類似條件（除 pH 值差異外，亦即檢定、緩衝液、離子強度）下處於其最佳 pH 值下之活性的 10%。

如本文中所使用，於 pH 5.5 下實質上具活性（substantially active at pH 5.5）意謂酵素在處於 pH 5.5 時展現大於酵素於類似條件（除 pH 值差異外，亦即檢定、緩衝液、離子強度）下處於其最佳 pH 值之活性的 10%（例如 20%、30%、40%、50%、60%、70%、80%、90%、95%、96%、97%、98%、99%或 100%）。

如本文中所使用，表皮下投藥（sub-epidermal administration）係指使酵素傳遞於皮膚最外層下方之任何投藥。表皮下投藥並不包括對皮膚外層上之表面施用。表皮下投藥之實例包括（但不限於）皮下、肌肉內、病灶內及皮內投藥途徑。

如本文中所使用，受質（substrate）係指由酵素裂解之分子。最低限度地，標靶受質包括含有由蛋白酶識別之裂解序列的肽，且因此長度可為 2、3、4、5、6 個或 6 個以上殘基。受質亦包括全長蛋白質、對偶基因變異體、同功異型物或其由酵素裂解之任何部分。另外，受質包括含有不影響酵素裂解該受質之另一部分的肽或蛋白質。舉例而言，受質可包括 4 個胺基酸之肽，或以化學方式與螢光部分連接之全長蛋白質。

如本文中所使用，裂解（cleavage）係指酵素使肽鍵或其他鍵斷開，此產生一或多種降解產物。

如本文中所使用，活性（activity）係指與全長（完整）蛋白質相關之多肽或其部分的功能活性。功能活性包括（但不限於）生物學活性、催化或酶促活性、抗原性（結合抗

多肽抗體或與多肽競爭結合抗多肽抗體之能力）、免疫原性、形成多聚體之能力及與該多肽之受體或配位體特異性結合的能力。

如本文中所使用，酶促活性（enzymatic activity）或催化活性（catalytic activity）或裂解活性（cleavage activity）係指如在偵測所選受質之蛋白水解的試管內蛋白水解檢定中所評估之蛋白酶之活性。

如本文中所使用，活性酵素（active enzyme）係指展現酶促活性之酵素。出於本文之目的，活性酵素為裂解 ECM 之任一或多種組份（諸如膠原蛋白）的彼等酵素。活性酵素包括呈單鏈或雙鏈形式者。

如本文中所使用，無活性酵素（inactive enzyme）係指展現實質上無活性（亦即催化活性或裂解活性）之酵素，諸如小於酵素最大活性之 10%。酵素可因其構形、其活性所需活化條件之不存在或抑制劑或使酵素實質上無活性之任何其他條件或因素或形式之存在而無活性。

如本文中所使用，人類蛋白質為由存在於人類基因組中之核酸分子（諸如 DNA）編碼的蛋白質，包括所有其對偶基因變異體及保守性變異。蛋白質之變異體或修飾為人類蛋白質，若該修飾係基於人類蛋白質之野生型或主要序列。

如本文中所使用，玻尿酸降解酵素（hyaluronan degrading enzyme）係指催化玻尿酸聚合物（亦稱為玻尿酸或 HA）裂解為較小分子量片段之酵素。玻尿酸降解酵素之

實例為玻尿酸酶，及具有使玻尿酸解聚之能力的特定軟骨素酶及解離酶。為玻尿酸降解酵素之例示性軟骨素酶包括（但不限於）軟骨素 ABC 解離酶（亦稱為軟骨素酶 ABC）、軟骨素 AC 解離酶（亦稱為硫酸軟骨素（chondroitin sulfate）解離酶或硫酸軟骨素消除酶）及軟骨素 C 解離酶。軟骨素-ABC 解離酶包含兩種酵素，硫酸軟骨素-ABC 內解離酶（EC 4.2.2.20）及硫酸軟骨素-ABC 外解離酶（EC 4.2.2.21）。例示性硫酸軟骨素-ABC 內解離酶及硫酸軟骨素-ABC 外解離酶包括（但不限於）來自普通變形桿菌（*Proteus vulgaris*）及肝素黃桿菌（*Flavobacterium heparinum*）者（普通變形桿菌硫酸軟骨素 ABC 內解離酶闡明於 SEQ ID NO:305 中；Sato 等人 (1994) *Appl. Microbiol. Biotechnol.* 41(1):39-46）。來自細菌之例示性軟骨素酶 AC 酵素包括（但不限於）來自肝素黃桿菌、SEQ ID NO:308 中所闡明之食物穀菌（*Victivallis vadensis*）及金黃節桿菌（*Arthrobacter aurescens*）者（Tkalec 等人 (2000) *Applied and Environmental Microbiology* 66(1):29-35；Ernst 等人 (1995) *Critical Reviews in Biochemistry and Molecular Biology* 30(5):387-444）。來自細菌之例示性軟骨素酶 C 酵素包括（但不限於）來自鏈球菌（*Streptococcus*）及黃桿菌（*Flavobacterium*）者（Hibi 等人 (1989) *FEMS-Microbiol-Lett.* 48(2):121-4；Michelacci 等人 (1976) *J. Biol. Chem.* 251:1154-8；Tsuda 等人 (1999) *Eur. J. Biochem.* 262:127-133）。

如本文中所使用，玻尿酸酶（hyaluronidase）係指降解玻尿酸之酵素。玻尿酸酶包括細菌玻尿酸酶（EC 4.2.99.1），來自水蛭、其他寄生蟲及甲殼動物之玻尿酸酶（EC 3.2.1.36），及哺乳動物型玻尿酸酶（EC 3.2.1.35）。玻尿酸酶亦包括包含（但不限於）鼠類、犬類、貓類、兔類、禽類、牛類、羊類、豬類、馬類、魚類、蛙類、細菌之非人類來源的任何玻尿酸酶，及來自水蛭、其他寄生蟲及甲殼動物之任何玻尿酸酶。例示性非人類玻尿酸酶包括 SEQ ID NO: 237-260 中之任一者中所查明之任何玻尿酸酶。例示性人類玻尿酸酶包括 HYAL1（SEQ ID NO:262）、HYAL2（SEQ ID NO:263）、HYAL3（SEQ ID NO:264）、HYAL4（SEQ ID NO:265）及 PH20（SEQ ID NO:232）。玻尿酸酶中亦包括可溶性人類 PH20 及可溶性 rHuPH20。

對玻尿酸酶之提及包括前軀體玻尿酸酶多肽及成熟玻尿酸酶多肽（諸如信號序列已移除者），其具有活性之截短形式，且包括對偶基因變異體及物種變異體，由剪接變異體編碼之變異體，及其他變異體，包括與 SEQ ID NO:232 中之任一者所闡明之前軀多肽或其成熟形式具有至少 40%、45%、50%、55%、65%、70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或更高序列一致性的多肽。玻尿酸酶亦包括含有化學或轉譯後修飾者及不含化學或轉譯後修飾者。該等修飾包括（但不限於）聚乙二醇化、白蛋白化、糖基化、法尼基化、羧基化、羥基化、磷酸化及此項技術中已知之其他多肽修飾。

如本文中所使用，可溶性人類 PH20 或 sHuPH20 包括缺乏全部或一部分 C-末端處之糖基磷脂醯肌醇（glycosylphospatidylinositol，GPI）連接位點以使得在表現後多肽為可溶性的成熟多肽。例示性 sHuPH20 多肽包括具有 SEQ ID NO:226-231 中之任一者中所闡明之胺基酸序列的成熟多肽。該等例示性 sHuPH20 多肽之前軀多肽包括胺基酸信號序列。前軀體之實例闡明於 SEQ ID NO:225 中，其於胺基酸位置 1-35 處含有 35 個胺基酸之信號序列。可溶性 HuPH20 多肽可在本文所述之製備及純化方法期間或之後降解。

如本文中所使用，可溶性 rHuPH20（soluble rHuPH20）係指重組表現於中國倉鼠卵巢（Chinese Hamster Ovary，CHO）細胞中之人類 PH20 之可溶性形式。可溶性 rHuPH20 由編碼 SEQ ID NO:225 中所闡明之胺基酸 1-482 的核酸編碼。亦包括為其對偶基因變異體及其他可溶性變異體之 DNA 分子。編碼可溶性 rHuPH20 之核酸表現於分泌成熟多肽之 CHO 細胞中。當產生於培養基中時，於 C-末端處存在異質性以使產物包括 SEQ ID NO:226-231 之物質的混合物。亦包括相應對偶基因變異體及其他變異體。其他變異體可與 SEQ ID NO:226-231 中之任一者具有 60%、70%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或更高序列一致性，只要其保留玻尿酸酶活性且為可溶性的即可。

如本文中所使用，玻尿酸酶活性（hyaluronidase

activity）係指由玻尿酸酶多肽展現之任何活性。該等活性可在試管內及/或活體內進行測試且包括（但不限於）酶促活性（諸如實現玻尿酸裂解）、充當分散劑或展布劑之能力及抗原性。例示性檢定包括微濁度檢定（microturbidity assay）（參見例如實施例 16），其藉由偵測未裂解之玻尿酸與血清白蛋白結合時所形成之不溶性沈澱物來間接量測玻尿酸酶對玻尿酸之裂解。

如本文中所使用，天然存在之 α-胺基酸之殘基為存在於自然界中之彼等 20 種 α-胺基酸之藉由在人類體內具有其同源 mRNA 密碼子之負載 tRNA 分子的特異性識別而併入蛋白質中的殘基。

如本文中所使用，核酸包括 DNA、RNA 及其類似物，包括肽核酸（peptide nucleic acid，PNA）及其混合物。核酸可為單鏈或雙鏈。當提及視情況經標記（諸如經可偵測標記進行標記，諸如螢光或放射性標記）之探針或引子時，涵蓋單鏈分子。該等分子典型地具有使得其標靶在統計學上獨特之長度或具有低複本數（典型地小於 5 個、通常小於 3 個）以用於探測或引發文庫。通常，探針或引子含有至少 14、16 或 30 個與所關注基因互補或一致之序列的相連核苷酸。探針及引子之長度可為 10、20、30、50、100 個或 100 個以上核酸。

如本文中所使用，肽（peptide）係指長度為 2 至 40 個胺基酸之多肽。

如本文中所使用，存在於本文所提供之各種胺基酸序

列中之胺基酸係根據其已知三字母或單字母縮寫來鑑別（表 1）。存在於各種核酸片段中之核苷酸係以此項技術中常規使用之標準單字母名稱來命名。

如本文中所使用，「胺基酸（amino acid）」為含有胺基及羧基之有機化合物。多肽含有兩個或兩個以上胺基酸。出於本文之目的，胺基酸包括 20 種天然存在之胺基酸、非天然胺基酸及胺基酸類似物（亦即 α-碳具有側鏈之胺基酸）。

如本文中所使用，「胺基酸殘基（amino acid residue）」係指化學消化（水解）多肽之肽鍵後所形成之胺基酸。假定本文所述之胺基酸殘基呈「L」異構形式。如此命名之呈「D」異構形式之殘基可取代任何 L-胺基酸殘基，只要多肽保留所需功能性質即可。NH_2 係指存在於多肽之胺基末端處的游離胺基。COOH 係指存在於多肽之羧基末端處的游離羧基。遵照 *J. Biol. Chem.*, 243:3552-3559 (1969)及被採納之 37 C.F.R.. §§ 1.821-1.822 中所述之標準多肽命名法，胺基酸殘基之縮寫展示於表 1 中：

表 1-對應表

符號		
1 字母	3 字母	胺基酸
Y	Tyr	酪胺酸
G	Gly	甘胺酸
F	Phe	苯丙胺酸
M	Met	甲硫胺酸
A	Ala	丙胺酸
S	Ser	絲胺酸
I	Ile	異白胺酸
L	Leu	白胺酸
T	Thr	蘇胺酸
V	Val	纈胺酸
P	Pro	脯胺酸
K	Lys	離胺酸
H	His	組胺酸
Q	Gln	麩胺醯胺
E	Glu	麩胺酸
Z	Glx	Glu 及/或 Gln
W	Trp	色胺酸
R	Arg	精胺酸
D	Asp	天冬胺酸
N	Asn	天冬醯胺
B	Asx	Asn 及/或 Asp
C	Cys	半胱胺酸
X	Xaa	未知或其他胺基酸

應注意本文由式表示之所有胺基酸殘基序列具有在胺基末端至羧基末端之習知方向上的左至右取向。另外，片語「胺基酸殘基」經廣泛定義以包括對應表（表 1）中所列之胺基酸及經修飾之胺基酸與稀有胺基酸，諸如 37 C.F.R. §§ 1.821-1.822 中所提及之彼等胺基酸，且以引用的方式併入本文中。此外，應注意胺基酸殘基序列之開始或結束時

之破折號指示與一或多個胺基酸殘基之另一序列、與諸如 NH_2 之胺基末端基或與諸如 COOH 之羧基末端基連接的肽鍵。

如本文中所使用，「天然存在之胺基酸（naturally occurring amino acid）」係指存在於多肽中之 20 種 L-胺基酸。

如本文中所使用，「非天然胺基酸（non-natural amino acid）」係指具有類似於天然胺基酸之結構、但結構上經修飾以模擬天然胺基酸及反應性之結構的有機化合物。因此，非天然存在之胺基酸包括（例如）除 20 種天然存在之胺基酸外的胺基酸或胺基酸之類似物且包括（但不限於）胺基酸之 D-立體異構體。例示性非天然胺基酸在本文中描述且為熟習此項技術者所已知。

如本文中所使用，DNA 構築體為含有以自然界中未見之方式組合及鄰接之 DNA 區段的單鏈或雙鏈、直鏈或環狀 DNA 分子。DNA 構築體作為人類操作之結果而存在，且包括所操作分子之純系及其他複本。

如本文中所使用，DNA 區段為具有指定屬性之較大 DNA 分子之一部分。舉例而言，編碼指定多肽之 DNA 區段為較長 DNA 分子之一部分，諸如質體或質體片段，當自 5' 至 3'方向讀取時，其編碼該指定多肽之胺基酸序列。

如本文中所使用，術語聚核苷酸意謂自 5'至 3'端讀取之脫氧核糖核苷酸或核糖核苷酸鹼基之單鏈或雙鏈聚合物。聚核苷酸包括 RNA 及 DNA，且可自天然來源分離，試

管內合成，或由天然分子與合成分子之組合來製備。本文根據核苷酸（簡寫「nt」）或鹼基對（簡寫「bp」）給出聚核苷酸分子之長度。當情況允許時，術語核苷酸用於單鏈及雙鏈分子。當該術語應用於雙鏈分子時，其用於表示全長且將理解為相當於術語鹼基對。熟習此項技術者將認識到，雙鏈聚核苷酸之兩條鏈的長度可略微不同且其末端可交錯；因此，雙鏈聚核苷酸分子中之所有核苷酸可均不配對。一般而言，該等未配對之末端的長度將不超過20個核苷酸。

如本文中所使用，兩種蛋白質或核酸之間的「相似性（similarity）」係指蛋白質之胺基酸序列或核酸之核苷酸序列之間的相關性。相似性可基於殘基序列之一致性及/或同源性之程度及其中所含之殘基。評估蛋白質或核酸之間的相似度之方法為熟習此項技術者所已知。舉例而言，在一種評估序列相似性之方法中，使兩個胺基酸或核苷酸序列以產生序列之間的最大一致性程度之方式比對。「一致性（identity）」係指胺基酸或核苷酸序列不變之程度。胺基酸序列及在某種程度上核苷酸序列之比對亦可考慮胺基酸（或核苷酸）中之保守性差異及/或頻繁取代。保守性差異為保持所涉及之殘基之物理化學性質的彼等差異。比對可為整體比對（比較序列在序列之整個長度上之比對且包括所有殘基）或局部比對（僅包括最類似區域之序列之一部分的比對）。

「一致性」本身具有業內公認之含義且可使用公開技術

計算。(參見例如：*Computational Molecular Biology*, Lesk, A.M.編, Oxford University Press, New York, 1988；*Biocomputing: Informatics and Genome Projects*, Smith, D.W.編, Academic Press, New York, 1993；*Computer Analysis of Sequence Data*, Part I, Griffin, A.M., 及 Griffin, H.G.編, Humana Press, New Jersey, 1994；*Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987；及 Sequence Analysis Primer, Gribskov, M.及 Devereux, J.編, M Stockton Press, New York, 1991)。雖然存在許多量測兩種聚核苷酸或多肽之間的一致性之方法，但術語「一致性」為熟習技術者所熟知(Carillo, H.及 Lipton, D., *SIAM J Applied Math 48*:1073 (1988))。

如本文中所使用，同源(對於核酸及/或胺基酸序列而言)意謂大約大於或等於 25%序列同源性，典型地大於或等於 25%、40%、50%、60%、70%、80%、85%、90%或 95%序列同源性；必要時可指定精確百分比。出於本文之目的，除非另有指示，否則術語「同源性(homology)」與「一致性」通常可互換使用。一般而言，對於測定同源性或一致性百分比而言，比對序列以便獲得最高順序匹配(參見例如：*Computational Molecular Biology*, Lesk, A.M.編, Oxford University Press, New York, 1988；*Biocomputing: Informatics and Genome Projects*, Smith, D.W.編, Academic Press, New York, 1993；*Computer Analysis of Sequence Data, Part I*, Griffin, A.M., and Griffin, H.G.編, Humana Press,

New Jersey, 1994；*Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987；及 *Sequence Analysis Primer*, Gribskov, M.及 Devereux, J.編, M Stockton Press, New York, 1991; Carillo 等人 (1988) *SIAM J Applied Math 48*:1073)。藉由序列同源性，藉由標準比對演算法程式確定保守性胺基酸之數目，且該數目可用於由各供應商制定之預設間隙懲罰。實質上同源核酸分子典型地會於中等嚴格度下或於高嚴格度下沿所關注之核酸的整個長度雜交。亦涵蓋含有簡并密碼子以替代雜交核酸分子中之密碼子的核酸分子。

任何兩個分子是否具有至少 60%、70%、80%、85%、90%、95%、96%、97%、98%或 99%「一致性」或「同源性」之核苷酸序列或胺基酸序列可使用已知電腦算法來判定，諸如使用例如預設參數之「FASTA」程式，如在 Pearson 等人 (1988) *Proc. Natl. Acad. Sci. USA 85*:2444 中（其他程式包括 GCG 程式包（Devereux, J.,等人, *Nucleic Acids Research 12(I)*:387 (1984))、BLASTP、BLASTN、FASTA (Atschul, S.F.,等人, *J Molec Biol 215*:403 (1990))；Guide to Huge Computers, Martin J. Bishop 編, Academic Press, San Diego, 1994 及 Carillo 等人 (1988) *SIAM J Applied Math 48*:1073)。舉例而言，國家生物技術資訊中心資料庫 (National Center for Biotechnology Information database) 之 BLAST 功能可用於測定一致性。其他商業或公開可用程式包括 DNAStar「MegAlign」程式（Madison, WI）及威斯

康星大學遺傳電腦組（University of Wisconsin Genetics Computer Group，UWG）「Gap」程式（Madison WI）。蛋白質及/或核酸分子之同源性或一致性百分比可例如藉由使用GAP電腦程式比較序列資訊來測定（例如 Needleman 等人(1970) *J. Mol. Biol.* 48:443，由 Smith 及 Waterman 修訂((1981) *Adv. Appl. Math.* 2:482））。簡言之，GAP程式將相似性定義為類似之所比對符號（亦即核苷酸或胺基酸）之數目除以兩個序列中之較短者中符號的總數。用於GAP程式之預設參數可包括：（1）一元比較矩陣（含有對於一致性為1及對於非一致性為0之值）及 Gribskov 等人(1986) *Nucl. Acids Res.* 14:6745 之加權比較矩陣，如 Schwartz 及 Dayhoff 編，*ATLAS OF PROTEIN SEQUENCE AND STRUCTURE*, National Biomedical Research Foundation, 第353-358頁 (1979)所述；（2）對於各間隙之3.0罰分及對於各間隙中之各符號的另一0.10罰分；及（3）對於末端間隙無罰分。

因此，如本文中所使用，術語「一致性」或「同源性」表示測試多肽或聚核苷酸與參考多肽或聚核苷酸之間的比較。如本文中所使用，術語至少「與...90%一致(90% identical to)」係指相對於多肽之參考核酸或胺基酸序列90至99.99之一致性百分比。90%或更高程度之一致性指示如下事實，假定出於舉例目的，比較 100 個胺基酸之測試多肽與參考多肽長度，不超過測試多肽中之胺基酸的 10%（亦即百分之十）不同於參考多肽中之胺基酸。可在測試聚核苷酸與

參考聚核苷酸之間進行類似比較。該等差異可表示為隨機分布於多肽之整個長度內之點突變或其可在不同長度之一或多個位置處叢集至最大允許（例如 10/100）胺基酸差異（約 90%一致性）。將差異定義為核酸或胺基酸取代、插入或缺失。在約 85-90%以上之同源性或一致性程度下，結果應與程式及間隙參數組無關；該等高一致性程度可易於通常藉由手動比對而不依賴於軟體來評估。

如本文中所使用，所比對序列（aligned sequence）係指使用同源性（相似性及/或一致性）來比對核苷酸或胺基酸之序列中的相應位置。典型地，比對相關性為 50%或更大之兩個或兩個以上序列。一組比對序列（an aligned set of sequences）係指於相應位置處比對之 2 個或 2 個以上序列且可包括與基因組 DNA 序列比對之來源於 RNA 之比對序列，諸如 EST 及其他 cDNA。

如本文中所使用，「引子（primer）」係指可於適當條件下（例如，在四種不同核苷三磷酸及諸如 DNA 聚合酶、RNA 聚合酶或逆轉錄酶之聚合劑存在下）在適當緩衝液中且於合適溫度下充當模板指導 DNA 合成之起始點的核酸分子。應瞭解某一核酸分子可充當「探針」及「引子」。然而，引子具有 3'羥基以供延長。引子可用於多種方法中，包括（例如）聚合酶鏈反應（polymerase chain reaction，PCR）、逆轉錄酶（reverse-transcriptase，RT）-PCR、RNA PCR、LCR、多重 PCR、鍋柄式 PCR、捕捉 PCR、表現 PCR、3'及 5' RACE、原位 PCR、連接介導 PCR 及其他擴增方案。

如本文中所使用，「引子對（primer pair）」係指包括與欲擴增（例如藉由 PCR）之序列的 5'末端雜交之 5'（上游）引子及與欲擴增之序列的 3'末端之互補序列雜交之 3'（下游）引子的一組引子。

如本文中所使用，「特異性雜交（specifically hybridizes）」係指藉由核酸分子（例如寡核苷酸）與標靶核酸分子之互補鹼基配對進行的黏接。熟習此項技術者熟悉影響特異性雜交之試管內及活體內參數，諸如特定分子之長度及組成。尤其與試管內雜交有關之參數進一步包括黏接及洗滌溫度、緩衝液組成及鹽濃度。移除非特異性結合核酸分子之例示性洗滌條件於高嚴格度下為 0.1×SSPE、0.1% SDS、65℃，且於中等嚴格度下為 0.2×SSPE、0.1% SDS、50℃。等效嚴格度條件為此項技術中所已知。熟習此項技術者可易於調整此等參數以達成適合於特定應用之核酸分子與標靶核酸分子之特異性雜交。當提及兩個核苷酸序列時，互補意謂兩個核苷酸序列能夠雜交，典型地相對核苷酸之間的錯配少於 25%、15%或 5%。必要時，將指定互補百分比。典型地，選擇兩個分子以使得其將於高嚴格度之條件下雜交。

如本文中所使用，與產物實質上一致意謂充分類似以便所關注之性質充分未改變以使可使用實質上一致產物來替代該產物。

如本文中所使用，亦應瞭解術語「實質上一致（substantially identical）」或「類似（similar）」如熟習相關

技術者所瞭解隨情形而變化。

如本文中所使用，對偶基因變異體（allelic variant）或對偶基因變異（allelic variation）係指佔據同一染色體位點之基因的兩種或兩種以上替代形式中之任一者。對偶基因變異經由突變天然發生，且會導致群體中之表型多態現象。基因突變可為沉默突變（所編碼之多肽無變化）或可編碼具有改變之胺基酸序列的多肽。術語「對偶基因變異體」在本文中亦用於表示由基因之對偶基因變異體編碼的蛋白質。典型地，該基因之參考形式編碼來自物種之群體或單一參考成員之多肽的野生型形式及/或主要形式。典型地，包括物種間及物種內之變異體的對偶基因變異體典型地與來自同一物種之野生型及/或主要形式具有至少 80%、90%或更高胺基酸一致性；一致性程度視基因及比較為種間或種內而定。通常，種內對偶基因變異體與野生型及/或主要形式具有至少約 80%、85%、90%或 95%或更高一致性，包括與多肽之野生型及/或主要形式具有 96%、97%、98%、99%或更高一致性。本文中對對偶基因變異體之提及通常指在相同物種之成員中蛋白質之變異。

如本文中所使用，在本文中可與「對偶變異體（allelic variant）」互換使用之「對偶基因（allele）」係指基因或其部分之替代形式。對偶基因佔據同源染色體上之同一基因座或位置。當個體具有基因之兩個一致對偶基因時，該個體稱為對於該基因或對偶基因為純合的。當個體具有基因之兩個不同對偶基因時，該個體稱為對於該基因為雜合

的。特定基因之對偶基因可在單一核苷酸或若干核苷酸中互不相同，且可包括核苷酸之取代、缺失及插入。基因之對偶基因亦可為含有突變之基因形式。

如本文中所使用，物種變異體（species variant）係指在不同物種中多肽之變異體，該等物種包括不同哺乳動物物種，諸如小鼠及人類。

如本文中所使用，剪接變異體（splice varian）係指藉由產生一種以上類型之mRNA的對基因組DNA之初級轉錄物的差異加工所產生之變異體。

如本文中所使用，修飾係指對多肽之胺基酸序列或核酸分子中之核苷酸序列的修飾且分別包括胺基酸及核苷酸之缺失、插入及置換。修飾多肽之方法對於熟習此項技術者而言為常規的，諸如藉由使用重組DNA方法。

如本文中所使用，術語啟動子（promoter）意謂含有提供RNA聚合酶結合及轉錄啟始之DNA序列之基因部分。啟動子序列通常（但並不始終）存在於基因之5'非編碼區中。

如本文中所使用，經分離或經純化之多肽或蛋白質或其生物學活性部分實質上不含細胞物質或來自蛋白質所來源之細胞或組織的其他污染蛋白質，或當以化學方式合成時實質上不含化學前軀體或其他化學物質。可確定製劑實質上不含雜質，若其藉由熟習此項技術者用來評估該純度之標準分析方法所測定時似乎不含可易於偵測之雜質，諸如薄層層析法（thin layer chromatography，TLC）、凝膠電

泳及高效液相層析法（high performance liquid chromatography，HPLC）；或足夠純以使得進一步純化不會可偵測地改變物質之物理及化學性質，諸如酶促及生物學活性。純化化合物以產生實質上化學純化合物之方法為熟習此項技術者所已知。然而，實質上化學純化合物可為立體異構體之混合物。在該等情況下，進一步純化可增加化合物之比活性。

術語實質上不含細胞物質包括蛋白質自其所分離或重組產生之細胞的細胞組份分離之蛋白質製劑。在一具體實例中，術語實質上不含細胞物質包括具有少於約 30%（以乾重計）之非酵素蛋白質（本文中亦稱為污染蛋白質）、通常少於約 20%之非酵素蛋白質或 10%之非酵素蛋白質或少於約 5%之非酵素蛋白質的酵素蛋白質之製劑。當重組產生酵素蛋白質時，其亦實質上不含培養基，亦即培養基佔少於約或少於 20%、10%或 5%之酵素蛋白質製劑的體積。

如本文中所使用，術語實質上不含化學前驅體或其他化學物質（substantially free of chemical precursors or other chemicals）包括蛋白質自蛋白質合成所涉及之化學前驅體或其他化學物質分離的酵素蛋白質之製劑。該術語包括具有少於約 30%（以乾重計）、20%、10%、5%或更少之化學前驅體或非酵素化學物質或組份之酵素蛋白質之製劑。

如本文中所使用，關於（例如）合成核酸分子或合成基因或合成肽之合成係指藉由重組方法及/或藉由化學合成方法產生之核酸分子或多肽分子。

如本文中所使用，藉由重組方法藉由使用重組 DNA 方法來製備意謂使用分子生物學之熟知方法來表現由經選殖 DNA 編碼之蛋白質。

如本文中所使用，載體（vector）（或質體（plasmid））係指用於將異源核酸引入細胞中以供其表現或複製之不連續元件。該等載體典型地保持游離型，但可經設計以實現基因或其部分整合於基因組之染色體中。亦涵蓋為人工染色體之載體，諸如酵母人工染色體及哺乳動物人工染色體。該等運載體之選擇及使用為熟習此項技術者所熟知。

如本文中所使用，表現載體包括能夠表現 DNA 之載體，該 DNA 係與能夠實現該等 DNA 片段之表現的調節序列（諸如啟動子區域）操作性連接。該等其他區段可包括啟動子及終止子序列，且視情況可包括一或多個複製起點、一或多個可選擇標誌、增強子、聚腺苷酸化信號及其類似物。表現載體通常來源於質體或病毒 DNA，或可含有兩者之元件。因此，表現載體係指在引入適當宿主細胞中後使得所選殖 DNA 表現的重組 DNA 或 RNA 構築體，諸如質體、噬菌體、重組病毒或其他載體。適當表現載體為熟習此項技術者所熟知且包括可在真核細胞及/或原核細胞內複製者及保持游離型者或整合於宿主細胞基因組中者。

如本文中所使用，載體亦包括「病毒載體（virus vector/viral vector）」。病毒載體為操作性連接於外源基因以將該等外源基因轉移（以運載體或穿梭體形式）至細胞中之工程化病毒。

如本文中所使用，當提及DNA區段時可操作或操作性連接意謂該等區段經排列以便其一齊起作用以實現其預定目的，例如轉錄在啟動子中啟始且自編碼區段進行至終止子。

如本文中所使用，術語評估（assessing）意欲包括在獲得樣品中存在之蛋白酶或其域之活性的絕對值且亦獲得指示活性程度之指數、比率、百分比、可見或其他值之意義上的定量及定性測定。評估可為直接或間接評估且當然實際偵測之化學物質無需自身為蛋白水解產物，但可例如為其衍生物或一些其他物質。舉例而言，諸如藉由SDS-PAGE及使用庫馬斯藍（Coomasie blue）之蛋白質染色偵測補體蛋白之裂解產物。

如本文中所使用，生物學活性（biological activity）係指化合物之活體內活性或活體內投予化合物、組成物或其他混合物後所產生之生理學反應。因此，生物學活性涵蓋該等化合物、組成物及混合物之治療作用及醫藥活性。生物學活性可在經設計以測試或使用該等活性之試管內系統中觀察到。因此，出於本文之目的，蛋白酶之生物學活性為其水解多肽之催化活性。

如本文中所使用，當提及兩個核酸序列時，等效意謂該所述兩個序列編碼相同胺基酸序列或等效蛋白質。當提及兩種蛋白質或肽時使用等效時，其意謂該兩種蛋白質或肽具有實質上相同的胺基酸序列，僅具有不實質上改變蛋白質或肽之活性或功能的胺基酸取代。當等效係指性質

時，該性質並不需要相同程度地存在（例如，兩種肽可展現不同速率之相同類型之酵素活性），但該等活性通常實質上相同。

如本文中所使用，「調節（modulate/modulation）」或「改變（alter）」係指分子（諸如蛋白質）之活性的變化。例示性活性包括（但不限於）生物學活性，諸如信號轉導。調節可包括活性增強（亦即上調或促效劑活性）、活性降低（亦即下調或抑制）或活性之任何其他變化（諸如週期性、頻率、持續時間、動力學或其他參數之變化）。調節可與環境相關且典型地將調節比作指定狀況，例如野生型蛋白質、組成性狀態之蛋白質或表現於指定細胞類型或條件中之蛋白質。

如本文中所使用，組成物（composition）係指任何混合物。其可為溶液、懸浮液、液體、粉末、糊狀物、水溶液、非水溶液或其任何組合。

如本文中所使用，組合（combination）係指兩種或兩種以上物品之間或之中的任何結合。該組合可為兩種或兩種以上分開的物品，諸如兩種組成物或兩種收集物，可為其混合物，諸如兩種或兩種以上物品之單一混合物，或其任何變化形式。組合之成份通常功能上相關或有關。

如本文中所使用，套組（kit）為包裝組合，其視情況包括其他成份（諸如其他試劑）及該組合或其成份之使用說明書。詳言之，出於本文之目的，「套組」係指本文所提供之可活化的基質降解酵素與另一物品之組合以實現包括

（但不限於）活化、投藥、診斷及評估生物學活性或性質之目的。套組視情況包括使用說明書。

如本文中所使用，「疾病或病症」係指由包括（但不限於）感染、後天性條件、遺傳條件之病因或條件引起且特徵為可鑑別症狀之生物體的病理學病狀。本文所關注之疾病及病症為涉及ECM之組份者。

如本文中所使用，ECM介導之疾病或病狀為任一或多種ECM組份與病理學或病源學有關之疾病或病狀。出於本文之目的，ECM介導之疾病或病狀包括由一或多種ECM組份之沈積或積累增加引起之彼等疾病或病狀。該等病狀包括（但不限於）脂肪團、杜普宜特朗氏症候群、帕榮雷氏病、凍肩、現有瘢痕（諸如瘢痕瘤）、硬皮病及淋巴水腫。

如本文中所使用，「治療（treating）」患有疾病或病狀之個體意謂在治療後該個體之症狀部分或完全減輕，或保持不變。因此，治療涵蓋預防、治療及/或治癒。預防係指預防潛在疾病及/或預防症狀惡化或疾病進展。治療亦涵蓋本文所提供之經修飾之干擾素及組成物的任何醫藥用途。

如本文中所使用，醫藥有效藥劑（pharmaceutically effective agent）包括任何治療劑或生物活性劑，其包括（但不限於）例如麻醉劑、血管收縮劑、分散劑、習知治療藥物（包括小分子藥物）及治療性蛋白質。

如本文中所使用，治療（treatment）意謂緩解或有利地以其他方式改變病狀、病症或疾病或其他適應症之症狀的任何方式。

如本文中所使用，治療作用（therapeutic effect）意謂由治療個體引起之改變、典型地改善或緩解疾病或病狀之症狀或治癒疾病或病狀的作用。治療有效量係指在向個體投藥後產生治療作用之組成物、分子或化合物之量。

如本文中所使用，術語「個體」係指動物，包括哺乳動物，諸如人類。

如本文中所使用，患者係指人類個體。

如本文中所使用，藉由治療、諸如藉由投予醫藥組成物或其他治療劑來緩解特定疾病或病症之症狀係指可歸因於投予組成物或治療劑或與投予組成物或治療劑相關之症狀的任何減輕（無論為持久性或暫時性、持續或瞬時）。

如本文中所使用，預防（prevention/prophylaxis）係指降低發展疾病或病狀之危險的方法。

如本文中所使用，有效量為預防、治癒、緩解、阻止或部分阻止疾病或病症之症狀所必需之治療劑的量。

如本文中所使用，單位劑型（unit dose form）係指適合於人類及動物個體且如此項技術中已知個別包裝之物理離散單位。

如本文中所使用，單劑量調配物（single dosage formulation）係指用於直接投藥之調配物。

如本文中所使用，「製品（article of manufacture）」為製造及出售之產品。如本申請案中通篇所使用，該術語意欲涵蓋包裝物品中所含之可活化的基質降解酵素。

如本文中所使用，流體（fluid）係指可流動之任何組

成物。因此，流體涵蓋呈半固體、糊狀物、溶液、水性混合物、凝膠、洗劑、乳膏及其他此類組成物之形式的組成物。

如本文中所使用，細胞萃取物或溶解物(cellular extract or lysate)係指由溶解或碎裂之細胞製成之製劑或部分。

如本文中所使用，動物包括任何動物，諸如（但不限於）靈長類動物，包括人類、大猩猩及猴子；齧齒動物，諸如小鼠及大鼠；家禽，諸如雞；反芻動物，諸如山羊、母牛、鹿、綿羊；羊類，諸如豬及其他動物。非人類動物不包括人類作為所涵蓋之動物。本文所提供之酵素來自任何來源，動物、植物、原核生物及真菌。大多數酵素具有動物來源，包括哺乳動物來源。

如本文中所使用，對照(control)係指與測試樣品實質上一致之樣品，其例外之處在於其未以測試參數處理，或若其為血漿樣品，則其可來自未感染所關注之病狀的正常志願者。對照亦可為內部對照。

如本文中所使用，除非上下文另外明確規定，否則單數形式「一(a/ an)」及「該(the)」包括複數個指示物。因此，舉例而言，對包含「細胞外域」之化合物的提及包括具有一個或複數個細胞外域之化合物。

如本文中所使用，範圍及量可以「約(about)」特定值或範圍來表示。約亦包括精確量。因此，「約5個鹼基」意謂「約5個鹼基」以及「5個鹼基」。

如本文中所使用，「可選(optional)」或「視情況

(optionally)」意謂隨後所述事件或情況出現或不出現且描述包括該事件或情況出現之情況及其不出現之情況。舉例而言，視情況經取代之基團（optionally substituted group）意謂該基團未經取代或經取代。

如本文中所使用，除非另外指示，否則任何保護基、胺基酸及其他化合物之縮寫根據其常見用途為公認的縮寫或 IUPAC-IUB 生物化學命名委員會（Commission on Biochemical Nomenclature）（參見 (1972) *Biochem.* 11:1726）。

B. 細胞外基質

本文提供以時間受控方式降解細胞外基質（ECM）之一或多種蛋白質組份之可活化的基質降解酵素（AMDE）。藉助於該靶向及暫時性活體內活化，可治療 ECM 之疾病及/或病狀。可活化的基質降解酵素可降解 ECM 之任何組份；酵素選擇可視所靶向組份及/或欲治療之特定疾病或病狀而定。

ECM 構成包圍細胞外空間及血管與淋巴系統之結締組織或間質，從而提供對不同組織及不同組織之間的機械及結構支撐。ECM 之複雜及動力學微環境代表結締組織（諸如皮膚）中之結構及信號傳輸系統。由於 ECM 之複雜性質，其可發揮多種功能，諸如提供對於細胞之支撐及固著、隔開組織、調節細胞間通訊及隔離細胞生長因子。ECM 之組織化或構成之缺陷或改變可造成許多疾病或病狀。舉例而言，膠原纖維之合成、降解及組織化之改變造成脂肪代謝

障礙（例如脂肪團）及淋巴水腫。

ECM 由以下各者組成：纖維結構蛋白，諸如膠原蛋白；多醣，諸如蛋白聚糖及玻尿酸；及使基質之組份彼此連接及連接於細胞之黏著蛋白。諸如腱及軟骨之一些結締組織主要由 ECM 構成。然而，構成皮膚之結締組織的 ECM 亦與纖維母細胞、血管及其他組份一起分布。ECM 亦充當水及其溶解組份自血漿移動至淋巴之空間。間質液幾乎與細胞質等張且為經緩衝之碳酸氫鹽，從而提供處於中性 pH 值之細胞外環境。

1. ECM 之組份

ECM（亦稱為間隙基質）為含有諸多結構大分子（包括纖維狀蛋白，諸如膠原蛋白、彈性蛋白及纖維結合蛋白）之複雜三維動態結構，其中葡糖胺聚糖（GAG）形成水合凝膠狀物質。ECM 之組份由固有細胞（典型地為纖維母細胞或纖維母細胞家族之細胞）產生，且經由其與 ECM 之其他組份相互作用之胞吐作用分泌。產生多種結締組織，諸如骨、皮膚或角膜在於相對量及組份組織化並共同形成之方式的變化（Albert 等人，「Cell Junctions, Cell Adhesions and the Extracellular Matrix.」 *Molecular Biology of the Cell*. New York: Garland Publishers, 1994. 第 972 頁.）。

a. 膠原蛋白

膠原蛋白為結締組織（諸如皮膚）之主要結構組份，且在組織結構、組織強度及細胞-細胞相互作用之發展及維持中起作用。膠原蛋白包括 ECM 之含有一或多個具有膠原

蛋白三股螺旋之構形的域之結構相關蛋白質之家族（Van der Rest 等人 (1991) FASEB J., 5:2814-2823）。膠原蛋白含有 Gly-X-Y 重複結構，其使得膠原蛋白鏈捲曲成螺旋結構。各膠原蛋白分子含有彼此捲繞以形成三股螺旋之 3 條鏈，稱為 α1-α3。該三股螺旋結構向膠原蛋白分子提供高機械強度。存在至少 27 種不同類型之膠原蛋白，其在胺基酸序列及鏈組成方面不同。舉例而言，視膠原蛋白之類型而定，形成三股螺旋之 3 條鏈可相同或不同。膠原蛋白可為同源三聚體（亦即三股螺旋之所有 3 條多肽鏈由相同膠原蛋白構成）或可為異型的（亦即原纖維由一種以上膠原蛋白類型組成）。膠原蛋白可分為若干個家族，其視其形成之結構而定。此等家族包括纖維狀膠原蛋白（亦稱為間質膠原蛋白；例如 I 型、II 型、III 型、V 型及 XI 型）及非纖維狀膠原蛋白，諸如斷續三股螺旋纖維結合膠原蛋白（facit）（例如 IX 型、XII 型、XIV 型）、短鏈（例如 VIII 型、X 型）、基底膜（例如 IV 型）及其他膠原蛋白（例如 VI 型、VII 型及 XIII 型）。下表 2 陳述常見膠原蛋白類型及其代表性位置（Van der Rest 等人 (1991) FASEB J., 5:2814-2823）；www.collagenlife.com/page_1167323108078.html ；www.indstate.edu/thcme/mwking/extracellularmatrix.html）。

在間質膠原蛋白中，膠原蛋白分子結合形成具有特殊帶型之大原纖維。該帶型由相鄰分子之間的重疊產生。膠原纖維之強度係基於形成結締組織之緻密膠原纖維網之膠原纖維的許多分子內及分子間鍵聯。最常見纖維狀膠原蛋

白包括 I 型、II 型及 III 型膠原蛋白。I 型膠原蛋白見於大多數結締組織中，諸如皮膚、骨、腱及角膜，且由兩條 α1(I) 鏈及一條 α2(I)鏈構成（$[\alpha1(I)]_2\ \alpha2(I)$）。II 型膠原蛋白為同源三聚體（$[\alpha1(II)]_3$）且主要見於軟骨中。III 型膠原蛋白亦為同源三聚體（$[\alpha1(III)]_3$）且主要見於皮膚及血管中。

並非所有膠原蛋白均形成原纖維網。舉例而言，基底膜 IV 型膠原蛋白為非纖維狀且在螺旋中具有非螺旋間斷，其充當鉸鏈，從而給予分子更大可撓性。因此，IV 型膠原蛋白形成由長絲網而非線性原纖維構成之薄片。

皮膚之最豐富蛋白質為膠原蛋白，其主要由皮膚之總膠原蛋白之 I 型（80-85%）及 III 型（8-11%）構成。I 型膠原蛋白與 III 型膠原蛋白結合形成真皮之主要膠原纖維。皮膚之拉伸強度主要歸因於此等纖維狀膠原蛋白分子，其以頭接尾及交錯之邊對邊橫向排列方式組裝成微原纖維。膠原蛋白分子變為與相鄰膠原蛋白分子交聯，產生膠原纖維之額外強度及穩定性。舉例而言，V 型膠原蛋白亦與 I 型/III 型膠原纖維結合，且調節原纖維直徑。皮膚中之其他膠原蛋白類型包括（例如）IV 型、VI 型、VII 型、XII 型、XIV 型及 XVII 型。

表2：膠原蛋白之類型		
類型	分子組成	代表性組織
纖維狀膠原蛋白		
I	$[\alpha1(I)]_2\,[\alpha2(I)]$	皮膚、骨、腱、牙質、韌帶、間質組織
II	$[\alpha1(II)]_3$	軟骨、玻璃狀液
III	$[\alpha1(III)]_3$	皮膚、肌肉、血管；常與I型結合
V	$[\alpha1(V)][\alpha2(v)][\alpha3(V)]$	類似於I型，亦為細胞培養物、胎兒組織；與I型結合
XI	$[\alpha1(XI)][\alpha2(XI)][\alpha3(XI)]$	軟骨、椎間軟骨及骨釉質
非纖維狀膠原蛋白		
IV	$[\alpha1(IV)]_2\,[\alpha2\,(IV)]$	基底膜
VI	$[\alpha1(VI)][\alpha2(VI)][\alpha3(VI)]$	大多數間質組織；與I型結合
VII	$[\alpha1(VII)]_3$	上皮
VIII	$[\alpha1(VIII)]_3$	未知，一些內皮細胞
IX	$[\alpha1(IX)][\alpha2(IX)][\alpha3(IX)]$	軟骨；與II型結合
X	$[\alpha1(X)]_3$	異養及礦質化軟骨
XII	$[\alpha1(XII)]_3$	韌帶、腱及牙釉質；與I型及III型相互作用

b. 彈性蛋白

ECM中之彈性纖維網向需要回彈性以在拉伸後彈回之組織（諸如皮膚、動脈及肺）提供可撓性。彈性纖維之主要組份為彈性蛋白分子，其與相鄰彈性蛋白分子形成交聯。此等分子形成彈性纖維之核心且由肌原纖維蛋白（fibrillin）覆蓋，肌原纖維蛋白為與彈性蛋白結合且對於彈性纖維之完整性至關重要的大醣蛋白。

c. 纖維結合蛋白

纖維結合蛋白為以一對由靠近羧基末端之一對二硫鍵聯接的兩個大亞單位形式存在之醣蛋白。各亞單位含有對於其他基質大分子及細胞表面上之受體具特異性的功能上

不同之域。舉例而言，纖維結合蛋白上之不同域結合膠原蛋白(對於I型、II型及III型為分開的域)、肝素(heparin)、纖維蛋白及細胞表面受體（諸如整合素（integrin））。纖維結合蛋白存在於血漿與組織中。在組織中，纖維結合蛋白起將不同類型之ECM分子與細胞連接在一起的作用。其亦含有由三個胺基酸Arg-Gly-Asp（RGD）構成之重要細胞結合域，此域由細胞之質膜中的整合素受體識別。纖維結合蛋白分子與細胞上之整合素受體的結合產生對信號傳輸路徑之刺激，促進細胞黏附、遷移及分化。此等特徵使得纖維結合蛋白在細胞黏著中發揮重要作用且在細胞與ECM組份之間傳遞信號。

d. 葡糖胺聚糖（GAG）

GAG為由強親水性重複雙醣單元構成之非支鏈多醣鏈。GAG高度帶負電且因此吸引滲透活性Na^+，引起大量水吸入其結構中以保持ECM水合。諸如硫酸皮膚素(dermatan sulfate)之GAG典型地含有自線性蛋白質核心分枝之長度為70-200個糖之多條葡糖胺聚糖鏈（由重複雙醣單元形成）。此使得GAG相對於其質量佔據極大體積且於極低濃度下形成凝膠。GAG之親水性引起膨脹壓力或膨壓，此使得ECM經受壓縮力。

在ECM中，GAG連接於ECM蛋白質以形成蛋白聚糖，或在玻尿酸（hyaluronic acid）（亦稱為玻尿酸(hyaluronan)）之情況下以非蛋白聚糖基質組份形式存在。細胞外蛋白聚糖為輔助ECM中之墊細胞之大的高度水合分

子。諸如玻尿酸之葡糖胺聚糖藉由對流過間質膠原性基質之大量流體流經由其黏度及水合水形成障壁而有助於「基底物質」。蛋白聚糖及非蛋白聚糖 GAG 在 ECM 中結合形成大聚合複合物。其相互結合，且亦與諸如膠原蛋白之纖維狀蛋白結合。

i. 蛋白聚糖

存在形成 ECM 之蛋白聚糖的三種主要類型之 GAG，包括硫酸皮膚素及硫酸軟骨素、肝素及硫酸乙醯肝素及硫酸角質素。通常，蛋白聚糖為 95 重量%碳水化合物，典型地呈長的未分枝 GAG 鏈之形式。除提供細胞周圍之水合空間外，蛋白聚糖亦調節分子及細胞之運輸，結合信號傳輸分子，從而在細胞活化中起作用，並結合諸如蛋白酶及蛋白酶抑制劑之其他分泌蛋白質以調節分泌蛋白質之活性（Albert 等人，「Cell Junctions, Cell Adhesions and the Extracellular Matrix.」 *Molecular Biology of the Cell*. New York: Garland Publishers, 1994. 第 972-978 頁.）。舉例而言，蛋白聚糖之硫酸肝素鏈與若干不同生長因子結合，包括纖維母細胞生長因子（fibroblast growth factor，FGF），從而有助於其與其特異性細胞表面受體結合。

聚集蛋白聚糖（aggrecan）為主要含有硫酸軟骨素及硫酸乙醯肝素 GAG 之蛋白聚糖，且典型地見於軟骨中，與玻尿酸形成大聚集體以提供機械支撐。核心蛋白聚糖（decorin）為主要由硫酸軟骨素及硫酸皮膚素 GAG 構成之結締組織的另一例示性 GAG。其與 I 型膠原原纖維結合。

基底膜蛋白聚糖（perlecan）及β聚糖（betaglycan）為 ECM 之其他例示性蛋白聚糖。並非所有蛋白聚糖均與 ECM 結合：舉例而言，絲甘蛋白聚糖（serglycin）與有助於包裝及儲存分泌分子之分泌小泡結合，且多配體蛋白聚糖（syndecan）見於細胞表面上且充當輔助受體（Albert 等人，「Cell Junctions, Cell Adhesions and the Extracellular Matrix.」 *Molecular Biology of the Cell*. New York: Garland Publishers, 1994. 第 972-978 頁）。

硫酸乙醯肝素蛋白聚糖（heparan sulfate proteoglycan，HSPG）為與多種脊椎動物及無脊椎動物組織之細胞的細胞表面及細胞外基質（ECM）結合之普遍存在的大分子（Wight, T. N., Kinsella, M. G., 及 Qwarnstromn, E. E. (1992) *Curr. Opin. Cell Biol.*, 4,793-801；Jackson, R. L., Busch, S. J., 及 Cardin, A. L. (1991) *Physiol. Rev.*, 71,481-539；Wight, T. N. (1989) *Arteriosclerosis,* 9,1-20; Kjellen, L.及 Lindahl, U. (1991) *Annu. Rev. Biochem.*, 60,443-475；及 Ruoslahti, E.及 Yamaguchi, Y. (1991) *Cell*, 64,867-869）。基礎 HSPG 結構由蛋白質核心組成，若干線性硫酸乙醯肝素鏈共價連接於該蛋白質核心。多醣鏈典型地由在不同程度上經 N-及 O-連接型硫酸酯部分及 N-連接型乙醯基取代之重複己醣醛酸及 D-葡糖胺雙醣單元構成。對 ECM 分子參與細胞黏附、生長及分化之研究揭露 HSPG 在胚胎形態發生、血管生成、癌轉移、神經突外生長及組織修復中之主要作用。在其結合眾多蛋白質之能力方面獨

特的硫酸乙醯肝素（heparan sulfate，HS）鏈確保多種效應分子黏著於細胞表面。HSPG亦為血管之主要組份。在大血管中，其主要集中於內膜及內介質中，而在毛細管中其主要見於內皮下基底膜中，在此處其支持內皮細胞增殖及遷移且使毛細管壁之結構穩定。HSPG與ECM大分子（諸如膠原蛋白、層黏蛋白（laminin）及纖維結合蛋白）及與質膜上之不同連接位點相互作用之能力表明此蛋白聚糖在自組裝及ECM組份之不溶性以及在細胞黏著及移動方面的關鍵作用。

ii. **玻尿酸**

玻尿酸（hyaluronic acid）（HA；亦稱為玻尿酸（hyaluronan））為吸引水之大GAG，且當與水結合時以黏性凝膠狀形式存在。因此，HA充當潤滑劑，使凝膠狀結締組織結合在一起。HA為雙醣之聚合物（長度有時多達25,000個重複）且由兩個經修飾之簡單糖葡糖醛酸及N-乙醯基葡糖胺之重複單元組成。HA為許多結締組織之ECM的部分。HA以最大量見於皮膚中，幾乎為見於皮膚中之身體HA之50%。HA藉由結合水而向皮膚提供連續水份。HA之產生降低（諸如因年齡）導致皮膚起皺且不健康。

HA主要經由其受體CD44亦在胚胎發育及形態發生、創口癒合、修復及再生、炎症及腫瘤發展及侵襲期間起調控細胞行為之作用（Harada 等人 (2006) *J. Biol. Chem.*, 8:5597-5607）。HA由玻尿酸酶降解。HA之降解產物可以增加量見於損傷或生長組織中，且見於多種發炎性病狀中。

HA片段促進血管生成且可刺激組織損傷及皮膚移植中之巨噬細胞及樹突狀細胞產生細胞激素。

2. 皮膚組織學

皮膚由若干不同層組成，主要為表皮及真皮。表皮為來源於外胚層之特化上皮，且在其下方為真皮，其為中胚層之衍生物並為血管緻密結締組織。此兩個層相互牢牢黏著且形成在身體之不同區域總厚度自約 0.5 mm 至 4 mm 變化之區域。在真皮下方為一層疏鬆結締組織，其在性質上自網形結締組織至脂肪不同。將其稱為下皮，但典型地認為其並非皮膚之部分。真皮藉由自一層延伸至另一層之連接組織纖維連接於下皮。

a. 表皮

表皮為直接位於真皮上方之皮層，且為皮膚之表面層。表皮之基本功能在於充當針對失水、化學損傷及侵襲性病原體之防護障壁。表皮為約 0.1 毫米至 1.5 毫米厚之約 15 個細胞層之薄層，其主要由角質細胞構成(Inlander, Skin, New York, N.Y.: People's Medical Society, 1-7 (1998))。表皮自身根據角質細胞之分化狀況分成若干層（例如基層、棘狀層、顆粒層、透明層、角質層）。角質細胞來源於基底層中之角質細胞幹細胞。當角質細胞生長及分裂時，其經歷逐漸分化，最終達到其形成一層稱為鱗狀細胞（稱為角質細胞）之無核、平坦、高度角質化細胞的角質層。除由角質細胞構成外，角質層亦含有皮脂。皮脂由皮脂腺分泌，其通常見於連接於毛囊之毛髮覆蓋區域中。皮脂為有助於

使角質細胞結合在一起且保持水份之微酸性層。此酸度歸因於構成皮脂之兩性胺基酸、乳酸及脂肪酸之存在。因此，皮膚表面之 pH 值通常介於 5 與 6 之間，典型地為約 5.5。皮脂起使毛髮及皮膚防水之作用，及使其不會變乾、變脆及開裂，並且其亦抑制皮膚上微生物之生長。術語「酸罩(acid mantle)」係指皮膚之大部分區域上存在水溶性物質。

b. 真皮

皮膚之結締組織稱為真皮。真皮為 1.5 毫米至 4 毫米厚。在皮膚中，真皮含有 ECM 組份；主要蛋白質組份為膠原蛋白及彈性蛋白。真皮亦為大多數皮膚結構之所在地，包括經由稱為毛孔之皮膚開口分泌物質的汗腺及脂腺、或粉刺、毛囊、神經末梢及血管與淋巴管(Inlander, Skin, New York, N.Y.: People's Medical Society, 1-7 (1998))。

c. 下皮

在真皮下方為下皮，其為脂肪層且為皮膚之最深層。其既充當保存身體熱量之隔離物，亦充當保護器官之減震器 (Inlander, Skin, New York, N.Y.: People's Medical Society, 1-7 (1998))。另外，下皮亦儲存脂肪用於能量儲備。

3. ECM 之疾病

某些疾病及病狀由因 ECM 組份之異常表現或產生所致之細胞外基質之結構的缺陷或變化引起。舉例而言，在一些發炎性病狀（諸如在創口癒合之後出現）中，分泌刺激纖維母細胞分泌 ECM 組份（諸如膠原蛋白）之細胞激素。

ECM 組份積累且變得局部沈積，導致多種纖維變性病狀。基質沈積為許多慢性發炎性疾病及其他疾病及病狀之常見特點。此等病狀包括膠原蛋白介導之疾病及病狀，諸如（但不限於）諸如瘢痕瘤及肥厚性瘢痕之瘢痕、杜普宜特朗氏症候群、帕榮雷氏病及淋巴水腫。脂肪團亦為 ECM 之主要疾病，除脂肪形成增加外，其特徵亦在於結締組織基質之變化導致膠原蛋白之異常纖維中隔網(Rawlings 等人 (2006) Int. J Cos. Science, 28:175-190)。

特徵在於基質組份之異常表現或過量產生、導致其積累及不當沈積的 ECM 之疾病及病狀可藉由本文所提供之可活化的基質降解酵素來治療。由於活體內投藥之後該等酵素之暫時性活化，調節該等疾病及病狀之治療以限制基質組份之酶促降解。舉例而言，藉由限制基質降解之作用持續時間，使與不受控蛋白質降解相關的不當副作用降至最少。

C. 基質降解酵素

本文提供含有可活化的基質降解酵素之組成物、組合及容器，及使用可活化的基質降解酵素治療 ECM 介導之疾病或病狀的方法。基質降解酵素降解 ECM 之蛋白質組份或醣蛋白，包括（但不限於）膠原蛋白、彈性蛋白、纖維結合蛋白及蛋白聚糖。藉助於其裂解一或多種 ECM 組份之能力，本文所提供之可活化的基質降解酵素可用於改良組織之基質，尤其展現由一或多種 ECM 蛋白質之過量或富含一或多種 ECM 蛋白質（諸如膠原蛋白）之纖維組織的不當積

累引起之結構缺陷或變化的彼等基質。因此，該等酵素適用於治療涉及ECM蛋白質之疾病或病狀。

基質降解酵素為蛋白酶及糖基水解酶。因此，基質降解酵素包括作為識別標靶蛋白質中之胺基酸序列或多肽受質的蛋白質降解酵素以及識別諸如酯鍵或糖基之非肽鍵的水解酶之蛋白質。蛋白酶為絲胺酸、半胱胺酸、天冬胺酸及金屬蛋白酶家族之外蛋白酶（exoprotease）。在識別受質序列之後，蛋白酶催化標靶蛋白質之水解或裂解。視標靶序列之全長序列範圍內之肽鍵的位置而定，標靶蛋白質之該水解可使標靶失活，或在一些情況下活化標靶。

蛋白酶使用若干不同類型之催化機制（Barret 等人(1994) *Meth. Enzymol.* 244:18-61；Barret 等人 (1994) *Meth. Enzymol* 244:461-486；Barret 等人 (1994) *Meth. Enzymol.* 248:105-120；Barret 等人 (1994) *Meth. Enzymol.* 248:183-228）。根據其催化機制，將裂解肽鍵之蛋白酶再分為絲胺酸、半胱胺酸、天冬胺酸、蘇胺酸及金屬蛋白酶。絲胺酸型肽酶（peptidase）具有參與活性中心之絲胺酸殘基，天冬胺酸型肽酶在催化中心中具有兩個天冬胺酸，半胱胺酸型肽酶具有半胱胺酸殘基，蘇胺酸型肽酶具有蘇胺酸殘基，且金屬肽酶在催化機制中使用金屬離子。蛋白酶之催化活性為裂解標靶受質所需。絲胺酸及金屬蛋白酶於中性pH值下最具活性，而主要見於溶酶體中之半胱胺酸及天冬胺酸蛋白酶具有酸性pH值最佳條件。因此，溶酶體蛋白酶包括半胱胺酸及天冬胺酸蛋白酶家族之蛋白酶。其他

酵素家族包括水解酶，諸如作用於酯鍵之酯酶及水解 O-糖基化合物或 S-糖基化合物或 N-糖基化合物之乙二醇酯酶（glycolase）。糖基水解酶之實例為肝素酶。

例示性基質降解酵素闡明於表 3 中（參見例如，Chapman 等人，*Am J. Physiol Heart Circ. Physiol.* (2004) 286:1-10；Iozzo RV, *Proteoglycans: Structure, biology, and Molecular Interactions*, CRC Press (2000), 第 94-96 頁；Owen 等人 (1999) J. Leuk. Biol., 65:137-150；Buhling 等人 (2004) *Eur. Respir. J.*, 23:620-628；Thomas Kreis and Ronald Cale, *Extracellular Matrix, Anchor and Adhesion Proteins*, Oxford University Press (1999) 第 515-523 頁；Ian M. Clark 及 Gillian Murphy.「Matrix Proteinases,」於 Dynamics of Bone and Cartilage Metabolism 中, Academic Press (2006), 第 181-198 頁；Buck 等人 (1992) Biochem J., 282:273-278）。各例示性蛋白酶之前軀多肽的核苷酸序列（mRNA）及所編碼之胺基酸序列的序列識別符（SEQ ID NO）描述於表中。各例示性蛋白酶之蛋白原（proprotein）的胺基酸序列之序列識別符（SEQ ID NO）以及蛋白原中對應於肽原之胺基酸位置亦描述於表中。此項技術中已知之對偶基因及物種變異體及其他變異體中亦存在變化，且亦涵蓋該等變異體以用作可活化的酵素。該表亦闡明各酵素之例示性 ECM 標靶受質。對該等受質之提及僅供參考及例示，且不欲代表所有標靶受質之詳細清單。熟習此項技術者已知或可憑經驗使用常規檢定（正如本文所述之任何檢

定）判定所需酵素之 ECM 標靶受質。

基質降解酵素可藉由此項技術中已知之任何方法（包括自天然來源分離，分離細胞、組織及生物體中重組產生之蛋白質）及藉由重組方法及藉由包括電腦（in silico）步驟之方法、合成方法及熟習此項技術者已知之任何方法產生或分離。酵素典型地以無活性形式產生或分離。條件性活化可如下文所述來達成。

表 3：基質降解酵素

蛋白酶	受質	酵素資料庫存取碼（EC）www.expasy.ch/sprot/enzyme.html	GenBank 編號	SEQ ID NO		
				前軀體		成熟
				nt	aa（信號序列（ss）之 aa；前肽（pp）之 aa）	aa
絲胺酸蛋白酶						
胰腺彈性蛋白酶（PE1；彈性蛋白酶-1）	彈性蛋白	3.4.21.36	Q9UNI1；NM_001971	19	20（ss aa 1-8；pp aa 9-18）	21
彈性蛋白酶-2A	彈性蛋白	3.4.21.71	P08217；NM_033440	22	23（ss aa 1-16；pp aa 17-28）	24
彈性蛋白酶-2B	彈性蛋白	3.4.21.71	P08218；NM_015849	25	26（aa aa 1-16；pp aa 17-28）	27
嗜中性白血球彈性蛋白酶（NE；白血球彈性蛋白酶；彈性蛋白酶-2）	彈性蛋白，纖維結合蛋白，層黏蛋白，II 型、IV 型、VI 型膠原蛋白，蛋白聚糖	3.4.21.37	P08246 NM_001972	28	29（ss aa 1-17；pp aa 28-29）	30
蛋白酶-3（PR-3；成髓細胞素）	彈性蛋白、纖維結合蛋白、層黏蛋白、玻連蛋白、IV 型膠原蛋白	3.4.21.76	P24158 NM_002777	31	32（ss aa 1-25；pp aa 26-27、249-256）	33
內源性血	彈性蛋白	3.4.21.46	S73894	34	35	36

表 3：基質降解酵素						
蛋白酶	受質	酵素資料庫存取碼（EC）www.expasy.ch/sprot/enzyme.html	GenBank 編號	SEQ ID NO		
				前軀體		成熟
				nt	aa（信號序列（ss）之 aa；前肽（pp）之 aa）	aa
管彈性蛋白酶（EVE；組織彈性蛋白酶；補體因子 D）			（鼠屬（*Rattus sp.*））		（ss aa 1-20；pp aa 21-25）	
組織蛋白酶 G	IV 型膠原蛋白、層黏蛋白、纖維結合蛋白、蛋白聚糖、彈性蛋白	EC 3.4.21.20	P08311 NM_001911	37	38（ss aa 1-18；pp aa 19-20）	39
肥大細胞凝乳酶	IV 型膠原蛋白、層黏蛋白、纖維結合蛋白、蛋白聚糖	3.4.21.39	P23946 NM_001836	40	41（ss aa 1-19；pp aa 20-21）	42
肥大細胞類胰蛋白酶	纖維結合蛋白、纖維蛋白原、IV 型膠原蛋白、蛋白聚糖	3.4.21.59	Q9BZJ3 NM_012217	43	44（ss aa 1-18；pp aa 19-30）	45
纖溶酶	蛋白聚糖、纖維結合蛋白、層黏蛋白	3.4.21.7	P00747 NM_000301	46	47（ss aa 1-19；pp aa 20-97）	48
凝血酶	蛋白聚糖	3.4.21.5	P00734 NM_000506	49	50（ss aa 1-24；pp aa 25-43）	51
顆粒酶 B	蛋白聚糖	3.4.21.79	P10144 NM_004131	52	53（ss aa 1-18；pp aa 19-20）	54
半胱胺酸蛋白酶						
組織蛋白酶 S	彈性蛋白、膠原蛋白	EC 3.4.22.27	P25774 NM_004079	55	56（ss 1-16；pp 17-114）	57
組織蛋白酶 K	彈性蛋白、膠原蛋白 I 及 III	EC 3.4.22.38	P43235 NM_000396	58	59（ss aa 1-15；pp aa 16-114）	60
組織蛋白酶 L	彈性蛋白、膠原蛋白 I 及 IV	EC 3.4.22.15	P07711	61	62（ss aa 17；pp aa 18-113）	1
組織蛋白酶 B	膠原蛋白 IV、層黏蛋白、纖維結合蛋白	EC 3.4.22.1	P07858 NM_001908	63	64（ss aa 1-17；pp aa 18-79）	65

表 3：基質降解酵素

蛋白酶	受質	酵素資料庫存取碼（EC）www.expasy.ch/sprot/enzyme.html	GenBank 編號	SEQ ID NO		
				前軀體		成熟
				nt	aa（信號序列（ss）之 aa；前肽（pp）之 aa）	aa
組織蛋白酶 C	蛋白聚糖（核心蛋白聚糖）	EC 3.4.14.1	P53634 NM_001814	178	179（ss aa 1-24；pp aa 135-230）	180
組織蛋白酶 H	纖維結合蛋白	EC 3.4.22.16	P09668 X16832	66	67（ss aa 1-22；pp aa 23-97）	68
組織蛋白酶 F	膠原蛋白片段	EC 3.4.22.41	Q9R013 NM_019861（小家鼠（*Mus musculus*））	69	70（ss aa 1-19；pp aa 20-248）	71
組織蛋白酶 F	膠原蛋白片段	EC 3.4.22.41	Q9UBX1 NM_003793	181	182（ss aa 1-19；pp 20-270）	183
組織蛋白酶 O	纖維蛋白原	EC 3.4.22.42	Q8BM88 NM_177662（小家鼠）	72	73（aa aa1-23；pp aa 24-98）	74
組織蛋白酶 O	纖維蛋白原	EC 3.4.22.42	P43234 NM_001334	184	185（ss aa 1-23；pp aa 24-107）	186
組織蛋白酶 R		EC3.4.22.-	Q9JIA9 NM_020284（小家鼠）	75	76（ss aa 1-17；pp aa 18-114）	77
組織蛋白酶 V（組織蛋白酶 L2）	膠原蛋白	EC 3.4.22.43	O60911 NM_001333	187	188（ss aa 1-17；pp aa 18-113）	189
組織蛋白酶 W		EC 3.4.22.-	P56202 NM_001335	78	79（ss aa 1-21；pp aa 22-127）	80
鈣激活中性蛋白酶 1	纖維結合蛋白、玻璃連結蛋白（vitronectin）、蛋白聚糖	EC 3.4.22.52	鈣激活中性蛋白酶 1 大亞單位：P07384 NM_005186	81		82
鈣激活中性蛋白酶 2	纖維結合蛋白、玻璃連結蛋白、蛋白聚糖	EC3.4.22.53	鈣激活中性蛋白酶 2 大亞單位：P17655 NM_001748	83	84（aa 1 起始甲硫胺酸）	85
		鈣激活中性蛋白酶小亞單位 1（與鈣激活中性蛋白酶 1 及		86		87

表 3：基質降解酵素						
蛋白酶	受質	酵素資料庫存取碼（EC）www.expasy.ch/sprot/enzyme.html	GenBank 編號	SEQ ID NO		
				前軀體		成熟
				nt	aa（信號序列（ss）之 aa；前肽（pp）之 aa）	aa
		2 大亞單位結合） P04632 NM_001749				
豆莢蛋白（Legumain）		EC 3.4.22.34	Q99538 NM_005606	190	191 （ss aa 1-17；pp aa 324-433）	192
組織蛋白酶 Z（組織蛋白酶 X）		EC 3.4.22.-	Q9UBR2 NM_001336	193	194 （ss aa 1-23；pp aa 24-61）	195
天冬胺酸蛋白酶						
組織蛋白酶 D	蛋白聚糖	EC 3.4.23.5	P07339 NM_001909	88	89 （ss aa 1-18；pp aa 19-64）	90
組織蛋白酶 E	蛋白聚糖	EC 3.4.23.34	P14091 同功異型物 a NM_001910 同功異型物 b NM_148964	91 94	92 （ss aa 1-17；pp aa 18-53） 95 （ss aa 1-17；pp aa 18-53）	93 96
金屬蛋白酶						
MMP-1（膠原酶-1）	膠原蛋白 I、II、III、VII、X，明膠，蛋白聚糖，纖維結合蛋白，醣蛋白	3.4.24.7	P03956, NM_002421	97	98 （ss aa 1-19；pp aa 20-99）	99
MMP-8（膠原酶-2）	膠原蛋白 I、II、III、VII、X，明膠，蛋白聚糖，聚集蛋白聚糖	3.4.24.34	P22894 NM_002424	100	101 （ss aa 1-20；pp aa 21-100）	102
MMP-13（膠原酶-3）	膠原蛋白 I、II、III，明膠，蛋白聚糖	3.4.24.-	P45452 NM_002427	103	104 （ss aa 1-19；pp aa 20-103）	105
MMP-18（膠原酶-4）	膠原蛋白 I	3.4.24.-	爪蟾（*Xenopus laevis*） O13065	106	107 （ss aa 1-17；pp aa 18-99）	108
MMP-2（明膠酶 A）	明膠，膠原蛋白 I、IV、V、VII，	3.4.24.24	P08253 NM_004530	109	110 （ss aa 1-29；pp	111

表 3：基質降解酵素

蛋白酶	受質	酵素資料庫存取碼（EC）www.expasy.ch/sprot/enzyme.html	GenBank 編號	SEQ ID NO		
				前軀體		成熟
				nt	aa（信號序列（ss）之 aa；前肽（pp）之 aa）	aa
	彈性蛋白，纖維結合蛋白，層黏蛋白，蛋白聚糖				30-109）	
MMP-9（明膠酶 B）	明膠，膠原蛋白 IV、V、XIV，彈性蛋白，蛋白聚糖，醣蛋白	3.4.24.35	P14780 NM_004994	112	113（ss aa 1-19；pp aa 20-93）	114
MMP-3（基質溶素-1）	纖維結合蛋白，層黏蛋白，膠原蛋白 III、IV、IX	3.4.24.17	P08254 NM_002422	115	116（ss aa 1-17；pp aa 18-99）	117
MMP-10（基質溶素-2）	膠原蛋白 III、IV、V，纖維結合蛋白，聚集蛋白聚糖	3.4.24.22	P09238 NM_002425	118	119（ss aa 1-17；pp aa 18-98）	120
MMP-11（基質溶素-3）	纖維結合蛋白、層黏蛋白、聚集蛋白聚糖	3.4.24.-	P24347 X57766	121	122（ss aa 1-31；pp aa 32-97）	123
MMP-7（基質溶素）	纖維結合蛋白，層黏蛋白，彈性蛋白，明膠，膠原蛋白 I、IV	3.4.24.23	P09237 NM_002423	124	125（ss aa 1-17；pp aa 18-94）	126
MMP-26（基質溶素-2）	膠原蛋白 IV、纖維結合蛋白	3.4.24.-	Q9NRE1 NM_021801	127	128（ss aa 1-17；pp aa 18-89）	129
MMP-12（金屬彈性蛋白酶（metalloelastase））	彈性蛋白、纖維結合蛋白、層黏蛋白、膠原蛋白 IV、蛋白聚糖	3.4.24.65	P39900 NM_002426	130	131（ss aa 1-16；pp aa 17-105）	132
MMP-14（MT1-MMP）	膠原蛋白 I、II、III，聚集蛋白聚糖，纖維結合蛋白，玻璃連結蛋白，層黏蛋白	3.4.24.80	P50281 NM_004995	133	134（ss aa 1-20；pp aa 21-111）	135
MMP-15（MT2-MMP）	聚集蛋白聚糖、纖維結合蛋白、層黏蛋白	EC 3.4.24.-	P51511 NM_002428	136	137（ss aa 1-41；pp aa 42-131）	138
MMP-16（MT3-MM	膠原蛋白 III、纖維結合蛋白、層黏蛋	EC 3.4.24.-	P51512 NM_005941	139	140（ss aa 1-31；pp	141

表3：基質降解酵素						
蛋白酶	受質	酵素資料庫存取碼（EC）www.expasy.ch/sprot/enzyme.html	GenBank 編號	SEQ ID NO		
				前軀體		成熟
				nt	aa（信號序列（ss）之aa；前肽（pp）之aa）	aa
P）	白				aa 32-119）	
MMP-17（MT4-MMP）	纖維結合蛋白	EC 3.4.24.-	Q9ULZ9 AB021225	142	143 （ss aa 1-38；pp aa 39-128）	144
MMP-19	膠原蛋白 I、IV，明膠，聚集蛋白聚糖	EC 3.4.24.-	Q99542 NM_002429	145	146 （ss aa 1-18；pp aa 19-97）	147
MMP-20（釉質溶解素（enamelysin））	聚集蛋白聚糖	EC 3.4.24.-	O60882 Y12779	148	149 （ss aa 1-22；pp aa 23-107）	150
MMP-x（MMP-21）（XMMP）	無確定受質	EC 3.4.24.-	O93470 NM_001085816 爪蟾屬（*Xenopus*）	151	152 （ss aa 1-22；pp aa 23-180）	153
ADAMTS-1	聚集蛋白聚糖	EC 3.4.24.	Q9UHI8 NM_006988	157	158 （ss aa 1-49；pp aa 50-252）	159
ADAMTS-2	原膠原 I、原膠原 II	EC 3.4.24.	O95450 AJ003125	160	161 （ss aa 1-29；pp aa 30-253）	162
ADAMTS-3	原膠原 II	EC 3.4.24.14	O15072 NM_014243	163	164 (aa 1-229）	165
ADAMTS-4（聚集蛋白聚糖酶-1）	聚集蛋白聚糖	EC 3.4.24.82	O75173 NM_005099	166	167 （ss aa 1-51；pp aa 52-212）	168
ADAMTS-5（聚集蛋白聚糖酶-2）	聚集蛋白聚糖	EC 3.4.24.	Q9UNA0 NM_007038	169	170 （ss aa 1-16；pp aa 17-261）	171
ADAMTS-14	原膠原 I	EC 3.4.24.	Q8WXS8 同功異型物 a NM_139155 同功異型物 a NM_080722	172 175	173 （ss aa 1-22；pp aa 23-252） 176 （ss aa 1-22；pp aa 23-252）	174 177
其他						

表 3：基質降解酵素						
蛋白酶	受質	酵素資料庫存取碼（EC）www.expasy.ch/sprot/enzyme.html	GenBank 編號	SEQ ID NO		
				前軀體		成熟
				nt	aa（信號序列（ss）之 aa；前肽（pp）之 aa）	aa
肝素酶	蛋白聚糖	EC 3.2.-.-	Q9Y251 AF152376	154	155（ss aa 1-35；pp aa 110-157）	156

1. 酵素活化

大多數蛋白酶係以無活性形式合成及分泌且需要進一步加工以變為具活性。活化典型地藉由暴露酵素活性位點之構形、空間或其他變化來達成。除鈣激活中性蛋白酶外，所有蛋白酶典型地以酵素原形式合成。酵素原活化防止蛋白酶始終以活性形式存在之情況下可能會出現之不當蛋白質降解。通常，酵素原含有空間上阻斷蛋白酶之活性位點且防止受質接近蛋白酶之活性位點的 N-末端部分（或前區）。酵素原之前區的尺寸在 2 個殘基至 150 個殘基之範圍內。自前酵素原（preproenzyme）形式分泌之後，酵素原（含有前區）無活性。

以自體催化方式或藉由其他蛋白酶來蛋白水解移除酵素原之前區之後，酵素之活性位點得以暴露，產生成熟蛋白酶，且典型地導致活化。然而，在一些情況下，完全活化亦需要其他輔助因素。舉例而言，pH 值變化引發半胱胺酸、天冬胺酸及金屬蛋白酶家族之酵素的活化。低 pH 值用於在酵素原轉化期間增加前區作為受質之敏感性或引起前區或酵素之構形變化（Jerala 等人 (1998) J Biol. Chem.,

273:11498-11504)。諸如半胱胺酸及天冬胺酸蛋白酶家族之組織蛋白酶的溶酶體酵素在達成完全活化之前需要酸性條件。除 pH 值外，其他輔助因素亦包括（但不限於）鹽濃度、還原劑（諸如半胱胺酸、DTT 及 TCEP）、金屬離子（諸如鈣）、熱量或溫度。因此，存在多種酵素原轉化機制且該等機制在蛋白酶家族之間不同（參見例如，Khan 等人 (1998) *Protein Science*, 7:815-836；Khan 等人 (1999) PNAS, 96: 10968-10975)。舉例而言，常常由於藉由自體催化或其他蛋白酶之作用、pH 值之變化或涉及輔助分子或離子或以上條件之組合或一或多者進行蛋白水解，發生酵素原轉化為活性酵素。對時間及作用位置之進一步控制通常藉由蛋白質抑制劑達成（Stroud 等人 (1977) Ann. Rev. Biophys. Bioeng., 6:177-93)。

a. 絲胺酸蛋白酶

包括分泌性酵素及隔離在細胞質儲存細胞器中之酵素的絲胺酸蛋白酶（SP）具有多種生理學作用，包括血液凝結、創口癒合、消化、免疫反應及腫瘤侵襲與轉移。許多絲胺酸蛋白酶降解細胞外基質之組份（參見上表 2)。舉例而言，參與細胞外基質（ECM）之降解及重塑之蛋白酶有助於組織重塑，且為癌症侵襲及轉移所必需。

絲胺酸蛋白酶家族中之蛋白酶的活性取決於形成其活性位點之一組胺基酸殘基。該等殘基中之一者始終為絲胺酸；因此，其稱為絲胺酸蛋白酶。由絲胺酸蛋白酶裂解標靶蛋白質之機制係基於絲胺酸對所靶向肽鍵之親核性攻

擊。催化性絲胺酸與受質之易斷肽鍵之羰基原子形成共價連接的四面體中間物。在許多情況下，基團之親核性質藉由組胺酸之存在而提高，由天冬胺酸保持於「質子受體狀態」。絲胺酸、組胺酸及天冬胺酸之對準側鏈形成為大多數絲胺酸蛋白酶所共有之催化性三合物。

大多數絲胺酸蛋白酶以呈前軀體形式之酵素原形式存在，且因此無活性。在蛋白酶之酵素原形式中，用於催化之活性位點與活性酵素相比經扭曲。事實上，絲胺酸蛋白酶為在酵素原與蛋白酶之活性形式之間在活性位點中具有構形差異的唯一蛋白酶家族。因此，催化性三合物以酵素原形式存在，但來自酵素原之扭曲環部分阻塞受質結合間隙。因此，受質多肽不會有效地結合，且不會發生蛋白水解。僅在活化之後，在此期間酵素原之構形及結構發生變化且打開活性位點，可進行蛋白水解。

絲胺酸蛋白酶於中性 pH 值下具活性。酵素原轉化在諸如藉由另一蛋白酶之高度特異性催化裂解或藉由自體活化進行之有限蛋白水解後進行。舉例而言，無活性凝血酵素原轉化為酵素（凝血酶）之活性形式係藉由另一凝固酶（因子 Xa）對前區之高度特異性催化裂解而達成。其他絲胺酸蛋白酶使用類似機制，但活化裂解位點不同且因此絲胺酸蛋白酶典型地藉由不同轉化酶活化。

包括（但不限於）顆粒酶 A 及 B、組織蛋白酶 G、嗜中性白血球彈性蛋白酶、蛋白酶 3 及肥大細胞類胰蛋白酶及凝乳酶之顆粒相關絲胺酸蛋白酶需要雙重蛋白水解事件

以便活化。此等酵素係以前酵素原形式合成；信號肽之裂解產生無活性之酵素原（proenzyme/zymogen）形式。顆粒相關絲胺酸蛋白酶於酵素之 N-末端處含有二肽原（prodipeptide），且亦含有羧基末端延伸部分，對於活化而言亦必須將其移除。該二肽原防止成熟酵素摺疊成催化活性形式。顆粒相關絲胺酸蛋白酶之活化係藉由羧基末端延伸部分與二肽原兩者之裂解而達成。組織蛋白酶 C 與至少一些顆粒相關絲胺酸蛋白酶中之二肽原之裂解有關（Kummer 等人 (1996) J Biol. Chem., 271:9281-9286）。

b. 半胱胺酸蛋白酶

半胱胺酸蛋白酶於其活性位點處含有 Cys-His 對，且其催化活化涉及半胱胺酸氫硫基。藉由相鄰組胺酸殘基使半胱胺酸氫硫基去質子化，隨後半胱胺酸對肽羰基碳進行親核性攻擊。使新羧基末端連接於半胱胺酸硫醇之硫基酯為反應之中間物（相當於絲胺酸蛋白酶之醯基-酵素中間物）。半胱胺酸蛋白酶包括木瓜蛋白酶（papain）、組織蛋白酶、卡斯蛋白酶（caspase）及鈣激活中性蛋白酶。此等半胱胺酸蛋白酶之不同家族的活化機制不同。

i. 組織蛋白酶

木瓜蛋白酶樣半胱胺酸蛋白酶（包括組織蛋白酶）為因結構相似性與木瓜蛋白酶有關之硫醇依賴性內肽酶之家族。其形成具有標記為 R 及 L（對於右及左而言）之兩個域的蛋白質且來自兩個域之環形成受質識別間隙。組織蛋白酶係以含有前區之酵素原形式合成；該前區充當 N-末端抑

制性前區。儘管成熟酵素之間存在約 25%序列一致性，但前區展現極少序列相似性。前區起成熟酵素之有效抑制劑的作用。前區亦發揮其他功能，諸如在於中性 pH 值下合成及運輸期間在酵素之摺疊及穩定性方面起作用。

半胱胺酸蛋白酶家族之組織蛋白酶為溶酶體酵素且因此在低於 pH 7 下具最佳活性並在高於 pH 7 下變為無活性。組織蛋白酶係以無活性前軀體（亦即酵素原）形式合成，且藉由蛋白水解移除前區而活化。此使得產生單鏈酵素。通常，單鏈酵素可加工成含有重鏈及輕鏈之雙鏈形式。典型地，兩條鏈經由非共價相互作用或經由二硫橋結合在一起。因此，成熟組織蛋白酶以單鏈形式或以雙鏈形式存在。

前區之移除可藉由其他蛋白酶之活化或藉由於酸性 pH 值下自體催化活化來促進（Turk 等人 (2001) The EMBO Journal, 20:4629-4633）。酵素原轉化過程之 pH 值依賴性由前區中之保守性鹽橋（例如，SEQ ID NO:62 中所闡明之組織蛋白酶原（procathepsin）L 中的 Asp82p 及 Arg38p 及 Glu87p 及 Arg48p）來調節。藉由於較低 pH 值下使羧酸酯基質子化破壞鹽橋破壞前區之疏水性核心，從而使得前區自活性位點解離（Khan 等人 (1998) *Protein Science*, 7:815-836）。使鹽橋形成之殘基可在組織蛋白酶之間不同。舉例而言，組織蛋白酶原 B 使用替代性鹽橋相互作用以實現其 pH 值依賴性酵素原轉化（Coulombe 等人 (1996) EMBO J., 15:5492-5503）。

酸性 pH 值條件為成熟組織蛋白酶之活性所需；酵素原

轉化自身對於酵素活性不足。除其用於活性之需求外，酸性 pH 值亦使酵素穩定。於較高 pH 值條件下組織蛋白酶之失活及不穩定係由活性位點-S^-/H^+im-離子對之咪唑部分的去質子化及結構沿活性位點凹槽之「解鏈（unzipping）」引起（Dehrmann 等人 (1995) Arch. Biochem. Biophys., 324:93-98）。因此，大多數組織蛋白酶於酸性 pH 值下具有最佳活性及穩定性。舉例而言，組織蛋白酶 B、F、H、K、L 及 V 於酸性環境中具最佳活性且於中性 pH 值下僅具弱活性或無活性（Lutgens 等人 (2007) *The FASEB J.*, 21: 3029-3041）。一些組織蛋白酶（例如組織蛋白酶 L）在於中性 pH 值下培養後快速喪失其活性。一些組織蛋白酶甚至在於中性 pH 值下培養後亦維持其酵素活性，且因此可於生理學條件下降解基質蛋白質。已發現組織蛋白酶 C 及 S 具有最高 pH 值穩定性，但組織蛋白酶 K 及 V 顯示中間物 pH 值穩定性。試管內研究已證明組織蛋白酶 K 可於中性 pH 值下降解原纖維蛋白質（Buhling 等人 (2004) Eur. Respir. J., 23:620-628）。

組織蛋白酶 L

組織蛋白酶 L（CatL）為屬於木瓜蛋白酶家族之溶酶體酸半胱胺酸蛋白酶。人類組織蛋白酶 L 基因編碼含有 17 個胺基酸之信號肽、96 個胺基酸之前肽及 220 個胺基酸之成熟區域的 333 個胺基酸之半胱胺酸蛋白酶（參見 SEQ ID NO:61 及 62 與 GenBank 寄存編號 P07711）。組織蛋白酶 L 亦包括對偶基因及物種變異體，及其他變異體。該等變異

體之實例為 SEQ ID NO:208 至 223 及 234 中所闡明之任何變異體。組織蛋白酶 L 係以無活性酵素原形式合成，且類似其他蛋白酶，含有對應於 SEQ ID NO:62 中所闡明之胺基酸序列的胺基酸 18-113 之前肽。該前肽抑制酵素之蛋白水解活性。前肽區段亦起使酵素原穩定避免自中性至鹼性 pH 值之變性作用之作用（Coulombe 等人 (1996) *The EMBO J.*, 15:5492-5503）。前肽之裂解藉由於酸性條件下自體加工而進行，從而產生具活性且於酸性條件下具有催化活性之成熟酵素。成熟組織蛋白酶 L（SEQ ID NO:1 中所闡明）可以約 28 kDa 之單鏈形式形式及/或以約 24 kDa 與 4 kDa（分別為重鏈與輕鏈）之雙鏈形式存在。組織蛋白酶 L 之對偶基因及物種變異體為已知的。例示性物種變異體為 SEQ ID NO:208-223 中所闡明之任何變異體，包括核酸及所編碼之多肽及其缺乏信號序列與前肽之成熟形式。例示性對偶基因變異體為 SEQ ID NO:234 中所闡明之任何變異體。

組織蛋白酶 L 主要定位於內體及溶酶體。成熟組織蛋白酶 L 之最佳蛋白水解能力係於約 5.5 之酸性 pH 值下達成，且其於中性 pH 值下無活性（Bohley P 等人，「Intracellular Protein Turnover.」在 S. Holzer 及 H. Tschcsche（編）. *Biological Functions of Proteinases*, 第 17-34 頁中, Berlin: Springer-Verlag. 1979）。組織蛋白酶 L 之最佳 pH 值可受離子強度影響，且因此最佳 pH 值在緩衝液之間不同（Dehrmann 等人 (1995) *Arch. Biochem. Biophys.*, 324: 93-98）。組織蛋白酶原 L 於中性及弱鹼性 pH

值條件下穩定，於該等條件下成熟組織蛋白酶 L 失活(Jerala 等人 (1998) *J. Biol. Chem.*, 273:11498-11504)。

組織蛋白酶 L 降解蛋白質受質，包括（但不限於）膠原蛋白、IL-8 前軀體、神經傳遞素前軀體（neurotransmitter precursor)、腦啡肽原（pro-enkephalin）及免疫球蛋白輕鏈相關（AL）澱粉樣蛋白（amyloid）沈積物及偶氮酪蛋白（azocasein)（Barret & Kirschke (1981) Methods Enzymol., 80:535-561 ; Mason 等人, (1985) Biochem. J., 226:233-241)。CatL 由 Z-Phe-Ala-CHN2 快速抑制。

ii. 鈣激活中性蛋白酶

鈣激活中性蛋白酶為 Ca^{2+}依賴性細胞質半胱胺酸蛋白酶，其以兩種主要形式 μ-鈣激活中性蛋白酶（鈣激活中性蛋白酶 1）及 m-鈣激活中性蛋白酶（鈣激活中性蛋白酶 2）存在。鈣激活中性蛋白酶受質包括細胞骨架蛋白質、信號轉導酵素、轉錄調控因子及整合膜蛋白。在 ECM 組份中，鈣激活中性蛋白酶降解纖維結合蛋白、玻璃連結蛋白及蛋白聚糖（Ian M. Clark 及 Gillian Murphy.「Matrix Proteinases,」在 Dynamics of Bone and Cartilage Metabolism, Academic Press (2006), 第 181-198 頁中)。

鈣激活中性蛋白酶以無活性雜二聚體（及約 80 kDa 與約 30 kDa 亞單位）形式存在，且需要 Ca^{2+}以供自體催化。μ-鈣激活中性蛋白酶及 m-鈣激活中性蛋白酶在其對活化所需之 Ca^{2+}之敏感性方面不同；μ-鈣激活中性蛋白酶於低微莫耳鈣濃度下活化至其最大活性的一半，其大致為低於活

化 m-鈣激活中性蛋白酶所需之彼等濃度的數量級（Meyer 等人 (1996) Biochem. J, 314:511-519）。活化之後，鈣激活中性蛋白酶之兩個亞單位經受有限自體分解，此移除 N-末端前區且增加鈣敏感性。自體分解本身並不足以活化鈣激活中性蛋白酶，因為自體分解之蛋白酶仍需要鈣來裂解受質（Meyer 等人 (1996) *Biochem. J.*, 314:511-519）。因此，鈣激活中性蛋白酶之持續活化需要鈣之存在。鈣需求顯著高於生理學 Ca^{2+}濃度，其通常為 1 μM。舉例而言，試管內 μ-鈣激活中性蛋白酶需要 10-50 μM之鈣濃度且 m-鈣激活中性蛋白酶需要 300-500 μM 之鈣濃度（Hosfield 等人 (1999) *The EMBO J.*, 18:6880-6889）。由於鈣需求，故鈣激活中性蛋白酶藉由區域性鈣通量及/或膜結合來調節（Molinari and Carafoli (1997) *J Membr. Biol.*, 43:543-5.）。鈣可能誘發構形變化以暴露蛋白酶之活性位點。鈣激活中性蛋白酶抑制蛋白（calpastatin）為鈣激活中性蛋白酶之特異性細胞抑制劑。

c. 天冬胺酸蛋白酶

天冬胺酸鹽蛋白酶包括見於溶酶體中之已證明降解 ECM 組份的一些蛋白酶。此等蛋白酶中包括組織蛋白酶 D 及 E。對於活性而言，兩個天冬胺酸殘基參與活性位點處之酸/鹼催化。在初始反應中，一個天冬胺酸接受來自活性位點 H_2O 之一個質子，其攻擊肽鍵之羰基碳。同時，另一天冬胺酸向肽羰基之氧提供一個質子。

天冬胺酸蛋白酶之酵素原形式含有帶正電之 N-末端前

區，其與該酵素之中心部分相互作用從而與帶負電區段形成鹽橋。由於前區之定位及鹽橋之形成，防止受質接近活性位點。酵素原轉化為活性酵素藉由於低 pH 值下破壞鹽橋來進行。暴露於低 pH 值使得 Asp 及 Glu 殘基之羧酸側鏈質子化，從而導致前區與成熟酵素之間的鹽橋不穩定。移除後，前區由活性酵素以自體催化方式降解。前區之後續水解確保活化不可逆，且所釋放之前區不會充當活性酵素之競爭性抑制劑。此外，轉化不需要其他輔助分子（Khan 等人 (1998) *Protein Science*, 7:815-836）。然而，類似半胱胺酸蛋白酶家族之組織蛋白酶，酸性 pH 值條件為成熟酵素之活性及穩定性所需。

d. 金屬蛋白酶

金屬蛋白酶（亦稱為鋅蛋白酶）包括消化酵素羧肽酶（carboxypeptidase）、由細胞分泌之各種基質金屬蛋白酶（matrix metalloprotease，MMP）、ADAM（解整合素（disintegrin）及金屬蛋白酶域）、ADAMTS（具有血小板反應蛋白基元之解整合素及金屬蛋白酶域）及溶酶體蛋白酶。包括 ADAM 及 MMP 之此等酵素在胚胎發育、細胞生長及增殖、發炎性反應、創傷修復、多發性硬化症、關節炎及癌症進展與轉移方面具有作用（Manzetti 等人, (2003) *J of Computer-Aided Mol. Design*, 17: 551）。大多數 MMP（例如膠原酶）參與細胞外基質之降解，例如在組織重塑期間。舉例而言，此等酵素中之許多可裂解基底膜及細胞外基質之組份。

金屬蛋白酶於酵素之活性中心處含有催化活性所需之Zn^{++}離子。金屬蛋白酶之活性位點處的鋅結合基元包括兩個組胺酸殘基，其咪唑側鏈為 Zn^{++}之配位體。在催化期間，Zn^{++}促使活性位點處水分子的氧原子對羰基碳之親核性攻擊。活性位點鹼（羧肽酶中之麩胺酸殘基）藉由自攻擊水分子提取一個質子而促進此反應。通常，此等酵素於其活性位點處具有常見鋅結合基元（HExxHxxGxxH），及在活性位點後之保守性甲硫胺酸轉角。組胺酸之任一者的突變消除催化活性。

金屬蛋白酶之酵素原形式含有長度為約 80-100 個殘基之前區。在酵素原形式中，成熟酵素之受質結合位點中的殘基與催化 Zn^{++}離子處於與活性形式相同之構形位置，且在酵素原轉化後並不改變。因為前區經定位以阻斷位點，由此防止接近受質，所以酵素無活性。酵素原轉化為活性酵素由前區自成熟酵素裂解引起。多種機制能夠啟動裂解事件，包括其他蛋白酶之作用、熱量、汞劑（例如乙酸 4-胺基-苯汞酯）、SH 反應劑、反應性氧及清潔劑（參見例如，Khan 等人 (1998) *Protein Science*, 7:815-836；Okada 等人 (1988) *Biochem J.*, 254:731-741；Okada & Nakanashi (1989) *FEBS Lett.*, 249:353-356; Nagase 等人 (1990) *Biochemistry*, 29:5783-5789；Koklitis 等人 (1991) *Biochem J.*, 276:217-221；Springman 等人 (1990) *PNAS*, 87:364-8；Murphy 等人 (1997) *Matrix Biol.*, 15:511-8）。

e. 肝素酶

肝素酶為參與某些葡糖胺聚糖之分解代謝的糖基化酵素。其為裂解特異性鏈內位點處之硫酸乙醯肝素的內-β-葡糖醛酸酶。肝素酶為 A 族糖基水解酶（glycosyl hydrolase clan A，GH-A）之成員，其共用涉及兩個保守性酸性殘基、Glu^{225}處之假定質子供體及Glu^{343}處之親核體的常見催化機制（Hulett 等人 (2000) *Biochemistry*, 39:15659-15667）。T 及 B 淋巴細胞、血小板、粒細胞、巨噬細胞及肥大細胞與內皮下細胞外基質（ECM）之相互作用與肝素酶活性對硫酸乙醯肝素之降解相關。

人類肝素酶 cDNA 編碼起初以前蛋白原（pre-pro-protein）形式合成之蛋白質，其具有在遷移至內質網（endoplasmic reticulum，ER）中後由信號肽酶移除之信號肽序列。所得 65 kDa 酵素原形式進一步藉由蛋白水解裂解加工，使得切除插入 6 kDa 片段，產生 8 kDa 多肽及 50 kDa 多肽，從而形成雜二聚體。成熟肝素酶之胺基酸序闡明於 SEQ ID NO:156 中。肝素酶活性及定位受到嚴格調節。舉例而言，酵素對於局部 pH 值之變化高度敏感，於存在於腫瘤附近及發炎部位中之酸性條件下發揮高酶促活性，其於生理學 pH 值下活性極小或無活性。因此，肝素酶介導之 HS 骨架的裂解為 pH 值依賴性過程；最大酶促活性於範圍為 4 至 6.8 之 pH 值下達成（Gilat 等人 (1995) *J Exp. Med.*, 181:1929-1934；Goldshmidt 等人 (2003) *The FASEB J.*, 17:1015-1025）。於生理學 pH 值下，肝素酶展現極小活性。pH 值依賴性確保 ECM 之結構破裂限於較高酸性條件，諸如

在內體中且於損傷或炎症部位處發生（McKenzie 等人 (2003) *Biochem. J.*, 373:423-435）。

D. 可活化的基質降解酵素（AMDE）

基質降解酵素需要酵素原轉化以藉由裂解前區產生成熟酵素而活化。如以上所討論，許多基質降解酵素之活性亦需要一或多種其他活化條件之持續存在。該等活化條件之實例包括（但不限於）pH 值、金屬離子、溫度、還原劑、氧化劑及鹽濃度。舉例而言，許多酵素之活性需要特定 pH 值或金屬離子濃度或鹽濃度或還原劑的存在。在一實例中，溶酶體酵素之活性需要酸性 pH 值條件。舉例而言，半胱胺酸及天冬胺酸家族之蛋白酶的組織蛋白酶之活性需要酸性 pH 值條件。肝素酶亦為積累於溶酶體中以在酸性環境中正常加工之溶酶體酵素。通常，酸性環境提供於溶酶體蛋白酶通常定位之酸性溶酶體中。在此環境外部，溶酶體蛋白酶無活性或活性較低且其活性需要外源性暴露於酸性 pH 值。在另一實例中，活化條件包括金屬離子濃度。舉例而言，鈣激活中性蛋白酶之活性需要足夠濃度的 Ca^{2+}。該酵素之活性在活化條件不存在之情況下為可逆的。

藉由利用對外源性活化條件之需求，可使可活化的基質降解酵素在活體內投藥後（例如向 ECM 投藥）在有限持續時間內暫時具活性。該等可活化的基質降解酵素僅當暴露於外源性活化條件時具活性。因為活化條件不存在於投藥位點處且必須外源性施用，所以活化條件將在活體內投予提供適當活化條件之活化劑後隨時間中和或耗散。因

此，因為活化劑耗散或以其他方式中和，所以 AMDE 之活化在活體內投藥後為可逆的。舉例而言，AMDE 之暫時性活化可在皮膚及其他組織之間質環境中藉由在不存在於投藥位點處之外源性活化條件（亦即活化劑）存在下投予 AMDE 而達成。典型地，該活化條件為在投予提供活化條件之活化劑之前不存在於 ECM 中的條件。因此，使可活化的基質降解酵素暴露於活化條件使得酵素在有限或預定時間內活化，因為活化條件在間質環境中耗散或中和。

因此，本文提供含有可活化的基質降解酵素之組成物、組合及容器，該等酵素在活體內投藥之後允許酵素在有限或預定時期內活化，在此期間酵素可發揮其生物作用。藉助於可活化的酵素之可逆活性，酵素變得失活，從而控制該等酵素之生物作用的持續時間。可活化的基質降解酵素係與提供活化條件之活化劑的組合提供及與其一起提供於容器中。另外，可活化的基質降解酵素及活化劑亦可與諸如麻醉劑、α腎上腺素劑或分散劑中之任一或多者的其他藥劑組合或以組合形式提供，諸如提供於容器中。可活化的基質降解酵素係以治療有效量提供，該量在投藥之後（諸如皮下投藥之後）在活化時降解 ECM 之一或多種組份。所得可活化的基質降解酵素可用作治療 ECM 介導之疾病或病狀的治療劑。

任何合成或自天然來源分離之基質降解酵素（諸如表 3 或本文其他地方所述者）、其對偶基因或物種變異體或其他變異體，或熟習此項技術者已知之任何酵素意欲用於本文

所提供之組成物、組合、方法及設備中，只要該酵素由於需要活化條件而可活化即可。可活化的基質降解酵素係以呈單鏈或雙鏈形式之無活性形式（以酵素原或無活性成熟多肽形式）提供。舉例而言，甚至呈其成熟形式之組織蛋白酶亦無活性且其構形穩定性需要酸性 pH 值條件。可活化的基質降解酵素包括溶酶體蛋白酶，諸如半胱胺酸及天冬胺酸家族之組織蛋白酶及肝素酶。例示性可活化的基質降解酵素為 SEQ ID NO:56、59、62、64、179、67、70、73、76、182、185、188、79、194、89、92、95 及 155 中之任一者中所闡明的任何酵素及 SEQ ID NO:57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93、96 及 156 中所闡明之其成熟形式，或其對偶基因變異體或物種變異體或其他變異體。熟習此項技術者已知或可鑑別可活化的基質降解酵素。舉例而言，熟習此項技術者可使用酵素活化之常規檢定（諸如本文所提供及此項技術中已知之任何檢定）來評估任何所需酵素之持續或可逆活化對外源性活化條件之需求。

可活化的基質降解酵素可經修飾以改變任一或多種性質或活性。舉例而言，經改變之性質或活性包括（但不限於）使酵素更穩定之修飾、改變受質特異性及/或賦予酵素溫度敏感性。需要時，酵素穩定性亦可藉由對酵素之聚乙二醇化或糖基化來增強。使用標準重組 DNA 技術修飾多肽對於熟習此項技術者為常規的。出於本文之目的，經修飾之基質降解酵素保留未經修飾之酵素的一或多種活性且為

可活化的。所保留之活性可為未經修飾之酵素之活性的40%、50%、60%、70%、80%、90%、95%或95%以上。

在一實例中，基質降解酵素（例如組織蛋白酶）可經修飾以使得其前區不具抑制性。修飾可藉由在前區自身中或在發生抑制性相互作用之活性位點區域中之胺基酸置換、取代或插入來進行。因此，組織蛋白酶可以酵素原形式提供，其中於酸性條件下發生自體催化；若以酵素原形式提供，則該經修飾之酵素的經裂解之前區不會導致野生型組織蛋白酶所發生之失活。

在另一實例中，可活化的酵素可經修飾以改變其受質特異性。舉例而言，酵素可經修飾以具有增強之對特定受質的特異性。因此，舉例而言，展現對I型及IV型膠原蛋白之受質特異性的組織蛋白酶L可經修飾以使其具有增強之對I型膠原蛋白而非IV型膠原蛋白的受質特異性，且反之亦然。對多肽之修飾可藉由常規分子生物學技術達成，且在熟習此項技術者之技能範圍內。可使用對於受質裂解之常規檢定（諸如本文所述或此項技術中已知）測試經修飾之酵素的受質特異性。舉例而言，可對螢光肽或對經純化之蛋白質評估受質裂解。可使用試管內或活體內檢定來評估裂解。舉例而言，可藉由將酵素與受質一起培養，且接著使混合物於SDS-PAGE凝膠上電泳來評估裂解。可藉由西方墨點法（Western Blot）或藉由使用諸如庫馬斯藍或銀染色（Silver Stain）試劑之標準蛋白質染色來評估降解。

在另一實例中，基質降解酵素可經修飾以具有溫度敏

感性。舉例而言，於生理學溫度（例如 37℃）下具活性之基質降解酵素可經修飾且選擇於較低溫度（例如低於37℃；例如 20℃、21℃、22℃、23℃、24℃、25℃、26℃、27℃、28℃、29℃或 30℃左右）下具活性、但於生理學溫度下不具活性之酵素。因此，該等經修飾之酵素可用作可活化的基質降解酵素，其中活化條件為低溫。與提供冷溫之活化條件（例如冷緩衝液）同時、間歇或相繼投予酵素使得酵素活化。因為活體內溫度恢復至 37℃之生理學溫度，所以酵素之活化得到暫時控制。

1. 活化可活化的基質降解酵素之活化條件及方法

可活化的基質降解酵素在活化條件不存在之情況下無活性。活體內投藥之後，該可活化的基質降解酵素之暫時性活化係藉由暴露（在相繼、間歇或同時投藥之前或之後）於一或多種提供足以活化酵素活化條件之特定活化劑而達成。舉例而言，活化可藉由使可活化的基質降解酵素暴露於（例如）溫度（例如熱或冷）、pH 值、鹽、含有用於活化之足夠濃度之金屬離子（例如 Ca^{2+}）的溶液、含有用於活化之足夠濃度之還原劑或氧化劑的溶液或如本文中所述或熟習此項技術者已知之其他方法來達成。活化劑之選擇將視如本文中所述或熟習此項技術者已知之酵素的選擇而變化。通常，使用足以產生活性酵素之量（例如濃度、含量或程度）的活化劑。此量可易於憑經驗確定且視所選酵素及所選應用而定。

藉助於可活化的酵素之可逆及條件性活化，達成暫時

性活化，從而調節對細胞外基質（ECM）組份之酶促作用的持續時間。此為本發明方法之優勢，以使得與酵素之不當延長活化相關的有害副作用可得到控制。因為可活化的基質降解酵素需要連續暴露於活化條件以便保持活性，所以達成暫時性活化。活化條件通常並不以足以活化酵素之量內源性存在於活體內投予可活化的基質降解酵素之位點處。舉例而言，皮膚間質具有中性pH值，且因此通常不存在低pH值活化條件。在另一實例中，皮膚間質中金屬離子（諸如鈣）之生理學含量遠低於活化一些酵素所需之有效量。因此，酵素之失活可在減少酵素暴露於外源性活化條件之後發生，如可在活體內投予可活化的酵素後，外源性提供之活化條件逐漸耗散或中和時發生。

因此，本文所提供之活化條件為活化可活化的基質降解酵素所需、但通常不以足夠量存在於投藥位點中之彼等條件。對活化可活化的基質降解酵素之活化條件的需求允許在有限時間內活化基質降解酵素，直至活化條件耗散或中和以致酵素變為無活性或變得不穩定且被降解。酵素具活性之時間量可歷時預定時間。舉例而言，可提供含有一定量之活化條件（諸如濃度、有效量、含量或程度）的活化劑，該量經選擇以使得於活體內投藥之後酵素所暴露的環境及條件下酵素在規定時間內具活性。在一實例中，當酸性pH值為活化條件時，酸性緩衝液之緩衝能力可經調整以調節其對pH值變化之抵抗力的時間。活化劑活化可條件性活化的基質降解酵素之預定時間可憑經驗確定且與欲治

療之疾病、所治療之個體、酵素之選擇及活化劑有關。可活化的基質降解酵素可在活體內投藥後在提供活化條件之活化劑存在下在以下時間內具活性：為或約為 1 分鐘、2 分鐘、3 分鐘、4 分鐘、5 分鐘、10 分鐘、20 分鐘、30 分鐘、40 分鐘、50 分鐘、1 小時、2 小時、3 小時、4 小時、5 小時、6 小時或更長時間。

例示性活化條件及活化劑及暫時性活化之方法在下文描述。鑒於該描述，其他具體實例對於熟習此項技術者將顯而易見。

a. 活化條件-酸性 pH 值

本文提供條件性活化基質降解酵素（藉由 pH 值調節其活性）之組成物及方法，及該等酵素治療 ECM 介導之疾病或病狀的用途。該等方法利用僅於酸性 pH 值下具有酵素活性而於中性 pH 值下保持無活性或變得不穩定且被降解之蛋白質。該等蛋白質包括溶酶體蛋白酶，包括（但不限於）半胱胺酸及天冬胺酸家族之組織蛋白酶，以及肝素酶。舉例而言，酸性細胞內隔室溶酶體含有多種降解蛋白質及由胞吞作用內化之其他物質之水解酶。所有溶酶體內蛋白酶（例如組織蛋白酶 L）展現最佳酸性 pH 值。該等蛋白酶之實例為 SEQ ID NO:57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93、96 及 156 中之任一者中所闡明之任何蛋白酶。

使用僅在暴露於某些 pH 值條件之後具活性的基質降解酵素之方法在本文中用於利用皮膚中之 pH 值差。人類表皮

系統在皮膚之層化層中維持pH值梯度。已報導外層展現5.5之平均pH值（W.P. Smith (1994) *Cosmetics and Toiletries*, 109:41-48）。表皮之連續層的pH值隨深度增加，在真皮層達到更接近生理學範圍（約pH 7.4）的最終pH值。

因此，本文涵蓋使用於酸性條件下展現活性、但於中性pH值下實質上無活性（諸如存在於ECM中）之可活化的基質降解酵素。實質上無活性酵素為於其最佳pH值下展現酵素活性之10%或10%以下的任何酵素，例如為或約為於酵素最佳pH值下存在時之1%、2%、3%、4%、5%、6%、7%、8%、9%、9.5%或10%。熟習此項技術者已知或可測定酵素之最佳pH值且可評估不同pH值條件下之活性差異。舉例而言，組織蛋白酶L之最佳pH值為或約為5.5，但可在4.5至6之範圍內變化，此視組織蛋白酶L之特定種類、緩衝條件或離子強度而定。組織蛋白酶L於pH 7.4下或高於pH 7.4下實質上無活性（Dehrmann等人 (1995) *Arch. Biochem. Biophys.*, 324:93-98）。在另一實例中，用於組織蛋白酶D之活性的最佳pH值為或約為3.0至4.0，且其於或約在6.0或更高pH值下實質上無活性（Rojas-Espinosa等人 (1973) Infection and Immunity, 8:1000-1008）。組織蛋白酶S為於pH 7.0下穩定之少數溶酶體蛋白酶中之一者（Bromme等人 (1993) J Biol. Chem., 268: 4832-4838）。

出於本文之目的，可活化的酵素於為或約為3、3.5、4、4.5、5、5.5、6或6.5之pH值條件下具活性，但於中性pH值下實質上無活性。可對酵素執行pH值活性概況，且評估

相對活性以於多種條件下測定其最佳 pH 值（Dehrmann 等人 (1995) *Arch. Biochem. Biophys.*, 324:93-98）。應瞭解最佳 pH 值可視所用受質、緩衝條件、離子強度及酵素種類而不同。因此，本文對最佳 pH 值之提及僅用於舉例。熟習此項技術者可憑經驗確定於特定條件下酵素之最佳 pH 值。舉例而言，可改變緩衝條件及離子強度以測定於各種 pH 值條件下之酵素活性。用於測定 pH 值活性概況之酵素檢定可使用諸如本文所述及熟習此項技術者已知之螢光受質來執行。所用螢光受質之選擇將在酵素之間不同，且為熟習此項技術者所已知或可憑經驗確定。

因此，藉由在通常不存在於投藥位點處之活化條件下投藥來條件性活化基質降解酵素之能力允許暫時調節及改變展現中性 pH 值之器官及組織（諸如間質）之生理學參數。於正常生理學條件下，間質之 pH 值為中性。因此，於低 pH 值下具活性之可活化的基質降解酵素（諸如本文所述之溶酶體酵素）在存在於間質中時通常將由於間質之中性 pH 值而無催化活性。當例如藉由投予經緩衝酸性溶液暫時使間質之 pH 值呈酸性時，具有最佳酸性 pH 值之溶酶體酵素在向間質投予時將變得活化。當間質之 pH 值恢復為中性時，則需要酸性 pH 值之基質降解酵素變得失活且停止發揮其酶促活性。

因此，本文涵蓋於中性 pH 值下實質上無活性之可活化的基質降解酵素可經由 pH 值為中性之皮膚經表皮下投予（亦即藉由皮下、皮內或肌肉內投予）。亦涵蓋可條件性活

化的基質降解酵素之其他投藥途徑且其可根據特定酵素之最佳 pH 值憑經驗確定以使得酵素之活性由於投藥後 pH 值條件之變化而變得可逆。其他投藥途徑包括（但不限於）經口、表面及經皮投藥途徑。

因為大多數組織及器官之間質展現中性 pH 值，所以暫時性酸化可藉由將酸性溶液注入組織或器官間質來達成。酸性緩衝液為當投予時暫時使間質之 pH 值降低至低於或大致為 3.0、3.5、4.0、4.5、5.0、5.5、6.0 或 6.5 以使可活化的基質降解酵素具活性之組成物。緩衝液之酸性組份易由間質之中性 pH 值中和。酸性緩衝液為熟習此項技術者所已知。出於本文之目的，緩衝液之酸性組份可為有機酸或無機酸。通常，溶液為弱酸溶液。例示性酸包括（但不限於）2-(N-嗎啉基)乙烷磺酸（MES）、乙酸、檸檬酸、丁二酸、乳酸、順丁烯二酸、甘胺酸-鹽酸、檸檬酸磷酸鹽及組胺酸。酸性緩衝液之有效 pH 值範圍為已知的，且因此可根據所選酵素之最佳 pH 值選擇適當緩衝液。例示性酸性緩衝液包括（但不限於）乙酸鹽、檸檬酸鹽、甲酸鹽、甘胺酸、蘋果酸鹽、MES、磷酸鹽、哌口井、丙酸鹽、吡啶及丁二酸鹽緩衝液。舉例而言，MES 緩衝液之有效 pH 值範圍為 5.5 至 6.7。

可酸活化的基質降解酵素之中和及隨後失活所需之時期視酸性緩衝液之調配物而定。舉例而言，若酸性緩衝液中之酸及/或緩衝劑相對於間質之中和能力較弱，則產生較短時期；若使用較強酸性或酸性緩衝液中使用較強緩衝劑，則產生較長時期。因此，對 pH 值變化之抵抗力視特定

緩衝液之緩衝能力而定。緩衝液之離子強度或濃度愈高，緩衝能力愈高。因此，在本文所提供之方法及組成物中，於給定pH值下活化之基質降解酵素的暫時性調節可進一步藉由所選緩衝液之緩衝能力來控制。此在實施例 7 中舉例說明。對給定應用所需緩衝液之判定為常規的且在熟習此項技術者之技術範圍內。

典型地，直接將酸性溶液注入需要降解一或多種 ECM 組份之位點以例如治療 ECM 介導之疾病或病狀。呈酸性溶液活化劑之形式之活化條件的輸注可與無活性可活化的基質降解酵素之投藥同時、依次或間歇執行。當同時進行投藥時，可活化的基質降解酵素及經緩衝酸性溶液可處於同一或分開的組成物中。當處於同一組成物中時，酵素及經緩衝酸性溶液可以混合物形式提供於組成物中。酵素之活化亦可在投藥之前藉由將酸性溶液添加至酵素之濃縮液體溶液或懸浮液或凍乾或粉末形式中來達成。通常，當提供可活化的基質降解酵素之液體溶液或懸浮液時，其為當暴露於提供適當活化條件之活化劑時經得起藉由活化條件活化酵素之溶液或懸浮液。

另外，在本文所提供之組合及方法中，可提供具有活化條件（例如經緩衝酸性溶液）之活化劑及可活化的基質降解酵素且與任一或多種其他藥劑（諸如麻醉劑、α腎上腺素能受體促效劑或分散劑中之任一或多者）組合投予。該等藥劑之實例在下文題為「組合療法」之部分中論述。該等其他藥劑可與活化劑及/或基質降解酵素同時、依次或間

歇投予。

在本文所提供之方法的一實例中，向皮膚間質或存在ECM病狀或疾病之其他組織投予經緩衝酸性溶液。該經緩衝酸性溶液可根據活化基質降解酵素所需之pH值及達成有限持續時間之活化之所需緩衝能力進行選擇。舉例而言，組織蛋白酶L為用於治療膠原蛋白介導之疾病（諸如脂肪團）之目的的例示性酵素。因此，將在用於活化組織蛋白酶L之最適pH值5.5下製備酸性緩衝液。該酸性緩衝液之實例為MES。酸性溶液之緩衝能力亦可視需要以實驗方式測定，例如實施例7中所述。通常，酸性緩衝液在即將投予基質降解酵素之前或與其一起投予。舉例而言，若基質降解酵素以凍乾形式提供，則酵素可在即將投予之前用酸性緩衝溶液復水，且共同投予酵素與活化劑之組合。在酸性緩衝液存在下，在活體內投藥之後活化酵素。視酸性緩衝液之緩衝能力而定，間質之pH值將在有限或預定時間後恢復至中性，從而逆轉基質降解酵素之降解作用。

在本文所提供之方法的另一實例中，麻醉劑與血管收縮劑（例如利多卡因/腎上腺素）之組合係在投予活化劑及基質降解酵素之前投予。通常，在該等方法中，諸如玻尿酸降解酵素（例如玻尿酸酶）之分散劑亦與麻醉劑及血管收縮劑（諸如α腎上腺素能受體促效劑）一起投予。

b. 活化條件-金屬陽離子濃度

本文提供含有需要暴露於適合於活化之金屬離子（例如Ca^{2+}、Mg^{2+}或Zn^{2+}）之可活化的基質降解酵素之組成物、

組合、容器及方法。該酵素之實例為需要 Ca^{2+}以供活化的鈣激活中性蛋白酶（例如 SEQ ID NO:82（鈣激活中性蛋白酶 1）及 SEQ IDNO:85（鈣激活中性蛋白酶 2）中所闡明之大亞單位及 SEQ ID NO:87 中所闡明之小亞單位，或其對偶基因或物種變異體或其他變異體）。金屬離子可以水性組成物之形式提供，例如以鈣鹽形式提供。無活性酵素可以與金屬離子之混合物形式提供，或可以分開的組成物形式提供。若以分開的組成物形式提供，諸如以濃縮液體組合物之形式或以凍乾或粉末形式提供，則將金屬離子添加至酵素中將產生經活化之酵素。

通常，活化係藉由使無活性酵素暴露於足以活化之濃度的金屬陽離子（例如 Ca^{2+}）來達成。精確量可憑經驗確定或為熟習此項技術者所已知。舉例而言，μ-鈣激活中性蛋白酶及 m-鈣激活中性蛋白酶之試管內活化分別需要 10-50 μM 及 300-500 μM 鈣濃度（Hosfield 等人 (1999) *The EMBO J.*, 18: 6880-6889.）。可執行酵素活性檢定以測定最佳濃度。典型地，出於本文之目的，可活化的基質降解酵素包括需要足以於超過存在於間質中之金屬離子的生理學含量之濃度下活化之金屬離子濃度的彼等酵素。對於 μ-鈣激活中性蛋白酶及 m-鈣激活中性蛋白酶而言，活化所需之鈣含量超過生理學含量（參見例如，美國專利第 6,620,592 號；Hosfield 等人 (1999) *The EMBO J.*, 18: 6880-6889.）。

一般而言，包裝或提供無活性酵素以便存在不足以引發酵素活化之金屬離子。因此，當無活性酵素以與金屬離

子活化劑分開之組成物形式提供時，可能必需添加乙二胺四乙酸（ethylenediaminetetraacetic acid，EDTA）或乙二醇四乙酸（ethylene glycol tetraacetic acid，EGTA）（濃度為約 5 mM 至約 100 mM 或 100 mM 以上，視應用而定）以凍結任何 Ca^{2+} 或其他金屬離子以防止引發活化反應直至需要時。接著可藉由添加足以克服螯合劑作用之濃度的 Ca^{2+}（或其他金屬陽離子）來引發活化反應。精確量可憑經驗確定。

視酵素而定，暫時性活化可僅藉由停止暴露於金屬離子而達成。舉例而言，鈣激活中性蛋白酶之持續活化需要鈣之存在。因此，無活性形式之鈣激活中性蛋白酶可藉由添加 Ca^{2+} 來活化，且可向器官或組織之間質投予處於同一或分開的組成物中之所得混合物。然而，投藥之後，持續活化所需之鈣的有效濃度不再可用；所得活性酵素將最終恢復至其無活性狀態。在其他實例中，活化需要金屬離子的酵素之暫時性調節可藉由投予金屬螯合劑或其他逆轉劑來控制。

2. 基質降解酵素與活化劑之組合

本文提供可活化的基質降解酵素與足以活化基質降解酵素之活化劑之組合。出於本文之目的，該可活化的基質降解酵素係以無活性形式提供。通常，可活化的基質降解酵素之組成物可與活化劑分開提供。該等組成物可分開提供於同一容器中或分開的容器中。通常，當單獨包裝時，提供酵素以便存在不足以使酵素具活性之活化條件。

基質降解酵素可以液體或凍乾形式以治療有效濃度提

供。或者，基質降解酵素可以濃縮液體形式提供，以使得添加足夠量之活化劑產生治療性有效濃度之酵素。酵素可以溶液或懸浮液形式提供或囊封於合適之傳遞媒劑中，諸如脂質體、玻璃粒子、毛細管、藥物傳遞媒劑、明膠、錠劑、膠囊、丸劑、定時釋放包衣以及經皮貼片製劑及乾粉吸入器或其他此類媒劑。活化劑典型地以液體溶液或懸浮液形式提供以供單獨或在復水及/或暴露於基質降解酵素後向間質投藥。如以下 F 部分中所述，亦提供含有此等組合以及製品（諸如容器）之套組。

因此，當需要時，使可活化的基質降解酵素經受使酵素暴露於活化劑以產生活性酵素活化條件。暴露於活化劑可在試管內或活體內達成。舉例而言，當分開提供可活化的酵素及活化劑時，其可共同或分開投予。當分開投予時，可條件性活化的基質降解酵素可與活化劑同時、相繼或間歇投予。在另一實例中，呈凍乾或濃縮液體形式之基質降解酵素可在即將使用之前用活化劑復水。在該實例中，基質降解酵素與活化劑之混合物係共同投予。該等活化方法可由熟習此項技術者憑經驗確定，且可視酵素及活化劑之選擇及所需治療方法與治療方案而不同。

可活化的基質降解酵素可單獨或與活化劑組合提供於製品中。舉例而言，若酵素與活化劑組合提供，則製品可在一個隔室中含有呈凍乾或液體形式之酵素，且在相鄰隔室中含有活化劑。該等隔室可由分隔部件分隔。此類製品在本文其他地方描述。

基質降解酵素與活化劑之組合亦可進一步含有下文詳細論述之其他藥劑。舉例而言，除活化劑及基質降解酵素外，提供亦含有麻醉劑、血管收縮劑或分散劑中之一或多者的組合。

E. 產生編碼基質降解酵素及其多肽之核酸的方法

本文所述之基質降解酵素的多肽可藉由此項技術中熟知用於蛋白質純化及重組蛋白質表現之方法來獲得。可使用熟習此項技術者已知用於鑑別編碼所需基因之核酸的任何方法。此項技術中可用之任何方法可用於獲得編碼所需基質降解酵素之全長（亦即涵蓋整個編碼區）cDNA 或基因組 DNA 純系，諸如自細胞或組織來源獲得。經修飾或變異型基質降解酵素可諸如藉由定點突變誘發自野生型多肽進行工程化。

多肽可使用此項技術中已知用於選殖及分離核酸分子之任何可用方法來選殖或分離。該等方法包括核酸之 PCR 擴增及文庫之篩選，包括核酸雜交篩選、基於抗體之篩選及基於活性之篩選。

擴增核酸之方法可用於分離編碼所需多肽之核酸分子，包括（例如）聚合酶鏈反應（polymerase chain reaction，PCR）方法。含核酸物質可用作起始物質，可自其分離所需多肽編碼核酸分子。舉例而言， DNA 及 mRNA 製劑、細胞提取物、組織提取物、流體樣品（例如血液、血清、唾液）、來自健康及/或患病個體之樣品可用於擴增方法。核酸文庫亦可用作起始物質之來源。可設計引子以擴增所需多

肽。舉例而言，可根據產生所需多肽之所表現序列設計引子。可根據多肽胺基酸序列之反向轉譯設計引子。可對藉由擴增所產生之核酸分子進行定序且證實其編碼所需多肽。

可將其他核苷酸序列連接於多肽編碼核酸分子，其包括含有限制性核酸內切酶位點之連接子序列以用於將合成基因選殖至載體（例如蛋白質表現載體或經設計用於擴增核心蛋白質編碼 DNA 序列之載體）中之目的。此外，可將表示功能性 DNA 元件之其他核苷酸序列操作性連接於多肽編碼核酸分子。該等序列之實例包括（但不限於）經設計以促進細胞內蛋白質表現之啟動子序列及經設計以促進蛋白質分泌之分泌序列（例如異源信號序列）。該等序列為熟習此項技術者所已知。舉例而言，例示性異源信號序列包括（但不限於）SEQ ID NO:2 中所闡明之人類 κ IgG 異源信號序列。諸如表示蛋白質結合區之鹼基序列的其他核苷酸殘基序列亦可連接於酵素編碼核酸分子。該等區域包括（但不限於）促進或編碼促進酵素吸收至指定標靶細胞中之蛋白質或者以其他方式改變合成基因之產物之藥物動力學的殘基序列。舉例而言，可將酵素連接於 PEG 部分。

另外，可例如添加標籤或其他部分以幫助偵測或親和力純化多肽。舉例而言，亦可將諸如表示抗原決定基標籤之鹼基序列或其他可偵測標誌的其他核苷酸殘基序列連接於酵素編碼核酸分子。該等序列之實例包括編碼 His 標籤（例如 6×His，HHHHHH；SEQ ID NO:235）或 Flag 標籤

（DYKDDDDK；SEQ ID NO:236）之核酸序列。

接著可將經鑑別及分離之核酸插入適當選殖載體中。可使用此項技術中已知之大量載體-宿主系統。可能載體包括（但不限於）質體或經修飾之病毒，但載體系統必須與所用宿主細胞相容。該等載體包括（但不限於）諸如 λ 衍生物之噬菌體，或諸如 pCMV4、pBR322 或 pUC 質體衍生物之質體，或 Bluescript 載體（Stratagene, La Jolla, CA）。其他表現載體包括本文所例示之 HZ24 表現載體。插入選殖載體中可例如藉由使 DNA 片段連接至具有互補黏性末端之選殖載體中來實現。插入可使用 TOPO 選殖載體（Invitrogen, Carlsbad, CA）來實現。若用於使 DNA 斷裂之互補限制性位點不存在於選殖載體中，則可酶促修飾 DNA 分子之末端。或者，任何所需位點可藉由使核苷酸序列（連接子）連接至 DNA 末端上來產生；此等經連接之連接子可含有編碼限制性核酸內切酶識別序列之特定化學合成寡核苷酸。在一替代性方法中，可將經裂解之載體及蛋白質基因藉由同聚物加尾（homopolymeric tailing）來修飾。可經由（例如）轉型、轉染、感染、電穿孔及音波穿孔（sonoporation）將重組分子引入宿主細胞中以便產生基因序列之許多複本。

在特定具體實例中，用併有經分離之蛋白質基因、cDNA 或合成 DNA 序列之重組 DNA 分子轉型宿主細胞使得能夠產生該基因之多個複本。因此，基因可藉由使轉型體生長、自轉型體分離重組 DNA 分子及必要時自經分離之重

組 DNA 回收所插入之基因而以大量獲得。

1. 載體及細胞

對於所需蛋白質之一或多者（諸如本文所述之任何蛋白質）的重組表現而言，可將含有編碼蛋白質之核苷酸序列的全部或一部分之核酸插入適當表現載體，亦即含有對於所插入蛋白質編碼序列之轉錄及轉譯必需之元件之載體中。必需轉錄及轉譯信號亦可由酵素基因之天然啟動子及/或其側接區域提供。

亦提供含有編碼酵素之核酸的載體。亦提供含有該等載體之細胞。該等細胞包括真核及原核細胞，且載體為適用於其中之任何載體。

提供含有載體之原核及真核細胞（包括內皮細胞）。該等細胞包括細菌細胞、酵母細胞、真菌細胞、古菌（Archea）、植物細胞、昆蟲細胞及動物細胞。藉由於由上述細胞表現所編碼之蛋白質的條件下使細胞生長及回收所表現之蛋白質來使用該等細胞產生其蛋白質。出於本文之目的，例如可使酵素分泌於培養基中。

提供含有編碼偶合於天然或異源信號序列之酵素原多肽之核苷酸序列以及其多個複本的載體。該等載體可選擇用於在細胞中表現酵素蛋白質或使得酵素蛋白質以分泌蛋白質形式表現。酵素原（proenzyme/zymogen）形式之酵素可經純化以用作本文之可活化的酵素。或者，分泌之後，前區可經催化或自體催化裂解以產生成熟酵素。必要時，酵素可經純化以使得前區自製劑移除。該等成熟形式若無

活性，則亦可在本文中用作呈單鏈或雙鏈形式之可活化的酵素。

可使用多種宿主-載體系統來表現蛋白質編碼序列。其包括（但不限於）受病毒（例如痘苗病毒、腺病毒及其他病毒）感染之哺乳動物細胞系統；受病毒（例如桿狀病毒）感染之昆蟲細胞系統；微生物，諸如含有酵母載體之酵母；或用噬菌體、DNA、質體 DNA 或黏質體 DNA 轉型之細菌。載體之表現元件在其強度及特異性方面不同。視所用宿主-載體系統而定，可使用許多合適之轉錄及轉譯元件中的任一者。

可使用熟習此項技術者已知用於將 DNA 片段插入載體中之任何方法來建構含有嵌合基因之表現載體，該嵌合基因含有適當轉錄/轉譯控制信號及蛋白質編碼序列。此等方法可包括試管內重組 DNA 及合成技術及活體內重組（遺傳重組）。編碼蛋白質或其域、衍生物、片段或同源物之核酸序列的表現可藉由第二核酸序列來調控以使基因或其片段表現於經重組 DNA 分子轉型之宿主中。舉例而言，蛋白質之表現可由此項技術中已知之任何啟動子/增強子來控制。在一特定具體實例中，啟動子對於所需蛋白質之基因而言非原生。可使用之啟動子包括（但不限於）SV40 早期啟動子（Bernoist 及 Chambon, *Nature 290*:304-310 (1981)）、勞斯肉瘤病毒（Rous sarcoma virus）之 3'長末端重複序列中所含之啟動子（Yamamoto 等人 *Cell 22*:787-797 (1980)）、疱疹胸苷激酶啟動子（Wagner 等人, *Proc. Natl. Acad. Sci.*

USA 78:1441-1445 (1981))、金屬硫蛋白基因之調控序列(Brinster 等人, *Nature 296*:39-42 (1982))；原核表現載體，諸如 β-內醯胺酶啟動子(Jay 等人, (1981) *Proc. Natl. Acad. Sci. USA 78*:5543)或 *tac* 啟動子(DeBoer 等人, *Proc. Natl. Acad. Sci. USA 80*:21-25 (1983)；亦參見「Useful Proteins from Recombinant Bacteria」：在 Scientific American *242*:79-94 中(1980))；含有胭脂鹼(nopaline)合成酶啟動子(Herrar-Estrella 等人, *Nature 303*:209-213 (1984))或花椰菜花葉病毒 35S RNA 啟動子(Gardner 等人, *Nucleic Acids Res. 9*:2871 (1981))之植物表現載體，及光合成酶二磷酸核酮糖羧化酶之啟動子(Herrera-Estrella 等人, *Nature 310*:115-120 (1984))；來自酵母及其他真菌之啟動子元件，諸如 Gal4 啟動子、乙醇脫氫酶啟動子、磷酸甘油激酶啟動子、鹼性磷酸酶啟動子，及以下展現組織特異性且已用於轉殖基因動物中之動物轉錄控制區：在胰腺腺泡細胞中具活性之彈性蛋白酶 I 基因控制區(Swift 等人, *Cell 38*:639-646 (1984)；Ornitz 等人, *Cold Spring Harbor Symp. Quant. Biol. 50*:399-409 (1986)；MacDonald, *Hepatology 7*:425-515 (1987))；在胰腺 β 細胞中具活性之胰島素基因控制區(Hanahan 等人, *Nature 315*:115-122 (1985))、在淋巴樣細胞中具活性之免疫球蛋白基因控制區(Grosschedl 等人, *Cell 38*:647-658 (1984)；Adams 等人, *Nature 318*:533-538 (1985)；Alexander 等人, *Mol. Cell Biol. 7*:1436-1444 (1987))、在睪丸、乳房、淋巴及肥大細胞中具活性之小鼠

乳腺瘤病毒控制區（Leder 等人，*Cell 45*:485-495 (1986)）、在肝中具活性之白蛋白基因控制區（Pinckert 等人，*Genes and Devel. 1*:268-276 (1987)）、在肝中具活性之 α 胎蛋白基因控制區（Krumlauf 等人，*Mol. Cell. Biol. 5*:1639-1648 (1985)；Hammer 等人，*Science 235*:53-58 1987)）、在肝中具活性之 α-1 抗胰蛋白酶基因控制區（Kelsey 等人，*Genes and Devel. 1*:161-171 (1987)）、在骨髓細胞中具活性之 β 球蛋白基因控制區（Kollias 等人，*Cell 46*:89-94 (1986)）、在腦之寡樹突神經膠質細胞中具活性之髓鞘質鹼性蛋白質基因控制區（Readhead 等人，*Cell 48*:703-712 (1987)）、在骨骼肌中具活性之肌凝蛋白輕鏈-2 基因控制區（Shani, *Nature 314*:283-286 (1985)）及在下視丘之促性腺細胞中具活性之促性腺釋放激素基因控制區（Mason 等人，*Science 234*:1372-1378 (1986)）。

在一特定具體實例中，使用含有操作性連接於編碼所需蛋白質或其域、片段、衍生物或同源物之核酸之啟動子、一或多個複製起點及視情況一或多個可選擇標誌（例如抗生素抗性基因）的載體。用於大腸桿菌（*E. coli*）細胞轉型之例示性質體載體包括（例如）pQE 表現載體（購自 Qiagen，Valencia, CA；亦參見由 Qiagen 公開之描述該系統的文獻）。pQE 載體具有噬菌體 T5 啟動子（由大腸桿菌 RNA 聚合酶識別）及提供重組蛋白質在大腸桿菌中之嚴格調控、高水準表現的雙重乳糖操縱子阻遏模組、用於有效轉譯之合成核糖體結合位點（RBS II）、6×His 標籤編碼序列、t_0

及 T1 轉錄終止子、ColE1 複製起點及用於賦予胺苄青黴素（ampicillin）抗性之 β-內醯胺酶基因。pQE 載體使得能夠將 6×His 標籤置於重組蛋白質之 N-末端或 C-末端。該等質體包括 pQE 32、pQE 30 及 pQE 31，其提供用於所有三種閱讀框架之多個選殖位點且提供 N-末端經 6×His 標籤標記之蛋白質的表現。用於大腸桿菌細胞轉型之其他例示性質體載體包括（例如）pET 表現載體（參見美國專利 4,952,496；購自 Novagen，Madison, WI；亦參見由 Novagen 公開之描述該系統的文獻）。該等質體包括 pET 11a，其含有 T7lac 啟動子、T7 終止子、誘導型大腸桿菌 lac 操縱子及 lac 阻遏基因；pET 12a-c，其含有 T7 啟動子、T7 終止子及大腸桿菌 ompT 分泌信號；及 pET 15b 與 pET19b（NOVAGEN, Madison, WI），其含有用於以 His 管柱純化之 His-Tag™ 前導序列及允許在經由管柱純化後裂解之凝血酶裂解位點、T7-lac 啟動子區及 T7 終止子。

用於哺乳動物細胞表現之載體之實例為 HZ24 表現載體。HZ24 表現載體係來源於 pCI 載體骨架（Promega）。其含有編碼 β-內醯胺酶抗性基因（AmpR）之 DNA、F1 複製起點、細胞巨大病毒極早期增強子/啟動子區（CMV）及 SV40 晚期聚腺苷酸化信號（SV40）。該表現載體亦具有來自 ECMV 病毒（Clontech）之內部核糖體進入位點（internal ribosome entry site，IRES）及小鼠二氫葉酸還原酶（dihydrofolate reductase，DHFR）基因。

2. 表現

基質降解酵素可藉由熟習此項技術者已知之任何方法（包括活體內及試管內方法）來產生。所需蛋白質可表現於適合於產生所需要之量及形式之蛋白質（例如投藥及治療所需）的任何生物體中。表現宿主包括原核及真核生物，諸如大腸桿菌、酵母、植物、昆蟲細胞、哺乳動物細胞，包括人類細胞系及轉殖基因動物。表現宿主可在其蛋白質產生量以及存在於所表現蛋白質上之轉譯後修飾的類型方面不同。表現宿主之選擇可根據此等及其他因素來進行，諸如調節及安全性考慮、生產成本及用於純化之需求與方法。

許多表現載體為可得的且為熟習此項技術者所已知並可用於蛋白質之表現。表現載體之選擇將受宿主表現系統之選擇影響。一般而言，表現載體可包括轉錄啟動子及視情況增強子、轉譯信號及轉錄與轉譯終止信號。用於穩定轉型之表現載體典型地具有允許選擇及維持經轉型細胞之可選擇標誌。在一些情況下，可使用複製起點來擴增載體之複本數。

基質降解酵素亦可以蛋白質融合體形式使用或表現為蛋白質融合體。舉例而言，可產生酵素融合體以將其他功能添加至酵素中。酵素融合蛋白之實例包括（但不限於）信號序列、諸如用於定位之標籤（例如 his_6 標籤或 myc 標籤）或用於純化之標籤（例如 GST 融合體）及用於指導蛋白質分泌及/或膜結合之序列的融合體。

通常，基質降解酵素係以無活性酵素原形式表現。酵

素原轉化可藉由暴露於其他蛋白酶或自體催化以產生成熟酵素來達成。本文涵蓋任何形式之酵素，只要其在活化劑不存在之情況下無活性即可。

a. 原核細胞

原核生物，尤其大腸桿菌提供用於產生大量蛋白質之系統。大腸桿菌之轉型為熟習此項技術者所熟知之簡單且快速之技術。用於大腸桿菌之表現載體可含有誘導型啟動子，該等啟動子適用於誘導高水準之蛋白質表現且表現對宿主細胞展現一些毒性之蛋白質。誘導型啟動子之實例包括 lac 啟動子、trp 啟動子、雜合 tac 啟動子、T7 及 SP6 RNA 啟動子及溫度調節型 λPL 啟動子。

可使蛋白質（諸如本文所提供之任何蛋白質）表現於大腸桿菌之細胞質環境中。該細胞質為還原環境且對於一些分子而言，此會導致形成不溶性包涵體。諸如二硫蘇糖醇及 β-巰基乙醇之還原劑與諸如胍-HCl 及脲之變性劑可用於使蛋白質重新溶解。一替代性方法為使蛋白質表現於細菌之提供氧化環境及伴侶蛋白樣及二硫化物異構酶的周質空間中且會使得產生可溶性蛋白質。典型地，使將蛋白質導向周質之前導序列與欲表現之蛋白質融合。接著藉由周質中之信號肽酶移除該前導序列。周質靶向前導序列之實例包括來自果膠酸解離酶基因之 pelB 前導序列及來源於鹼性磷酸酶基因之前導序列。在一些情況下，周質表現允許所表現之蛋白質滲漏至培養基中。蛋白質之分泌允許自培養上清液快速及簡單純化。未分泌之蛋白質可藉由滲透溶

解自周質獲得。類似於細胞質表現，在一些情況下，蛋白質可變得不溶且可使用變性劑及還原劑促進溶解及再摺疊。誘導及生長之溫度亦可影響表現量及溶解度，典型地使用介於 25℃與 37℃之間的溫度。典型地，細菌產生無糖基化之蛋白質。因此，若蛋白質之功能需要糖基化，則可在自宿主細胞純化後試管內添加糖基化。

b. 酵母細胞

諸如釀酒酵母（*Saccharomyces cerevisae*）、粟酒裂殖酵母（*Schizosaccharomyces pombe*）、解脂耶氏酵母（*Yarrowia lipolytica*）、乳酸刻魯維酵母（*Kluyveromyces lactis*）及甲醇酵母（*Pichia pastoris*）之酵母為可用於產生蛋白質（諸如本文所述之任何蛋白質）之熟知酵母表現宿主。酵母可用游離型複製載體或藉由經由同源重組進行之穩定染色體整合來轉型。典型地，使用誘導型啟動子來調控基因表現。該等啟動子之實例包括 GAL1、GAL7 及 GAL5 及諸如 CUP1、AOX1 或其他畢赤酵母（*Pichia*）或其他酵母啟動子之金屬硫蛋白啟動子。表現載體通常包括用於選擇及維持經轉型 DNA 之可選擇標誌，諸如 LEU2、TRP1、HIS3 及 URA3。表現於酵母中之蛋白質通常為可溶性的。與諸如 Bip 之伴侶蛋白及蛋白質二硫化物異構酶共表現可改良表現量及溶解度。另外，可指導表現於酵母中之蛋白質使用分泌信號肽融合體（諸如來自釀酒酵母之酵母接合型 α-因子分泌信號）及與酵母細胞表面蛋白質（諸如 Aga2p 接合黏著受體或 *Arxula adeninivorans* 葡糖澱粉酶）之融合體進行分

泌。諸如用於 Kex-2 蛋白酶之裂解位點的蛋白酶裂解位點可經工程化以在所表現之多肽離開分泌路徑時自該多肽移除融合序列。酵母亦能夠於 Asn-X-Ser/Thr 基元處糖基化。

c. 昆蟲細胞

昆蟲細胞，尤其使用桿狀病毒表現之昆蟲細胞適用於表現多肽，諸如基質降解酵素。昆蟲細胞表現高含量之蛋白質且能夠進行高等真核生物所使用之大多數轉譯後修飾。桿狀病毒具有改良安全性且減少真核表現之調控問題的限定宿主範圍。典型表現載體使用用於高水準表現之啟動子，諸如桿狀病毒之多角體蛋白啟動子。常用桿狀病毒系統包括以下桿狀病毒，諸如苜蓿銀紋夜蛾核多角體病病毒（*Autographa californica* nuclear polyhedrosis virus，AcNPV）及家蠶核多角體病病毒（*Bombyx mori* nuclear polyhedrosis virus，BmNPV）及昆蟲細胞系，諸如來源於草地黏蟲（*Spodoptera frugiperda*）之 Sf9、美州黏蟲（*Pseudaletia unipuncta*）（A7S）及黑脈金斑蝶（*Danaus plexippus*）（DpN1）。對於高水準表現而言，直接將欲表現之分子的核苷酸序列融合於病毒之多角體蛋白起始密碼子的下游。哺乳動物分泌信號在昆蟲細胞中經準確加工且可用於使所表現之蛋白質分泌至培養基中。另外，細胞系美州黏蟲（A7S）及黑脈金斑蝶（DpN1）產生具有類似於哺乳動物細胞系統之糖基化模式之蛋白質。

昆蟲細胞中之一替代性表現系統使用經穩定轉型之細胞。諸如 Schneider 2（S2）及 Kc 細胞（黑腹果蠅（*Drosophila*

melanogaster))及C7細胞(白紋伊蚊(*Aedes albopictus*))之細胞系可用於表現。果蠅屬(*Drosophila*)金屬硫蛋白啟動子可用於在重金屬誘導存在下用鎘或銅誘導高水準表現。表現載體典型地藉由使用諸如新黴素(neomycin)及潮黴素(hygromycin)之可選擇標誌來維持。

d. 哺乳動物細胞

哺乳動物表現系統可用於表現包括基質降解酵素之蛋白質。表現構築體可藉由病毒感染(諸如腺病毒)或藉由直接DNA轉移(諸如脂質體、磷酸鈣、DEAE-葡聚糖)及藉由物理方式(諸如電穿孔及顯微注射)轉移至哺乳動物細胞中。用於哺乳動物細胞之表現載體典型地包括mRNA加帽位點、TATA盒、轉譯起始序列(Kozak一致序列)及聚腺苷酸化元件。亦可添加IRES元件以允許與另一基因(諸如可選擇標誌)一起雙順反子表現。該等載體通常包括用於高水準表現之轉錄啟動子-增強子,例如SV40啟動子-增強子、人類細胞巨大病毒(cytomegalovirus,CMV)啟動子及勞斯肉瘤病毒(RSV)之長末端重複序列。此等啟動子-增強子在許多細胞類型中具活性。組織及細胞型啟動子及增強子區域亦可用於表現。例示性啟動子/增強子區域包括(但不限於)來自諸如彈性蛋白酶I、胰島素、免疫球蛋白、小鼠乳房腫瘤病毒、白蛋白、α胎蛋白、α1抗胰蛋白酶、β球蛋白、髓鞘質鹼性蛋白質、肌凝蛋白輕鏈2及促性腺釋放激素基因控制序列之基因的彼等區域。可選擇標誌可用於選擇及維持具有表現構築體之細胞。可選擇標誌基因之

實例包括（但不限於）潮黴素 B 磷酸轉移酶、腺苷去胺酶、黃嘌呤-鳥嘌呤磷酸核糖轉移酶、胺基糖苷磷酸轉移酶、二氫葉酸還原酶（DHFR）及胸苷激酶。舉例而言，可在甲胺喋呤（methotrexate）存在下執行表現以僅選擇表現 DHFR 基因之彼等細胞。與細胞表面信號傳輸分子（諸如 TCR-ζ 及 FcεRI-γ）之融合體可指導蛋白質以活性狀態表現於細胞表面上。

許多細胞系可用於哺乳動物表現，包括小鼠、大鼠、人類、猴、雞及倉鼠細胞。例示性細胞系包括（但不限於）CHO、Balb/3T3、海拉（HeLa）、MT2、小鼠 NS0（非分泌性）及其他骨髓瘤細胞系、融合瘤及異融合瘤細胞系、淋巴細胞、纖維母細胞、Sp2/0、COS、NIH3T3、HEK293、293S、2B8 及 HKB 細胞。亦可用適應於促進分泌性蛋白自細胞培養基純化之無血清培養基的細胞系。實例包括 CHO-S 細胞（Invitrogen, Carlsbad, CA，目錄號 11619-012）及無血清 EBNA-1 細胞系（Pham 等人, (2003) *Biotechnol. Bioeng.* *84*:332-42.）。亦可用適應於生長於經優化用於最大表現之特殊培養基中之細胞系。舉例而言，DG44 CHO 細胞適於以懸浮液培養形式生長於化學上界定之無動物產物培養基中。

e. 植物

轉殖基因植物細胞及植物可用於表現蛋白質，諸如本文所述之任何蛋白質。典型地使用直接 DNA 轉移（諸如微粒轟擊）將表現構築體轉移至植物中且使用 PEG 介導之轉

移將其轉移至原生質體中，且用農桿菌屬（agrobacterium）介導之轉型進行轉移。表現載體可包括啟動子及增強子序列、轉錄終止元件及轉譯控制元件。表現載體及轉型技術通常在雙子葉植物宿主（諸如芥菜屬（*Arabidopsis*）及煙草）與單子葉植物宿主（諸如玉米及稻穀）之間不同。用於表現之植物啟動子的實例包括花椰菜花葉病毒（cauliflower mosaic virus）啟動子、胭脂鹼合成酶啟動子、核糖二磷酸羧化酶啟動子及泛素與 UBQ3 啟動子。諸如潮黴素、磷酸甘露糖異構酶及新黴素磷酸轉移酶之可選擇標誌通常用於促進經轉型細胞之選擇及維持。經轉型之植物細胞可以細胞、聚集體（胼胝體組織）形式維持於培養物中或再生為完整植物。轉殖基因植物細胞亦可包括經工程化以產生基質降解酵素之藻類。因為植物具有與哺乳動物細胞不同之糖基化模式，所以此可影響此等宿主中所產生之蛋白質的選擇。

3. 純化技術

自宿主細胞純化多肽（包括基質降解酵素或其他蛋白質）之方法將視所選之宿主細胞及表現系統而定。對於分泌性分子而言，通常在移除細胞後自培養基純化蛋白質。對於細胞內表現而言，可溶解細胞且自提取物純化蛋白質。當使用諸如轉殖基因植物及動物之轉殖基因生物體進行表現時，組織或器官可用作起始物質以產生溶解之細胞提取物。另外，轉殖基因動物生產可包括於可收集之奶或蛋中產生多肽，且必要時可提取蛋白質且使用此項技術中

之標準方法進行進一步純化。

通常，使基質降解酵素表現且純化為無活性形式（酵素原形式）以用於隨後如本文所提供之系統及方法中所述的活化。在一些應用中，基質降解酵素如本文中所述在活化劑不存在的情況下其成熟形式無活性。因此，在表現後，成熟形式可藉由自體催化以移除前區而產生。對於許多酵素而言，該自體催化需要活化劑之存在。必要時，可執行其他純化步驟以自經純化之製劑移除前區。在一些情況下，諸如對於用作對照而言，所表現之基質降解酵素可藉由自體催化以移除前區或藉由添加活化劑而純化為活性形式。在該等實例中，自體活化可在純化過程期間進行，或藉由於室溫下培養 24-72 小時來進行。活化之速率及程度視蛋白質濃度及特定酵素而定，以使得例如可能需要將較稀之樣品於室溫下培養較長時期。活化可藉由 SDS-PAGE（例如 3 千道爾頓（kilodalton）位移）及藉由酵素活性（螢光受質之裂解）來監測。當需要活性酵素時，典型地，在純化之前使酵素達到>75%活化。

諸如基質降解酵素之蛋白質可使用此項技術中已知之標準蛋白質純化技術來純化，該等技術包括（但不限於）SDS-PAGE、尺寸分級及尺寸排阻層析法、硫酸銨沈澱及離子交換層析法（諸如陰離子交換）。親和力純化技術亦可用於改良製劑之效能及純度。舉例而言，結合基質降解酵素之抗體、受體及其他分子可用於親和力純化。表現構築體亦可經工程化以將親和力標籤（諸如 myc 抗原決定基、GST

融合體或 His_6）添加至蛋白質中且分別用 myc 抗體、麩胱甘肽樹脂及 Ni-樹脂進行親和力純化。純度可藉由此項技術中已知之任何方法來評估，包括凝膠電泳及染色與分光光度技術。

F. 可活化的基質降解酵素之製備、調配及投藥

本文所提供之醫藥組成物含有以無活性形式提供之可活化的基質降解酵素。亦提供含有活化劑之組成物。該等化合物可經調配為合適之醫藥製劑，諸如用於經口、非經腸投藥之溶液、懸浮液、凝膠、錠劑、可分散錠劑、丸劑、膠囊、散劑、持續釋放調配物或酏劑，以及經皮貼片製劑及乾粉吸入器。典型地，使用此項技術中熟知之技術及程序將化合物調配為醫藥組成物（參見例如，Ansel *Introduction to Pharmaceutical Dosage Forms*, Fourth Edition, 1985, 126）。

所選基質降解酵素係以活化時在不存在對所治療患者之不當副作用的情況下發揮治療有效作用之足夠量包括在內。含有可活化的基質降解酵素之組成物可包括醫藥學上可接受之載劑。治療有效濃度可藉由在已知試管內及活體內系統（諸如本文所提供之檢定）中測試化合物憑經驗確定。組成物中之所選基質降解酵素的濃度視複合物之吸收、失活及排出率，複合物之物理化學特徵，劑量時程及投藥量以及熟習此項技術者已知之其他因素而定。舉例而言，應瞭解治療之精確劑量及持續時間與所治療之組織有關且可使用已知測試方案憑經驗確定或藉由自活體內或試

管內測試資料推斷來確定。應注意濃度及劑量值亦可隨所治療個體之年齡而變化。應進一步瞭解對於任何特定個體而言，特定給藥方案應隨時間根據個體需求及投予調配物或監督調配物之投藥之人員的專業判斷而調整，且本文所述之濃度範圍僅為例示性的且不欲限制其範疇。欲投予以治療疾病或病狀（例如 ECM 介導之疾病或病狀，諸如脂肪團或淋巴水腫）之所選基質降解酵素的量可藉由標準臨床技術來確定。另外，試管內檢定及動物模型可用於幫助確定最佳劑量範圍。可憑經驗確定之精確劑量可視特定酵素、投藥途徑、欲治療之疾病類型及疾病之嚴重性而定。例示性劑量範圍為或約為 10 μg 至 100 mg、尤其 50 μg 至 75 mg、100 μg 至 50 mg、250 μg 至 25 mg、500 μg 至 10 mg、1 mg 至 5 mg 或 2 mg 至 4 mg。特定劑量及其調配物視適應症及個體而定。必要時，劑量可憑經驗確定。典型地，對於本文所述之適應症而言，以復水（諸如藉由添加活化劑）後為 1-100 ml、尤其 1-50 ml、10-50 ml、10-30 ml、1-20 ml 或 1-10 ml 之體積投予劑量。典型地，該等劑量為或約為 100 μg 至 50 mg、通常 1 mg 至 5 mg，最終體積為 10-50 ml。

所選活化劑典型地以經緩衝溶液形式以在暴露於基質降解酵素時活化基質降解酵素之量提供。典型地，緩衝液中之活化劑的量為暫時使存在於間質中之該活化劑的生理量改變至足以暫時活化所選可活化的基質降解酵素之含量的量。舉例而言，當酸性 pH 值為活化條件時，呈酸性緩衝液組成物之形式的活化劑含有至少一種酸，當與基質降解

酵素一起或分開向ECM投予時，該酸暫時使ECM之pH值降低至生理學pH值以下，亦即中性pH值以下。如本文其他地方所述，酸性緩衝液為具有在所選酵素之最佳pH值中的有效pH值範圍之緩衝液。酸性緩衝液之中和將由於間質之中性pH值環境而在投藥之後發生，且與緩衝能力有關。本文亦涵蓋其他經緩衝溶液，其視所選可活化的基質降解酵素及所選活化劑而定。舉例而言，緩衝液可於不同溫度下，或用不同量之鹽、還原劑或金屬離子製備。含有低pH值活化條件之經緩衝活化劑溶液亦可含有醫藥學上可接受之載劑或賦形劑。

基質降解酵素可一次性投予，或可分為許多較小劑量以一定時間間隔投予。所選基質降解酵素可在治療時間過程中（例如在若干小時、天、週或月中）以一或多個劑量投予。在一些情況下，連續投藥為適用的。應瞭解精確劑量及投藥過程視所預期之活化的方法及系統而定。舉例而言，基質降解酵素可與活化劑一起或分開投予。典型地，若共同投予，則在即將使用之前使活化劑暴露於基質降解酵素，例如藉由凍乾粉末之復水。在其他陳述中，活化劑可為AMDE調配物之組份或可與AMDE之液體基劑型混合。又，AMDE可在混合活化劑之前用適當稀釋劑稀釋。若分開投予，基質降解酵素組成物可與活化劑製劑依次、同時或間歇投予。

又，應瞭解治療之精確劑量及持續時間與所治療之疾病有關且可使用已知測試方案憑經驗確定或藉由自活體內

或試管內測試資料推斷來確定。應注意濃度及劑量值亦可隨欲減輕之病狀的嚴重性而變化。應進一步瞭解對於任何特定個體而言，特定給藥方案應隨時間根據個體需求及投予組成物或監督投予組成物之人員的專業判斷而調整，且本文所述之濃度範圍僅為例示性的且不欲限制組成物及含有其之組合的範疇或用途。該等組成物可每小時、每日、每週、每月、每年投予一次或一次性投予。通常，給藥方案經選擇以限制毒性。應注意主治醫師將瞭解由於毒性或骨髓、肝或腎或其他組織功能障礙而如何及何時終止、中斷或調整療法以降低劑量。相反地，主治醫師亦將瞭解在臨床反應不足（排除毒性副作用）之情況下如何及何時將治療調整至較高含量。

鑒於管理機構或其他機構之批准，根據通常認可用於動物及人類之藥典來製備醫藥學上可接受之組成物。組成物可採用溶液、懸浮液、乳液、凝膠、錠劑、丸劑、膠囊、散劑及持續釋放調配物之形式。組成物可用傳統黏合劑及載劑（諸如甘油三酯）調配為栓劑。經口調配物可包括標準載劑，諸如醫藥級甘露糖醇、乳糖、澱粉、硬脂酸鎂、糖精鈉、纖維素、碳酸鎂及其他此類藥劑。該調配物應適合投藥方式。

醫藥組成物可包括與酵素或活化劑一起投予之載劑，諸如稀釋劑、佐劑、賦形劑或媒劑。合適之醫藥載劑的實例描述於 E. W. Martin 之「Remington's Pharmaceutical Sciences」中。該等組成物將含有治療有效量之通常呈經純

化形式的化合物，以及適量載劑以便提供用於向患者適當投藥之形式。該等醫藥載劑可為無菌液體，諸如水及油，包括石油、動物、蔬菜或合成來源者，諸如花生油、大豆油、礦物油及芝麻油。水為靜脈內投予醫藥組成物時之典型載劑。生理食鹽水溶液及右旋糖與甘油水溶液亦可用作液體載劑，尤其用於可注射溶液。組成物可含有活性成份以及：稀釋劑，諸如生理食鹽水、乳糖、蔗糖、右旋糖、林格氏乳酸鹽（Ringers lactate）、磷酸氫鈣或羧甲基纖維素；潤滑劑，諸如硬脂酸鎂、硬脂酸鈣及滑石粉；及黏合劑，諸如澱粉、天然膠（諸如阿拉伯膠明膠）、葡萄糖、糖蜜、聚乙烯吡咯啶、纖維素及其衍生物、聚乙烯吡咯酮、交聯聚乙烯吡咯酮及熟習此項技術者已知之其他此類黏合劑。合適之醫藥賦形劑包括澱粉、葡萄糖、乳糖、蔗糖、麥芽糖、甘露糖、海藻糖、甘露糖醇、山梨糖醇、明膠、麥芽、稻穀、麵粉、白堊、矽膠、硬脂酸鈉、單硬脂酸甘油酯、滑石粉、氯化鈉、脫脂奶粉、甘油、丙二醇、水及乙醇。需要時，組成物亦可含有少量濕潤劑或乳化劑或pH值緩衝劑，例如乙酸鹽、檸檬酸鈉、順丁烯二酸鹽、甘胺酸鹽、組胺酸、丁二酸鹽、乳酸鹽、環糊精衍生物、脫水山梨糖醇單月桂酸酯、三乙醇胺乙酸鈉、三乙醇胺油酸酯、聚乙二醇及其他此類藥劑。調配物中之其他賦形劑可包括氧化劑或還原劑，諸如半胱胺酸、氧化型麩胱甘肽或半胱胺酸、還原型麩胱甘肽；界面活性劑，諸如聚山梨醇酯80、聚山梨酸酯20、泊洛尼克（pluronic）（F68）或防腐劑。如

上所述，出於本文之目的，酸性緩衝劑可作為活化劑提供，其通常以與基質降解酵素分開之組合提供直至使用。

提供調配物以便以單位劑型向人類及動物投藥，該等單位劑型諸如錠劑、膠囊、丸劑、散劑、顆粒、無菌非經腸溶液或懸浮液、及經口溶液或懸浮液、及含有適量化合物或其醫藥學上可接受之衍生物的油水乳液。醫藥治療活性化合物及其衍生物典型地以單位劑型或多劑型調配及投予。每一單位劑量含有足以產生所需治療作用之預定量的治療活性化合物，以及所需醫藥載劑、媒劑或稀釋劑。單位劑型之實例包括安瓶、小瓶及注射器以及個別包裝之錠劑或膠囊。單位劑型可以其部分或多個投予。多劑型為包裝於單一容器中之欲以分開之單位劑型投予的複數個相同單位劑型。多劑型之實例包括小瓶、錠劑或膠囊瓶或品脫（pint）或加侖（gallon）瓶。因此，多劑型為在包裝時不分開之多個單位劑量。通常，可製備含有在0.005%至100%之範圍內的活性成份及由無毒載劑組成之其餘部分的劑型或組成物。

組成物可經調配以藉由熟習此項技術者已知之任何途徑投予，該等途徑包括肌肉內、靜脈內、皮內、病灶內、腹膜內注射、皮下、表皮下、硬膜外、經鼻、經口、經陰道、經直腸、表面、局部、經耳、吸入、頰內（例如舌下）及經皮投藥或任何途徑。視治療部位而定，投藥可為局部、表面或全身性投藥。向需要治療之區域局部投藥可藉由例如（但不限於）在手術期間局部輸注、表面施用（例如手

術後結合傷口敷裹）、藉由注射、藉助於導管、藉助於栓劑或藉助於植入物來達成。組成物亦可與其他生物活性劑一起依次、間歇或以同一組成物形式投予。投藥亦可包括受控釋放系統，包括受控釋放調配物及受控釋放裝置，諸如藉助於泵。

在任何給定情況下最合適之途徑視多種因素而定，諸如疾病性質、疾病進展、疾病嚴重性、所使用之特定組成物。出於本文之目的，希望投予基質降解酵素及活化劑以便其到達皮膚或組織之間質。因此，涵蓋直接投予皮膚下方，諸如藉由表皮下投藥方法。此等方法包括（例如）皮下、皮內及肌肉內投藥途徑。因此，在一實例中，局部投藥可藉由注射達成，諸如自含有注射裝置（諸如針）之注射器或其他製品注射。亦涵蓋其他投藥方式。醫藥組成物可以適合於各投藥途徑之劑型調配。

在一實例中，醫藥製劑可呈液體形式，例如溶液、糖漿或懸浮液。若以液體形式提供，則可活化的基質降解酵素之醫藥製劑可以在添加活化劑之後稀釋至治療有效濃度之濃縮製劑形式提供。活化劑可在投藥之前添加至製劑中，或活化劑可與基質降解酵素製劑同時、間歇或依次添加。該等液體製劑可藉由習知方法用醫藥學上可接受之添加劑來製備，該等添加劑諸如懸浮劑（例如山梨糖醇糖漿、纖維素衍生物或氫化食用脂肪）；乳化劑（例如卵磷脂或阿拉伯膠）；非水性媒劑（例如杏仁油、油性酯或分餾植物油）；及防腐劑（例如對羥基苯甲酸甲酯或對羥基苯甲酸丙

酯或山梨酸）。

在另一實例中，醫藥製劑可以凍乾形式提供以在使用之前用水或其他合適之媒劑復水。舉例而言，基質降解酵素之醫藥製劑可用含有適當活化劑之溶液復水。製劑之復水產生於合適活化劑中含有治療有效量之基質降解酵素的混合物，其可使用任何所需投藥途徑共同投予。

投藥方法可用於減少所選基質降解酵素暴露於降解過程，諸如蛋白水解降解及經由抗原性及免疫原性反應之免疫干預。該等方法之實例包括於治療部位處之局部投藥。已報導治療劑之聚乙二醇化增加對蛋白水解之抵抗力，增加血漿半衰期，且降低抗原性及免疫原性。聚乙二醇化方法之實例為此項技術所已知（參見例如，Lu及Felix, *Int. J. Peptide Protein Res., 43*: 127-138, 1994；Lu及Felix, *Peptide Res., 6:* 142-6, 1993；Felix等人, *Int. J. Peptide Res., 46* : 253-64, 1995；Benhar等人, *J. Biol. Chem., 269*: 13398-404, 1994；Brumeanu等人, *J Immunol., 154*: 3088-95, 1995；亦參見Caliceti等人 (2003) *Adv. Drug Deliv. Rev. 55(10)*:1261-77及Molineux (2003) *Pharmacotherapy 23 (8 Pt 2)*:3S-8S）。聚乙二醇化亦可用於活體內傳遞核酸分子。舉例而言，腺病毒之聚乙二醇化可增加穩定性及基因轉移（參見例如，Cheng等人 (2003) *Pharm. Res. 20(9)*: 1444-51）。

1. 可注射劑、溶液及乳液

本文涵蓋通常特徵在於皮下、肌肉內或皮內注射之非

經腸投藥。可注射劑可以習知形式，以液體溶液或懸浮液、適合於在注射之前溶解或懸浮於液體中之固體形式或乳液形式製備。合適賦形劑為（例如）水、生理食鹽水、右旋糖、甘油或乙醇。另外，需要時，欲投予之醫藥組成物亦可含有呈溶劑形式之活化劑，諸如 pH 值緩衝劑、還原劑或氧化劑、金屬離子鹽或其他此類緩衝液。醫藥組成物亦可含有其他少量無毒助劑物質，諸如濕潤劑或乳化劑、pH 值緩衝劑、穩定劑、溶解度增強劑及其他此類藥劑，例如乙酸鈉、脫水山梨糖醇單月桂酸酯、三乙醇胺油酸酯及環糊精。本文亦涵蓋植入緩慢釋放或持續釋放系統以使得維持恆定劑量水準（參見例如美國專利第 3,710,795 號）。該等非經腸組成物中所含之活性化合物的百分比高度視其特定性質以及化合物之活性及個體之需求而定。

組成物之非經腸投藥通常包括表皮下投藥途徑，諸如皮內、皮下及肌肉內投藥。需要時，亦涵蓋靜脈內投藥。可注射劑經設計用於局部及全身性投藥。出於本文之目的，對於向受影響間質直接投藥，局部投藥為合意的。用於非經腸投藥之製劑包括備用於注射之無菌溶液、備用於在即將使用之前與溶劑組合的無菌乾燥可溶性產物（諸如凍乾粉末）（包括皮下錠劑）、備用於注射之無菌懸浮液、備用於在使用之前與媒劑組合之無菌乾燥不溶性產物及無菌乳液。該等溶液可為水性或非水性溶液。若靜脈內投予，則合適載劑包括生理食鹽水或磷酸鹽緩衝生理食鹽水（phosphate buffered saline，PBS），及含有增稠劑及增溶劑

之溶液，諸如葡萄糖、聚乙二醇及聚丙二醇及其混合物。

用於非經腸製劑中之醫藥學上可接受之載劑包括水性媒劑、非水性媒劑、抗微生物劑、等張劑、緩衝劑、抗氧化劑、局部麻醉劑、懸浮劑及分散劑、乳化劑、錯隔劑或螯合劑、胺基酸、肽及其他醫藥學上可接受之物質。水性媒劑之實例包括氯化鈉注射液、林格氏注射液（Ringers Injection）、等張右旋糖注射液、無菌水注射液、右旋糖及乳酸鹽林格氏注射液。非水性非經腸媒劑包括植物來源之不揮發性油、棉籽油、玉米油、芝麻油及花生油。可將抗細菌或抗真菌濃度之抗微生物劑添加至包裝於多劑量容器中之非經腸製劑中，該等抗微生物劑包括酚或甲酚、汞劑、苄醇、氯丁醇、對羥基苯甲酸酯（諸如對羥基苯甲酸甲酯及對羥基苯甲酸丙酯）、硫柳汞、氯苄烷銨及苄索氯銨。等張劑包括氯化鈉及右旋糖。緩衝劑包括磷酸鹽及檸檬酸鹽。抗氧化劑包括硫酸氫鈉。局部麻醉劑包括鹽酸普魯卡因（procaine hydrochloride）。懸浮劑及分散劑包括羧甲基纖維素鈉、羥丙基甲基纖維素及聚乙烯吡咯啶酮。乳化劑包括聚山梨醇酯 80（TWEEN 80）、聚山梨酸酯 20（TWEEN 20）、泊洛尼克（F68）。金屬離子之錯隔劑或螯合劑包括EDTA。醫藥載劑亦包括用於水混溶性媒劑及氫氧化鈉之乙醇、聚乙二醇及丙二醇，用於調整 pH 值之鹽酸、檸檬酸或乳酸。

調整醫藥活性化合物之濃度以便注射液提供產生所需藥理學作用之有效量。如此項技術中所已知，精確劑量視

患者或動物之年齡、體重及病狀而定。將單位劑量非經腸製劑包裝於安瓶、小瓶或具有針之注射器中。含有醫藥活性化合物之液體溶液或復水粉末製劑之體積與欲治療之疾病及選用於包裝之特定製品有關。舉例而言，對於脂肪團之治療而言，預期對於非經腸注射液而言，所注射體積為或約為 10 毫升至 50 毫升。通常，此體積代表活化劑及基質降解酵素在兩者共同投予時之體積。因此，在一實例中，提供一種雙重容器或雙腔室注射器，其含有與含有 10 毫升至 50 毫升活化劑之第二隔室分開的凍乾酵素製劑。用活化劑使酵素復水後，可投予混合物。如此項技術中所已知及實踐，用於非經腸投藥之所有制劑必須無菌。可將可注射調配物儲存於適當條件下，諸如為或約為-80℃、-40℃、-20℃、2-8℃、15℃、室溫或受控室溫。

凍乾粉末

本文關注凍乾粉末，其可經復水用於以溶液、乳液及其他混合物形式投予。其亦可復水及調配為固體或凝膠。

無菌凍乾粉末藉由將無活性酵素之化合物溶解於緩衝溶液中來製備。該緩衝溶液可含有改良粉末或由該粉末製備之復水溶液之穩定性或其他藥理學組份的賦形劑。隨後無菌過濾溶液，接著於熟習此項技術者已知之標準條件下凍乾提供所需調配物。簡言之，凍乾粉末係藉由將賦形劑（諸如右旋糖、山梨糖、果糖、玉米糖漿、木糖醇、甘油、葡萄糖、蔗糖、甘露糖、山梨糖醇、海藻糖、甘露糖醇、山梨糖醇、羥乙基澱粉或其他合適藥劑）溶解於合適緩衝

液（諸如檸檬酸鹽、磷酸鈉或磷酸鉀或熟習此項技術者已知之其他此類緩衝液）來製備。可添加之其他賦形劑包括胺基酸，諸如甘胺酸、丙胺酸、脯胺酸；胺，諸如甜菜鹼、三甲胺 N-氧化物；及銨、鈉或鎂之鹽。接著將所選酵素添加至所得混合物中，且攪拌直至其溶解。將所得混合物無菌過濾或處理以移除微粒且確保無菌，並分配至小瓶中以進行凍乾。各小瓶將含有單劑量（1 mg-1 g，通常 1-100 mg，諸如 1-5 mg）或多劑量之化合物。凍乾粉末可儲存於適當條件下，諸如儲存於約 4℃至室溫下。

用緩衝溶液使此凍乾粉末復水提供用於非經腸投藥之調配物。選用於復水之溶液可為任何緩衝液，但典型地為含有活化劑之緩衝液。根據欲復水之酵素來選擇活化劑。舉例而言，用約 pH 5.5 之酸性緩衝液使組織蛋白酶 L 之凍乾製劑復水。對於復水而言，每毫升緩衝液或其他合適載劑添加約 1 μg-20 mg、較佳 10 μg-1 mg、更佳約 100 μg。精確量視所治療之適應症及所選化合物而定。該量可憑經驗確定。

2. 表面投藥

如關於局部及全身性投藥所述來製備表面混合物。所得混合物可為溶液、懸浮液、乳液或其類似物且調配為乳膏、凝膠、軟膏、乳液、溶液、酏劑、洗劑、懸浮液、酊劑、糊狀物、泡沫、氣溶膠、灌洗劑、噴霧、栓劑、繃帶、皮膚貼片或適合於表面投藥之任何其他調配物。

化合物或其醫藥學上可接受之衍生物可以氣溶膠形式

調配以用於表面施用，諸如藉由吸入（參見例如美國專利第 4,044,126 號；第 4,414,209 號；及第 4,364,923 號，其描述用於傳遞適用於治療發炎性疾病、尤其哮喘之類固醇的氟溶膠）。此等用於向呼吸道投藥之調配物可單獨或與諸如乳糖之惰性載劑組合呈用於霧化器之氟溶膠或溶液之形式，或呈用於吹入之微細粉末形式。在該情況下，調配物之粒子典型地將具有小於 50 微米、較佳小於 10 微米之直徑。

化合物可經調配用於以凝膠、乳膏及洗劑之形式局部或表面施用，諸如表面施用於皮膚及黏膜（諸如眼睛中），及施用於眼睛或用於腦池內或脊椎內施用。預期表面投藥用於經皮傳遞以及向眼睛或黏膜投藥，或用於吸入療法。亦可投予單獨或與其他醫藥學上可接受之賦形劑組合的活性化合物之經鼻溶液。

提供適合於經皮投藥之調配物。其可以任何合適之形式提供，諸如適於保持與受體表皮緊密接觸較長時期之離散貼片。該等貼片含有於相對於活性化合物（例如）0.1 至 0.2 M 濃度之視情況經緩衝水溶液中的活性化合物。適合於經皮投藥之調配物亦可藉由離子導入療法（參見例如 *Pharmaceutical Research 3(6)*, 318 (1986)）傳遞且典型地採用活性化合物之視情況經緩衝水溶液之形式。

3. 用於其他投藥途徑之組成物

視所治療之病狀而定，本文亦涵蓋其他投藥途徑，諸如表面施用、經皮貼片、經口及經直腸投藥。舉例而言，

用於經直腸投藥之醫藥劑型為用於全身性作用之直腸栓劑、膠囊及錠劑。直腸栓劑包括用於插入直腸中之固體，其於體溫下熔融或變軟，從而釋放一或多種藥理學或治療活性成份。直腸栓劑中所用之醫藥學上可接受之物質為主劑或媒劑及升高熔點之藥劑。主劑之實例包括可可脂（可可油）、甘油-明膠、碳蠟（聚氧乙二醇）及脂肪酸之甘油單酯、甘油二酯及甘油三酯的適當混合物。可使用各種主劑之組合。升高栓劑熔點之藥劑包括鯨蠟及蠟。直腸栓劑可藉由壓縮方法或藉由模製來製備。直腸栓劑之典型重量為約 2 gm 至 3 gm。用於經直腸投藥之錠劑及膠囊係使用與用於經口投藥之調配物相同的醫藥學上可接受之物質且藉由相同方法製造。

適合於經直腸投藥之調配物可以單位劑量栓劑形式提供。其可藉由將活性化合物與一或多種習知固體載劑（例如可可脂）混合且接著使所得混合物成形來製備。

對於經口投藥而言，醫藥組成物可採用（例如）藉由習知方法用以下醫藥學上可接受之賦形劑製備的錠劑或膠囊形式：諸如黏合劑（例如預膠凝化玉米澱粉、聚乙烯吡咯啶酮或羥丙基甲基纖維素）；填充劑（例如乳糖、微晶纖維素或磷酸氫鈣）；潤滑劑（例如硬脂酸鎂、滑石粉或二氧化矽）；崩解劑（例如馬鈴薯澱粉或羥基乙酸澱粉鈉）；或濕潤劑（例如十二烷基硫酸鈉）。錠劑可藉由此項技術中熟知之方法來包衣。

適合於頰內（舌下）投藥之調配物包括（例如）於經

調味主劑（通常蔗糖及阿拉伯膠或黃蓍膠）中含有活性化合物的含片；及於惰性主劑（諸如明膠及甘油或蔗糖及阿拉伯膠）中含有化合物的片劑。

醫藥組成物亦可藉由受控釋放調配物及/或傳遞裝置來投予（參見例如美國專利第 3,536,809 號；第 3,598,123 號；第 3,630,200 號；第 3,845,770 號；第 3,847,770 號；第 3,916,899 號；第 4,008,719 號；第 4,687,610 號；第 4,769,027 號；第 5,059,595 號；第 5,073,543 號；第 5,120,548 號；第 5,354,566 號；第 5,591,767 號；第 5,639,476 號；第 5,674,533 號及第 5,733,566 號）。

已知各種傳遞系統且可用於投予所選基質降解酵素，諸如（但不限於）囊封於脂質體、微粒、微膠囊中，能夠表現化合物之重組細胞，受體介導之內飲作用，及傳遞編碼所選基質降解酵素之核酸分子（諸如反轉錄病毒傳遞系統）。

因此，在某些具體實例中，脂質體及/或奈米粒子亦可用於投予基質降解酵素。脂質體由分散於水性介質中且自發地形成多層微脂粒同心雙層小泡（亦稱為多層微脂粒（multilamellar vesicle，MLV））之磷脂形成。MLV 通常具有 25 nm 至 4 μm 之直徑。典型地，亦製備含有用於使奈米粒子穩定之膽固醇的脂質體。對 MLV 之超音波處理使得形成於核心中含有水性溶液、直徑在 200 埃（angstrom）至 500 埃之範圍內的單層小微脂粒（small unilamellar vesicle，SUV）。

磷脂在分散於水中時可形成不同於脂質體之多種結構，其視脂質與水之莫耳比而定。於低比率下，形成脂質體。脂質體之物理特徵視 pH 值、離子強度及二價陽離子之存在而定。脂質體可展示對離子及極性物質之低滲透性，但於高溫下經歷顯著改變其滲透性之相轉變。該相轉變涉及自稱為凝膠狀態之緊密堆積有序結構變為稱為流體狀態之疏鬆堆積有序性較小的結構。此於特徵相轉變溫度下發生且使得對離子、糖及藥物之滲透性增加。

脂質體經由不同機制與細胞相互作用：藉由網狀內皮系統之巨噬細胞（諸如巨噬細胞及嗜中性白血球）的胞吞作用；藉由非特異性弱疏水力或靜電力或藉由與細胞表面組份之特異性相互作用而吸附至細胞表面；藉由將脂質體之脂質雙層插入質膜中而與漿細胞膜融合，同時將脂質體內含物釋放至細胞質中；且藉由將脂質體脂質轉移至細胞或亞細胞膜中，或反之亦然，而無脂質體內含物之任何結合。改變脂質體調配物可改變運作之機制，但可同時運作一種以上機制。奈米膠囊通常可以穩定及可再現方式包埋化合物。為避免由細胞內聚合超負荷引起之副作用，該等超細粒子（尺寸為約 0.1 μm）應使用能夠活體內降解之聚合物來設計。本文涵蓋使用滿足此等需求之生物可降解的聚烷基-氰基丙烯酸酯奈米粒子，且該等粒子可易於製造。

4. 組合療法

本文所述之可活化的基質降解酵素及活化劑組合中之任一者可進一步與其他治療劑或藥理劑或程序一起、在其

之前、與其間歇或在其之後共調配或共投予。該等藥劑包括（但不限於）其他生物製劑、小分子化合物、分散劑、麻醉劑、血管收縮劑及手術及其組合。舉例而言，對於其他藥劑及治療可用之任何疾病或病狀（包括上文所有所例示者）而言，用於該等疾病及病狀之所選可活化的基質降解酵素及活化劑組合可與其組合使用。在另一實例中，可投予局部麻醉劑（例如利多卡因）以提供疼痛緩解。在一些實例中，該麻醉劑可與血管收縮劑組合提供以增加麻醉作用之持續時間。本文所提供之藥理劑中的任一者可與促進接近藥理劑之組織（例如在皮下投藥後）的分散劑組合。該等物質為此項技術所已知且包括（例如）可溶性葡糖胺聚糖酶（glycosaminoglycanase），諸如玻尿酸降解酵素，例如玻尿酸酶醣蛋白家族之成員（參見例如美國公開案第20050260186號及第20060104968號）。

本文所提供之可活化的基質降解酵素之組成物可與局部麻醉共調配或共投予。舉例而言，當以活化條件形式提供pH值時，需要施用局部麻醉以使與暴露於酸性pH值相關之疼痛降至最低。麻醉包括短效及持久局部麻醉藥物調配物。短效局部麻醉藥物調配物含有利多卡因或溶解於生理食鹽水或其他合適注射媒劑中的有關局部麻醉藥物。典型地，用短效局部麻醉劑進行局部麻醉持續約20-30分鐘。例示性麻醉劑包括（例如）非吸入局部麻醉劑，諸如胺布卡因（ambucaines）；阿莫卡因（amoxecaines）；阿米卡因（amylocaines）；阿托卡因（aptocaines）；阿替卡因

（articaines）；奧布卡因（benoxinates）；苄醇；苯佐卡因（benzocaines）；貝托卡因（betoxycaines）；珍尼柳酯（biphenamines）；丁吖卡因（bucricaines）；布美卡因（bumecaines）；布比卡因（bupivacaines）；布他卡因（butacaines）；胺苯丁酯（butambens）；布坦卡因（butanilicaines）；carbizocaines；氯普魯卡因（chloroprocaine）；氯丁卡因（clibucaines）；氯達卡因（clodacaines）；可卡因（cocaines）；地昔卡因（dexivacaines）；二胺卡因（diamocaines）；狄步卡因（dibucaines）；達克羅寧（dyclonines）；依魯卡因（elucaines）；依替卡因（etidocaines）；尤普羅辛（euprocins）；苯氧卡因（fexicaines）；福莫卡因（fomocaines）；海普他卡因（heptacaines）；海克卡因（hexylcaines）；羥普魯卡因（hydroxyprocaines）；羥丁卡因（hydroxytetracaines）；胺苯異丁酯（isobutambens）；凱托卡因（ketocaines）；亮胺卡因（leucinocaines）；利多卡因（lidocaines）；甲哌卡因（mepivacaines）；美普卡因（meprylcaines）；奧妥卡因（octocaines）；奧索卡因（orthocaines）；奧昔卡因（oxethacaines）；奧布卡因（oxybuprocaines）；非那卡因（phenacaines）；哌諾卡因（pinolcaines）；哌羅卡因（piperocaines）；匹多卡因（piridocaines）；聚醚醇（polidocanols）；普莫卡因（pramocaines）；丙胺卡因（prilocaines）；普魯卡因（procaines）；丙泮卡因（propanocaines）；丙哌卡因

(propipocaines)；丙氧卡因(propoxycaines)；丙美卡因(proxymetacaines)；吡咯卡因(pyrrocaines)；誇他卡因(quatacaines)；奎尼卡因(quinisocaines)；利索卡因(risocaines)；羅多卡因(rodocaines)；羅哌卡因(ropivacaines)；水楊醇(salicyl alcohols)；蘇卡因(suicaines)；丁卡因(tetracaines)；曲噴卡因(trapencaines)；及三甲卡因(trimecaines)；以及各種其他非吸入麻醉劑，諸如阿法沙龍(alfaxalones)；阿莫拉酮(amolanones)；乙苯惡啶(etoxadrols)；芬太尼(fentanyls)；氯胺酮(ketamines)；左沙屈爾(levoxadrols)；美西妥拉(methohexitals)；美索比妥(methohexitals)；咪達唑侖(midazolams)；米那索龍(minaxolones)；丙泮尼地(propanidids)；丙帕酯(propoxates)；普莫卡因(pramoxines)；丙泊酚(propofols)；瑞芬太尼(remifentanyls)；舒芬太尼(sufentanyls)；替來他明(tiletamines)；及佐拉敏(zolamine)。調配物之有效量將視特定患者、欲治療之疾病、投藥途徑及其他考慮因素而不同。該等劑量可憑經驗確定。

由於局部麻醉劑之短半衰期，因此通常需要將該等麻醉劑與血管收縮劑共投予或共調配。血管收縮劑之實例包括α腎上腺素能受體促效劑，包括兒茶酚胺及兒茶酚胺衍生物。特定實例包括(但不限於)可巴君、腎上腺素及去甲腎上腺素。舉例而言，諸如利多卡因之局部麻醉調配物可經調配以含有低濃度之腎上腺素或另一腎上腺素能受體

促效劑（諸如可巴君）。將局部麻醉劑與腎上腺素能受體促效劑組合在醫藥製劑中為常見的（參見例如，美國專利第7,261,889號及第5,976,556號）。血管收縮劑為增加麻醉劑之半衰期所必需。諸如腎上腺素之血管收縮劑刺激經注射組織中之血管上的 α-腎上腺素能受體。此具有收縮組織中之血管的作用。血管收縮使得局部麻醉劑在組織中停留更長時間，使得麻醉作用之持續時間大大增加。

通常，血管收縮劑在本文中與麻醉劑組合使用。麻醉劑及血管收縮劑可作為單一醫藥組成物之部分或作為分開的醫藥組成物之部分共同投予，只要血管收縮劑起作用收縮無論是否已投予麻醉劑之處附近的血管以使得麻醉延長即可。在一實例中，麻醉劑及血管收縮劑係以溶液形式共同投予。另外，麻醉劑及血管收縮劑可共同調配或與可活化的基質降解酵素及活化劑分開。單一調配物較佳。麻醉劑及血管收縮劑可藉由注射、藉由浸潤或藉由表面投藥（例如作為凝膠或糊狀物之部分）來投予。典型地，麻醉劑及血管收縮劑係藉由直接注入欲麻醉之部位，例如藉由皮下投藥來投予。調配物之有效量將視特定患者、欲治療之疾病、投藥途徑及其他考慮因素而不同。該等劑量可憑經驗確定。舉例而言，利多卡因之例示量為或約為 10 mg 至 1000 mg、100 mg 至 500 mg、200 mg 至 400 mg、20 mg 至 60 mg 或 30 mg 至 50 mg。所投予之利多卡因之劑量將視個體及投藥途徑而不同。腎上腺素可以諸如 10 μg 至 5 mg、50 μg 至 1 mg、50 μg 至 500 μg、50 μg 至 250 μg、100 μg 至 500 μg、

200 μg 至 400 μg、1 mg 至 5 mg 或 2 mg 至 4 mg 之量投予。典型地，腎上腺素可以 1:100,000 至 1:200,000 稀釋度與利多卡因組合，其意謂 100 ml 麻醉劑含有 0.5 mg 至 1 mg 腎上腺素。所投予之體積可視欲治療之疾病及投藥途徑而調整。本文涵蓋 1-100 ml、1-50 ml、10-50 ml、10-30 ml、1-20 ml 或 1-10 ml（典型地 10-50 ml）麻醉劑/血管收縮劑調配物可經皮下投予以用於治療 ECM 介導之疾病或病狀（諸如脂肪團）。該投藥可與投予可活化的基質降解酵素及活化劑相繼、同時或間歇進行。

本文所提供之可活化的基質降解酵素之組成物亦可與分散劑共調配或共投予。該分散劑亦可與諸如麻醉劑、血管收縮劑或其他生物藥劑之其他藥理劑共調配或共投予。分散劑之實例為經由降解葡糖胺聚糖而打開間質間隙中之通道的葡糖胺聚糖酶，諸如玻尿酸降解酵素，例如玻尿酸酶。視劑量及調配物而定，此等通道可保持相對打開歷時 24-48 小時之時期。該等通道可用於促進外源性添加分子之擴散，該等分子諸如流體、小分子、蛋白質（諸如基質降解酵素）、核酸及基因治療載體及尺寸小於約 500 nm 之其他分子。另外，認為該等通道之形成可促進大量流體在間質間隙中流動，其又可促使在有時稱為「對流運輸」或簡稱為對流之過程中有效地由流體攜帶之溶質（諸如可偵測分子或其他診斷劑、麻醉劑或其他組織調節劑、藥理劑或醫藥有效藥劑或化妝品或其他美容劑）的分散或移動。該對流運輸可實質上超過分子擴散之速率及積累作用且因此

可使得治療劑或其他所投予分子更快速及有效地灌注組織。此外，當諸如基質降解酵素、麻醉劑或其他藥劑之藥劑與葡糖胺聚糖酶共調配或共投予且將兩者注入相對有限局部部位（諸如非靜脈內非經腸投藥（例如皮內、皮下、肌肉內）之部位）中或注入其他內部組織、器官或身體內之其他相對有限間隙中或周圍時，則與所投予劑量相關之流體可提供局部驅動力（亦即流體靜壓）以及較低流動阻力（藉由打開基質中之通道），其兩者皆可增加流體流動，及流體中所含之治療劑或其他分子與其之對流運輸。因此，葡糖胺聚糖酶之使用可對於改良生物可用性以及操作共調配或共投予藥劑（諸如基質降解酵素）之其他藥物動力學及/或藥效學特徵具有實質效用。

a. 玻尿酸降解酵素

葡糖胺聚糖酶之實例為玻尿酸降解酵素。玻尿酸降解酵素包括降解玻尿酸之任何酵素。例示性玻尿酸降解酵素包括（但不限於）玻尿酸酶及具有裂解玻尿酸之能力的特定軟骨素酶及裂解酶。本文所提供之組成物、組合及方法中之玻尿酸降解酵素的實例為可溶性玻尿酸降解酵素。舉例而言，葡糖胺聚糖酶之實例為玻尿酸酶。諸如玻尿酸酶之玻尿酸降解酵素為降解玻尿酸之酵素家族。藉由催化玻尿酸之水解，間質障壁之主要組份玻尿酸酶降低玻尿酸之黏度，從而增加組織滲透性。

亦稱為玻尿酸（hyaluronic acid）或玻尿酸酯之玻尿酸（hyaluronan）為廣泛分布於結締、上皮及神經組織中之非

硫酸化葡糖胺聚糖。玻尿酸為細胞外基質之基本組份及間質障壁之主要組份。藉由催化玻尿酸之水解，玻尿酸降解酵素降低玻尿酸之黏度，從而增加組織滲透性且增加非經腸投予之流體的吸收速率。因此，諸如玻尿酸酶之玻尿酸降解酵素已例如用作結合其他藥劑、藥物及蛋白質來增強其分散及傳遞之擴散劑或分散劑。

玻尿酸降解酵素用於藉由裂解玻尿酸聚合物來降解玻尿酸，該等聚合物由經由交替 β-1→4 及 β-1→3 糖苷鍵連接在一起之重複雙醣單元、D-葡糖醛酸（GlcA）及 N-乙醯基-D-葡糖胺（GlcNAc）組成。玻尿酸鏈長度可達約 25,000 個雙醣重複或更長且玻尿酸之聚合物的尺寸在活體內可在約 5,000 Da 至 20,000,000 Da 之範圍內。因此，用於所提供之用途及方法的玻尿酸降解酵素包括具有催化玻尿酸雙醣鏈或聚合物裂解之能力的任何酵素。在一些實例中，玻尿酸降解酵素裂解玻尿酸鏈或聚合物中之 β-1→4 糖苷鍵。在其他實例中，玻尿酸降解酵素催化玻尿酸鏈或聚合物中之 β-1→3 糖苷鍵的裂解。

i. 玻尿酸酶

存在三種玻尿酸酶大體類別：哺乳動物型玻尿酸酶（EC 3.2.1.35），其為內-β-N-乙醯基己醣胺酶，其中四醣及六醣作為主要終產物；降解玻尿酸及在各種程度上降解硫酸軟骨素（CS）及硫酸皮膚素（DS）之細菌玻尿酸酶（EC 4.2.99.1），其為藉由 β 消去反應操作之內-β-N-乙醯基己醣胺酶，主要產生雙醣終產物；及來自水蛭、其他寄生蟲及

甲殼動物之玻尿酸酶 EC3.2.1.36），其為經由水解 β-1-3 鍵聯而產生四醣及六醣終產物的內-β-葡萄糖苷酸酶（glucuronidase）。

1）哺乳動物型玻尿酸酶

哺乳動物型玻尿酸酶具有水解與轉糖苷酶兩種活性，且可降解玻尿酸及硫酸軟骨素（CS），通常為 C4-S 及 C6-S。此類型之玻尿酸酶包括（但不限於）來自母牛（牛類）（SEQ ID NO:237、266 及 272 及 BH55）（美國專利第 5,747,027 號及第 5,827,721 號）、綿羊（家綿羊（ovis aries））（SEQ ID NO:252、267、271 及 272）、黃蜂（SEQ ID NO:238 及 239）、蜜蜂（SEQ ID NO:240）、白臉大黃蜂（SEQ ID NO:241）、胡蜂（SEQ ID NO:242）、小鼠（SEQ ID NO:243-245、257）、豬（SEQ ID NO:246、247）、大鼠（SEQ ID NO:248 - 250、256）、兔（SEQ ID NO:251）、猩猩（SEQ ID NO:253）、獼猴（SEQ ID NO:254）、豚鼠（SEQ ID NO:255）之玻尿酸酶及人類玻尿酸酶。本文所提供之組成物、組合及方法中之玻尿酸酶的實例為可溶性玻尿酸酶。

人類基因組中存在 6 種玻尿酸酶樣基因：HYAL1（SEQ ID NO:262）、HYAL2（SEQ ID NO: 263）、HYAL3（SEQ ID NO:264）、HYAL4（SEQ ID NO:265）及 PH20/SPAM1（SEQ ID NO:232）。在玻尿酸酶中，PH20 為原型中性活性酵素，而其他玻尿酸酶對玻尿酸或任何已知受質不展現催化活性，或僅於 pH 值條件下具活性。玻尿酸酶類酵素之特徵亦可為通常經由糖基磷脂醯肌醇錨鎖定於質膜者（諸如人類

HYAL2及人類PH20）（Danilkovitch-Miagkova,等人 (2003) Proc Natl Acad Sci USA. 100(8):4580-5），及通常可溶者（諸如人類HYAL1）（Frost等人, (1997) Biochem Biophys Res Commun. 236(1):10-5）。一些玻尿酸酶之N-連接型糖基化對於其催化活性及穩定性可極其重要。雖然改變修飾醣蛋白之聚糖的類型可對蛋白質之抗原性、結構摺疊、溶解度及穩定性具有顯著影響，但並不認為許多酵素之最佳酵素活性需要糖基化。因此，在此方面玻尿酸酶為獨特的，因為N-連接型糖基化之移除會導致玻尿酸酶活性近乎完全失活。對於該等玻尿酸酶而言，N-連接聚糖之存在對於產生活性酵素至關重要。

因此，哺乳動物玻尿酸酶可進一步再分為主要見於睪丸提取物中之具中性活性者及主要見於諸如肝之器官中之具酸性活性者。例示性中性活性玻尿酸酶包括PH20，其包括（但不限於）來源於諸如羊類（SEQ ID NO:267）、牛類（SEQ ID NO:266）及人類（SEQ ID NO:232）之不同物種之PH20。

人類PH20（亦稱為精子表面蛋白PH20）天然參與精子-卵子黏著且藉由消化玻尿酸而幫助精子穿透卵丘細胞層。PH20 mRNA轉錄物（對應於SEQ ID NO:224中所闡明之序列的核苷酸1058-2503）通常經轉譯產生於N-末端含有35個胺基酸之信號序列（胺基酸殘基位置1-35）及於C-末端含有19個胺基酸之GPI錨（對應於胺基酸殘基491-509）的509個胺基酸之前軀體蛋白質。前軀體序列闡明於SEQ

ID NO:232 中。亦存在於 SEQ ID NO:224 中所闡明之胺基酸序列的核苷酸位置 2188 處含有 C 至 T 之突變的 mRNA 轉錄物且其為產生 SEQ ID NO:232 中所闡明之轉譯產物的沉默突變。因此，成熟 PH20 為 SEQ ID NO:233 中所闡明之 474 個胺基酸的多肽。於 SEQ ID NO:232 中所例示之人類 PH20 的 N82、N166、N235、N254、N368、N393、N490 處存在玻尿酸酶活性所需之潛在 N-連接型糖基化位點。在半胱胺酸殘基 C60 與 C351 之間及在 C224 與 C238 之間（對應於 SEQ ID NO:232 中所闡明之胺基酸）形成二硫鍵以形成核心玻尿酸酶域。然而，中性酵素催化活性需要羧基末端具有額外半胱胺酸以使得 SEQ ID NO:232 之胺基酸 36 至 464 含有活性最小之人類 PH20 玻尿酸酶域。

牛類 PH20 為 553 個胺基酸之前軀體多肽（SEQ ID NO:266）。牛類 PH20 與人類 PH20 之比對僅展示弱同源性，其中由於牛類多肽中不存在 GPI 錨，故自胺基酸 470 至各別羧基末端存在多個間隙（參見例如，Frost GI (2007) *Expert Opin. Drug. Deliv.* 4: 427-440）。預計在除人類外之其他 PH20 種類中無明顯 GPI 錨。舉例而言，由羊類及牛類產生之 PH20 多肽以可溶性形式存在。儘管存在極鬆散地連接於質膜之牛類 PH20，但其並不經由磷脂酶敏感性錨來錨定（Lalancette 等人 (2001) *Biol Reprod.* 65(2):628-36）。牛類玻尿酸酶之此獨特特性已允許使用可溶性牛類睾丸玻尿酸酶酵素以提取物形式供臨床使用（Wydase™、Hyalase™）。

2）細菌玻尿酸酶

細菌玻尿酸酶（EC 4.2.2.1 或 EC 4.2.99.1）降解玻尿酸及在各種程度上降解硫酸軟骨素及硫酸皮膚素。自細菌分離之玻尿酸解離酶因其作用方式而不同於玻尿酸酶（來自其他來源，例如玻尿酸葡糖胺酶（hyaluronoglucosaminidases）、EC 3.2.1.35）。其為催化玻尿酸中之 N-乙醯基-β-D-葡糖胺與 D-葡糖醛酸殘基之間的β1→4-糖苷鍵之消去反應、而非水解反應之內-β-N-乙醯基己醣胺酶，產生 3-(4-脫氧-β-D-糖-4-烯醛酸基)-N-乙醯基-D-葡糖胺四醣及六醣及雙醣終產物。該反應使得形成於其非還原性末端處具有不飽和己糖醛酸殘基之寡醣。

用於所提供之組成物、組合及方法中之來自細菌的例示性玻尿酸酶包括（但不限於）微生物中之玻尿酸降解酵素，該等微生物包括節桿菌屬（*Arthrobacter*）、蛭弧菌屬（*Bdellovibrio*）、梭狀芽胞桿菌屬（*Clostridium*）、微球菌屬（*Micrococcus*）、鏈球菌屬（*Streptococcus*）、消化球菌屬（*Peptococcus*）、丙酸桿菌屬（*Propionibacterium*）、擬桿菌屬（*Bacteroides*）及鏈黴菌屬（*Streptomyces*）之菌株。該等酵素之特定實例包括（但不限於）節桿菌屬（*Arthrobacter sp.*）（菌株 FB24）（SEQ ID NO:275）、噬菌蛭弧菌（*Bdellovibrio bacteriovorus*）（SEQ ID NO:276）、痤皰丙酸桿菌（*Propionibacterium acnes*）（SEQ ID NO:277）、無乳鏈球菌（*Streptococcus agalactiae*）（SEQ ID NO:278）；18RS21（SEQ ID NO:279）；血清型 Ia（SEQ ID NO:280）；

血清型 III（SEQ ID NO:281），金黃色葡萄球菌（Staphylococcus aureus）（菌株 COL（SEQ ID NO:282）；菌株 MRSA252（SEQ ID NO:283 及 284）；菌株 MSSA476（SEQ ID NO:285）；菌株 NCTC 8325（SEQ ID NO:286）；菌株牛類 RF122（SEQ ID NO:287 及 288）；菌株 USA300（SEQ ID NO:289）、肺炎鏈球菌（*Streptococcus pneumoniae*）（SEQ ID NO:290）；菌株 ATCC BAA-255/R6（SEQ ID NO:291）；血清型 2，菌株 D39/NCTC 7466（SEQ ID NO:292）、化膿鏈球菌（*Streptococcus pyogenes*）（血清型 M1）（SEQ ID NO:293）；血清型 M2，菌株 MGAS10270（SEQ ID NO:294）；血清型 M4，菌株 MGAS10750（SEQ ID NO:295）；血清型 M6（SEQ ID NO:296）；血清型 M12，菌株 MGAS2096（SEQ ID NO:297 及 298）；血清型 M12，菌株 MGAS9429（SEQ ID NO:299）；血清型 M28（SEQ ID NO:300）；豬鏈球菌（*Streptococcus suis*）（SEQ ID NO:301 - 303）；費氏弧菌（*Vibrio fischeri*）（菌株 ATCC 700601/ES114（SEQ ID NO:304）），及鏈黴菌（*Streptomyces hyaluronolyticus*）玻尿酸酶酵素，其對玻尿酸具特異性且並不裂解軟骨素或硫酸軟骨素（Ohya, T.及 Kaneko, Y. (1970) *Biochim. Biophys. Acta* 198:607）。

3）來自水蛭、其他寄生蟲及甲殼動物之玻尿酸酶

來自水蛭、其他寄生蟲及甲殼動物之玻尿酸酶（EC 3.2.1.36）為產生四醣及六醣終產物之內-β-葡萄糖醛酸酶。此等酵素催化玻尿酸酯中之 β-D-葡萄糖醛酸與 N-乙醯基

-D-葡糖胺殘基之間的 β1→3-鍵之水解。來自水蛭之例示性玻尿酸酶包括（但不限於）來自以下各科之玻尿酸酶：水蛭科（Hirudinidae）（例如醫蛭（*Hirudo medicinalis*））、石蛭科（Erpobdellidae）（例如 *Nephelopsis obscura* 及斑點石蛭（*Erpobdella punctata*））、舌蛭科（Glossiphoniidae）（例如 *Desserobdella picta*、靜澤蛭（*Helobdella stagnalis*）、平扁舌蛭（*Glossiphonia complanata*）、潤飾盾蛭（*Placobdella ornata*）及晶蛭屬（*Theromyzon sp.*））及黃蛭科（Haemopidae）（黃蛭（*Haemopis marmorata*））（Hovingh 等人 (1999) *Comp Biochem Physiol B Biochem Mol Biol.* 124(3):319-26）。具有與水蛭玻尿酸酶相同之作用機制的來自細菌之一例示性玻尿酸酶為來自藍細菌（cyanobacteria）、聚球藻屬（Synechococcus sp.）（菌株 RCC307，SEQ ID NO:305）之玻尿酸酶。

ii. 其他玻尿酸降解酵素

除玻尿酸酶家族外，在所提供之組成物、組合及方法中可結合可活化的基質降解酵素使用其他玻尿酸降解酵素。舉例而言，可使用具有裂解玻尿酸之能力的酵素，包括特定軟骨素酶及裂解酶。可降解玻尿酸之例示性軟骨素酶包括（但不限於）軟骨素 ABC 解離酶（亦稱為軟骨素酶 ABC）、軟骨素 AC 解離酶（亦稱為硫酸軟骨素解離酶或硫酸軟骨素消除酶）及軟骨素 C 解離酶。產生及純化用於所提供之組成物、組合及方法中之該等酵素的方法為此項技術所已知（例如美國專利第 6,054,569 號；Yamagata,等人

(1968) *J. Biol. Chem.* 243(7):1523-1535；Yang 等人 (1985) *J. Biol. Chem.* 160(30):1849-18570)。

軟骨素-ABC 解離酶含有兩種酵素，硫酸軟骨素-ABC 內解離酶（EC 4.2.2.20）及硫酸軟骨素-ABC 外解離酶（EC 4.2.2.21）（Hamai 等人 (1997) *J Biol Chem.* 272(14):9123-30)，其降解硫酸軟骨素及硫酸皮膚素類型之多種葡糖胺聚糖。硫酸軟骨素、硫酸軟骨素蛋白聚糖及硫酸皮膚素為硫酸軟骨素-ABC 內解離酶之較佳受質，但該酵素亦可以較低速率作用於玻尿酸。硫酸軟骨素-ABC 內解離酶降解硫酸軟骨素及硫酸皮膚素類型之多種葡糖胺聚糖，產生不同大小之 Δ4-不飽和寡醣的混合物，其最終降解為 Δ4-不飽和四醣及雙醣。硫酸軟骨素-ABC 外解離酶具有相同受質特異性，但移除來自由硫酸軟骨素-ABC 內解離酶所產生之兩種聚合硫酸軟骨素及其寡醣片段之非還原末端的雙醣殘基（Hamai, A. 等人 (1997) *J. Biol. Chem.* 272:9123-9130)。例示性硫酸軟骨素-ABC 內解離酶及硫酸軟骨素-ABC 外解離酶包括（但不限於）來自普通變形桿菌及肝素黃桿菌者（普通變形桿菌硫酸軟骨素-ABC 內解離酶闡明於 SEQ ID NO:306 中（Sato 等人 (1994) *Appl. Microbiol. Biotechnol.* 41(1):39-46))。

軟骨素 AC 解離酶（EC 4.2.2.5）對硫酸軟骨素 A 及 C、軟骨素及玻尿酸具活性，但對硫酸皮膚素（硫酸軟骨素 B）無活性。來自細菌之例示性軟骨素酶 AC 酵素包括（但不限於）來自肝素黃桿菌及食物穀菌（分別在 SEQ ID NO:307

及 308 中闡明）以及金黃節桿菌者（Tkalec 等人 (2000) *Applied and Environmental Microbiology* 66(1):29-35；Ernst 等人 (1995) *Critical Reviews in Biochemistry and Molecular Biology* 30(5):387-444）。

軟骨素酶 C 裂解硫酸軟骨素 C，產生四糖加不飽和 6-硫酸化雙醣（ΔDi-6S）。其亦裂解玻尿酸，產生不飽和非硫酸化雙醣（ΔDi-OS）。來自細菌之例示性軟骨素酶 C 酵素包括（但不限於）來自鏈球菌及黃桿菌者（Hibi 等人 (1989) *FEMS-Microbiol-Lett.* 48(2):121-4；Michelacci 等人 (1976) *J. Biol. Chem.* 251:1154-8；Tsuda 等人 (1999) *Eur. J. Biochem.* 262:127-133）。

iii. 可溶性玻尿酸降解酵素

包括可溶性玻尿酸酶之可溶性玻尿酸降解酵素可用於本文所提供之方法、組合或組成物中以與基質降解酵素、活化劑、麻醉劑、血管收縮劑、其他藥理劑或治療劑或其組合共投予或共調配，以允許擴散至組織中。可溶性玻尿酸降解酵素包括以可溶性形式存在之任何玻尿酸降解酵素，其包括（但不限於）諸如牛類 PH20 及羊類 PH20 之玻尿酸酶、其對偶基因變異體及其他變異體。在可溶性玻尿酸降解酵素中亦包括已經修飾為可溶性之任何玻尿酸降解酵素。舉例而言，含有 GPI 錨之玻尿酸降解酵素可藉由截短及移除 GPI 錨之全部或一部分而變得可溶。在一實例中，通常經由 GPI 錨錨定於膜之人類玻尿酸酶 PH20 可藉由於 C-末端處截短及移除 GPI 錨之全部或一部分而變得可溶。

可溶性玻尿酸降解酵素亦包括中性活性及酸性活性玻尿酸酶。視諸如（但不限於）投藥後酵素之所需活性程度及/或投藥位點而定，可選擇中性活性及酸性活性玻尿酸酶。在一特定實例中，用於組成物、組合及方法中之玻尿酸降解酵素為可溶性中性活性玻尿酸酶。

可溶性玻尿酸酶之實例為來自任何物種之PH20，諸如SEQ ID NO:232、233、266、251、267、255、257、271-274中之任一者中所闡明之任何玻尿酸酶，或其缺乏C-末端GPI錨之全部或一部分的截短形式，只要玻尿酸酶為可溶性的且保留玻尿酸酶活性即可。在可溶性玻尿酸酶中亦包括SEQ ID NO:232、233、266、251、267、255、257、271-274或其截短形式之對偶基因變異體或其他變異體。對偶基因變異體及其他變異體為熟習此項技術者所已知，且包括與SEQ ID NO:232、233、266、251、267、255、257、271-274中之任一者或其截短形式具有60%、70%、80%、90%、91%、92%、93%、94%、95%或更高序列一致性的多肽。

典型地，對於用於本文之組成物、組合及方法中而言，使用可溶性人類PH20。儘管可使用來自其他動物之PH20，但因為其為動物蛋白質，所以該等製劑潛在地具免疫原性。舉例而言，高比例之患者顯示繼發於攝取食物之先敏化，且因為其為動物蛋白質，所以所有患者均具有隨後敏化之危險。因此，非人類製劑可能不適合於長期使用。若需要非人類製劑，則本文涵蓋該等多肽可製備為具有降低之免疫原性。該等修改在熟習此項技術者之技藝範圍內且

可包括（例如）移除及/或置換分子上之一或多個抗原性抗原決定基。

用於本文之方法中的包括玻尿酸酶（例如 PH20）之玻尿酸降解酵素可重組產生或可自天然來源（諸如自睾丸提取物）純化或部分純化。本文其他地方提供產生重組蛋白質（包括重組玻尿酸降解酵素）之方法且其為此項技術所熟知。

1） 可溶性人類 PH20

舉例而言，已產生可溶性形式之重組人類 PH20 且其可用於本文所述之方法中以與基質降解酵素、活化劑、麻醉劑、血管收縮劑、其他藥理劑或治療劑或其組合共投藥或共調配，以允許擴散至組織中。該等可溶性形式之 PH20 的產生描述於相關申請案第 11/065,716 號及第 11/238,171 號及以下實施例 12-15 中。可溶性形式包括（但不限於）具有 C-末端截短以產生含有 SEQ ID NO:232 中所闡明之胺基酸序列之胺基酸 1 至胺基酸 347、372、394、413、430、447、467、477、478、479、480、481、482 及 483 的多肽之任何形式。當表現於哺乳動物細胞中時，35 個胺基酸之 N-末端信號序列在加工期間裂解，且分泌蛋白質之成熟形式。因此，成熟可溶性多肽含有 SEQ ID NO:232 之胺基酸 36 至 347、372、394、413、430、447、467、477、478、479、480、481、482 及 483。結束於胺基酸位置 477 至 483（對應於 SEQ ID NO:232 中所闡明之前軀體多肽）的缺失突變體展現高於全長 GPI 錨定形式之分泌性玻尿酸酶活性。因

此，可溶性形式包括（但不限於）具有 C-末端截短以產生含有 SEQ ID NO 226-231 中之任一者中分別闡明之胺基酸序列的胺基酸 1 至胺基酸 442、443、444、445、446 及 447 之多肽的任何形式，或其對偶基因或物種變異體或其他變異體。通常，使用促進正確 N-糖基化以確保多肽保留活性之蛋白質表現系統來產生可溶性形式之 PH20，因為糖基化對於玻尿酸酶之催化活性及穩定性而言至關重要。該等細胞包括（例如）中國倉鼠卵巢（CHO）細胞（例如 DG44 CHO 細胞）。

2） rHuPH20

已產生重組可溶性形式之人類PH20且可使用本文所述之方法產生及純化。該等可溶性形式之重組人類 PH20 的產生描述於相關申請案第 11/065,716 號及第 11/238,171 號及以下實施例 12-15 中。該多肽之實例為自編碼 SEQ ID NO:225 中所闡明之胺基酸 1-482 的核酸分子產生者。此 PH20 之產生、製備及純化描述於以下實施例 12-15 中。由於產生及純化之後培養基中存在肽酶，故所得經純化之 rHuPH20 可為異質的。當產生於培養基中時，於 C-末端處存在異質性從而稱為 rHuPH20 之產物包括可包括各種量之 SEQ ID NO. 226 -231 之任一或多者的物質之混合物。通常，使用促進正確 N-糖基化以確保多肽保留活性之蛋白質表現系統產生可溶性形式之 PH20（諸如 rHuPH20），因為糖基化對於玻尿酸酶之催化活性及穩定性而言至關重要。該等細胞包括（例如）中國倉鼠卵巢（CHO）細胞（例如

DG44 CHO 細胞）。

諸如任何玻尿酸酶（尤其可溶性 PH20，諸如 rHuPH20）之玻尿酸降解酵素可藉由如本文其他地方所述之任何合適之途徑來投予。典型地，投藥係藉由非經腸投藥進行，諸如藉由皮內、肌肉內、皮下或血管內投藥進行。本文所提供之化合物可經調配用於藉由注射（例如藉由快速注射或連續輸注）進行非經腸投藥。用於注射之調配物可以添加防腐劑之單位劑型提供，例如於安瓶中或於多劑量容器中。組成物可為於油性或水性媒劑中之懸浮液、溶液或乳液，且可含有調配劑，諸如懸浮劑、穩定劑及/或分散劑。或者，活性成份可呈粉末形式以在使用之前用合適媒劑（例如無菌無熱原質水或其他溶劑）復水。舉例而言，本文提供呈經穩定溶液或懸浮液或凍乾形式之含有有效量之可溶性 PH20 的非經腸調配物，諸如 10 單位至 500,000 單位、100 單位至 100,000 單位、500 單位至 50,000 單位、1000 單位至 10,000 單位、5000 單位至 7500 單位、5000 單位至 50,000 單位或 1,000 單位至 10,000 單位，通常為 10,000 單位至 50,000 單位。該等調配物可以單位劑型提供，諸如（但不限於）安瓶、注射器及個別包裝之錠劑或膠囊。該分散劑可單獨投予，或以 1-100 ml、1-50 ml、10-50 ml、10-30 ml、1-20 ml 或 1-10 ml（典型地 10-50 ml）之總體積與其他藥理學有效藥劑一起投予。

在組合療法之一實例中，本文涵蓋將麻醉劑、血管收縮劑及分散劑與可活化的基質降解酵素及/或活化劑共投予

或共調配，該可活化的基質降解酵素及/或活化劑欲與其相繼、同時或間歇投予。一例示性調配物為含有利多卡因、腎上腺素及可溶性 PH20 之調配物，例如 SEQ ID NO:226 中所闡明之可溶性 PH20。可溶性 PH20 可直接與利多卡因（木卡因（Xylocaine））混合，且視情況與腎上腺素混合。該調配物可以單位劑型製備，諸如於注射器中。舉例而言，利多卡因/腎上腺素/可溶性 PH20 調配物可以諸如 1-100 ml、1-50 ml、10-50 ml、10-30 ml、1-20 ml 或 1-10 ml（典型地 10-50 ml）之體積提供，預先包裝於注射器中以供使用。

在組合療法中，諸如利多卡因/腎上腺素/可溶性 PH20 調配物之其他藥理學藥劑可與可活化的基質降解酵素（及活化劑）一起共投予或與可活化的基質降解酵素（及活化劑）之投予在時間上極接近地共投予。典型地，較佳麻醉劑及/或分散劑在藥理劑之前不久（例如之前 5 至 60 分鐘）或出於最大方便性與其一起投予。如熟習此項技術者應瞭解，共投藥之所需接近度在很大程度上視在特定組織環境中藥劑之有效半衰期及所治療之特定疾病而定，且可易於藉由在合適模型中（諸如在合適動物模型中）測試以不同時間投予藥劑之作用來優化。

iv. 修飾玻尿酸降解酵素以改良其藥物動力學性質

玻尿酸降解酵素可經修飾以改良其藥物動力學性質，諸如增加其活體內半衰期及/或活性。對用於所提供之組成物、組合及/或方法中之玻尿酸降解酵素的修飾可包括直接或經由連接子、諸如葡聚糖、聚乙二醇（聚乙二醇化(PEG)）

或唾液酸基部分之聚合物或諸如天然或糖聚合物之其他此類聚合物間接連接（諸如共價或藉由其他穩定鍵聯）。

已知治療劑之聚乙二醇化增加對蛋白水解之抵抗力，增加血漿半衰期，且降低抗原性及免疫原性。因此諸如聚乙二醇部分（PEG）之聚合分子之共價或其他穩定連接（接合）於玻尿酸降解酵素可賦予所得酵素-聚合物組成物有益性質。該等性質包括改良之生物相容性，蛋白質（及酵素活性）在血液、細胞及/或在個體體內之其他組織中半衰期延長，有效保護蛋白質以免蛋白酶作用及水解，生物分布改良，藥物動力學及/或藥效學增強，及水溶性增加。

可與玻尿酸降解酵素接合之例示性聚合物包括天然及合成均聚物，諸如多元醇（亦即 poly-OH）、多元胺（亦即 poly-NH_2）及聚羧酸（亦即 poly-COOH），且進一步包括雜聚物，亦即包含一或多種不同偶合基團（例如羥基及胺基）之聚合物。合適聚合分子的實例包括選自以下各物之聚合分子：聚伸烷基氧化物（polyalkylene oxide，PAO），諸如聚伸烷基二醇（polyalkylene glycol，PAG），包括聚丙二醇（polypropylene glycol，PEG）、甲氧基聚乙二醇（methoxypolyethylene glycol，mPEG）及聚丙二醇；PEG-縮水甘油醚（Epox-PEG）；PEG-氧羰基咪唑（CDI-PEG）；支鏈聚乙二醇（PEG）；聚乙烯醇（polyvinyl alcohol，PVA）；聚羧酸酯；聚乙烯吡咯啶酮；聚-D,L-胺基酸；聚乙烯-共-順丁烯二酸酐；聚苯乙烯-共-順丁烯二酸酐；葡聚糖，包括羧甲基-葡聚糖；肝素；同源白蛋白；纖維素，包括甲基纖

維素、羧甲基纖維素、乙基纖維素、羥乙基纖維素、羧乙基纖維素及羥丙基纖維素；聚葡萄胺糖（chitosan）之水解物；澱粉，諸如羥乙基-澱粉及羥丙基-澱粉；糖原；瓊脂糖及其衍生物；瓜爾膠（guar gum）；支鏈澱粉；菊糖；三仙膠（xanthan gum）；角叉菜膠；果膠；海藻酸水解物及生物聚合物。

典型地，該等聚合物為聚伸烷基氧化物（PAO），諸如聚氧化乙烯，諸如 PEG，典型地為 mPEG，與諸如葡聚糖、支鏈澱粉及其類似物之多醣相比，其具有能夠交聯之反應性更小的基團。典型地，該等聚合物為無毒聚合分子，諸如(m)聚乙二醇（mPEG），其可使用相對簡單化學與玻尿酸降解酵素（例如與蛋白質表面上之連接基團）共價接合。

適合於連接於玻尿酸降解酵素之聚合分子包括（但不限於）聚乙二醇（PEG）及 PEG 衍生物，諸如甲氧基-聚乙二醇（mPEG）、PEG-縮水甘油醚（Epox-PEG）、PEG-氧羰基咪唑（CDI-PEG）、支鏈 PEG 及聚氧化乙烯（PEO）（參見例如，Roberts 等人, Advanced Drug Delivery Review 2002, 54: 459-476；Harris 及 Zalipsky, S (eds.)「Poly(ethylene glycol), Chemistry and Biological Applications」ACS Symposium Series 680, 1997；Mehvar 等人, *J. Pharm. Pharmaceut. Sci.*, 3(1):125-136, 2000；Harris, Nature Reviews 2:215 以及下列等等 (2003)；及 Tsubery, *J Biol. Chem* 279(37):38118-24, 2004）。該聚合分子可具有典型地範圍為約 3 kDa 至約 60 kDa 之分子量。在一些具體實例中，

與蛋白質（諸如 rHuPH20）接合之聚合分子具有 5 kDa、10 kDa、15 kDa、20 kDa、25 kDa、30 kDa、35 kDa、40 kDa、45 kDa、50 kDa、55 kDa、60 kDa 或大於 60 kDa 之分子量。

藉由共價連接（接合）PEG 或 PEG 衍生物（亦即「聚乙二醇化（PEGylation）」）來修飾多肽之各種方法為此項技術所已知（參見例如，美國專利第 5,672,662 號及 US 6,737,505；及美國公開案第 2006/0104968 號及第 2004/0235734 號）。聚乙二醇化之技術包括（但不限於）指定連接子及偶合化學（參見例如，Harris, *Adv. Drug Deliv. Rev.* 54:459-476, 2002）、使多個 PEG 部分連接於單一接合位點（諸如經由使用支鏈 PEG；參見例如，Veronese 等人, *Bioorg. Med. Chem. Lett.* 12:177-180, 2002）、位點特異性聚乙二醇化及/或單聚乙二醇化（參見例如，Chapman 等人, *Nature Biotech.* 17:780-783, 1999）及定點酶促聚乙二醇化（參見例如，Sato, *Adv. Drug Deliv. Rev.*, 54:487-504, 2002）（亦參見例如，Lu 及 Felix (1994) *Int. J. Peptide Protein Res.* 43:127-138；Lu 及 Felix (1993) *Peptide Res.* 6:142-6, 1993; Felix 等人 (1995) *Int. J. Peptide Res.* 46:253-64；Benhar 等人 (1994) *J. Biol. Chem.* 269:13398-404；Brumeanu 等人 (1995) *J Immunol.* 154:3088-95；亦參見 Caliceti 等人 (2003) *Adv. Drug Deliv. Rev.* 55(10):1261-77 及 Molineux (2003) *Pharmacotherapy* 23 (8 Pt 2):3S-8S）。此項技術中所述之方法及技術可製備具有 1、2、3、4、5、6、7、8、9、10 個或大於 10 個連接於單一蛋白質分子之 PEG 或 PEG 衍生物

的蛋白質（參見例如，美國公開案第 2006/0104968 號）。

用於聚乙二醇化之諸多試劑已在此項技術中描述。該等試劑包括（但不限於）經 N-羥基丁二醯亞胺基（N-hydroxysuccinimidyl，NHS）活化之 PEG、丁二醯亞胺基 mPEG、mPEG2-N-羥基丁二醯亞胺、mPEG 丁二醯亞胺基 α-甲基丁酸酯、mPEG 丁二醯亞胺基丙酸酯、mPEG 丁二醯亞胺基丁酸酯、mPEG 羧甲基 3-羥基丁酸丁二醯亞胺基酯、同雙官能 PEG-琥珀醯亞胺基丙酸酯、同雙官能 PEG 丙醛、同雙官能 PEG 丁醛、PEG 順丁烯二醯亞胺、PEG 醯肼、對硝基苯基-碳酸酯 PEG、mPEG-苯并三唑碳酸酯、丙醛 PEG、mPEG 丁醛、支鏈 mPEG2 丁醛、mPEG 乙醯基、mPEG 哌啶酮、mPEG 甲基酮、mPEG「無連接子」順丁烯二醯亞胺、mPEG 乙烯碸、mPEG 硫醇、mPEG 鄰吡啶基硫酯（orthopyridylthioester）、mPEG 鄰吡啶基二硫化物、Fmoc-PEG-NHS、Boc-PEG-NHS、乙烯碸 PEG-NHS、丙烯酸酯 PEG-NHS、螢光素 PEG-NHS 及生物素 PEG-NHS（參見例如，Monfardini 等人，*Bioconjugate Chem.* 6:62-69, 1995；Veronese 等人，*J. Bioactive Compatible Polymers* 12:197-207, 1997；US 5,672,662；US 5,932,462；US 6,495,659；US 6,737,505；US 4,002,531；US 4,179,337；US 5,122,614；US 5,183,550；US 5,324, 844；US 5,446,090；US 5,612,460；US 5,643,575；US 5,766,581；US 5,795, 569；US 5,808,096；US 5,900,461；US 5,919,455；US 5,985,263；US 5,990, 237；US 6,113,906；US 6,214,966；US 6,258,351；

US 6,340,742；US 6,413,507；US 6,420,339；US 6,437,025；US 6,448,369；US 6,461,802；US 6,828,401；US 6,858,736；US 2001/0021763；US 2001/0044526；US 2001/0046481；US 2002/0052430；US 2002/0072573；US 2002/0156047；US 2003/0114647；US 2003/0143596；US 2003/0158333；US 2003/0220447；US 2004/0013637；US 2004/0235734；US 2005/000360；US 2005/0114037；US 2005/0171328；US 2005/0209416；EP 01064951；EP 0822199；WO 00176640；WO 0002017；WO 0249673；WO 9428024；及 WO 0187925)。

在一實例中，用於所提供之方法、組成物及組合中之玻尿酸降解酵素為經聚乙二醇化之可溶性玻尿酸酶。在一特定實例中，該可溶性玻尿酸酶為經聚乙二醇化之 PH20 玻尿酸酶。在另一特定實例中，可溶性玻尿酸酶為經聚乙二醇化之 rHuPH20。

G. 可活化的基質降解酵素之包裝及製品

所選基質降解酵素或編碼所選基質降解酵素之核酸或其衍生物或變異體的醫藥化合物可包裝為含有包裝材料、有效治療疾病或病症之醫藥組成物及指示所選基質降解酵素或核酸分子欲用於治療疾病或病症之標籤的製品。所選基質降解酵素或其衍生物或變異體與活化劑之組合亦可包裝於製品中。

本文所提供之製品含有包裝材料。用於包裝醫藥產品之包裝材料為熟習此項技術者所熟知。參見例如，美國專利第 5,323,907 號、第 5,052,558 號及第 5,033,252 號，其中

每一者係以全文引用的方式併入本文中。醫藥包裝材料之實例包括（但不限於）發泡包裝、瓶、管、吸入器、泵、袋、小瓶、容器、注射器、瓶及適合於所選調配物及所欲投藥方式及治療之任何包裝材料。出於局部注射目的，該製品可包括針或其他注射裝置以便於投藥（例如表皮下投藥）。涵蓋本文所提供之化合物及組成物之各種調配物，以及用於任何ECM介導之疾病或病症的各種治療。

包裝之選擇視基質降解酵素及活化劑及該等組成物是否將包裝在一起或分開包裝而定。一般而言，該包裝不與其中所含之組成物反應以使可活化的基質降解酵素之活化不在添加活化劑之前發生。在一實例中，該可活化的基質降解酵素可以與活化劑之混合物形式包裝。因此，舉例而言，需要低pH值以供活化的溶酶體酵素（例如組織蛋白酶L）可以與緩衝酸性溶液之混合物形式包裝。

在另一實例中，該等組份可以分開的組成物形式包裝，此在混合之後使基質降解酵素活化。舉例而言，含有基質降解酵素之組成物可與含有活化劑（諸如經緩衝酸性溶液）之組成物分開提供，且與其一起使用。因此，在該等實例中，將可活化的基質降解酵素包裝於與活化劑分開之容器中，且在使用者願意時藉由暴露於活化劑而達成活化。暴露於活化劑可在投藥之前的任何時間藉由將活化劑添加至酵素中來進行。舉例而言，該容器可具有單一隔室，其含有基質降解酵素且經受得住使用者添加活化劑，例如經由該隔室中之開口。涵蓋經受得住具有容納基質降解酵

素之界定空間且經受得住簡單操作以允許添加活化所必需之最終組份的任何容器或其他製品。在使用之前添加該活化劑。暴露於活化劑亦可在向間質投藥之後進行。舉例而言，若熱量為活化劑，則可投予基質降解酵素且使局部注射部位經受加熱。在一替代性實例中，可向間質投予酸性緩衝溶液，接著投予基質降解酵素，例如需要酸性 pH 值來活化的任何酵素，諸如組織蛋白酶。

在其他實例中，將可活化的基質降解酵素與活化劑一起包裝於容器中，以使基質降解酵素之活化在該容器中經受使用者隨意活化。通常，該等容器之實例包括具有含有基質降解酵素之密封界定空間及含有活化劑之分開的密封界定空間的彼等容器，以使兩個空間由易於移動之膜分隔，該膜在移除之後允許組份混合且從而反應，使蛋白酶活化。涵蓋任何容器或其他製品，只要基質降解酵素與活化劑分開即可。在使用之前使活化劑暴露於基質降解酵素。舉例而言，物理分隔方法為易於由使用者移除以允許混合、使酵素活化之方法。舉例而言，製品可在一個隔室中含有基質降解酵素且在相鄰隔室中含有活化劑。該等隔室由分隔部件（諸如膜）分隔，在壓縮製品之後其破裂，允許分開之組份混合。對於合適之具體實例而言，參見例如美國專利第 3,539,794 號及第 5,171,081 號中所述之容器。

以下為可活化的基質降解酵素之各種最終用途之包裝需求的一些實例。此等實例僅作為實例提供且決不意欲作為限制。

1. 單腔室設備

在本文之最簡單具體實例中為設備含有單一腔室或容器且需要時含有噴射構件者。單腔室外殼或容器包括基質降解酵素包括於容器中之任何物品。基質降解酵素以液相或以粉末或其他糊狀物或其他習知組成物形式容納於容器中。在即將使用之前引入活化劑組份。在使用之前，添加典型地以緩衝溶液形式提供之活化劑且使其與基質降解酵素接觸以允許混合及/或基質降解酵素之復水。舉例而言，當需要時且視基質降解酵素而定，將含有 Ca^{2+}之液體，諸如於適當緩衝液或酸性緩衝溶液或含有活化條件之其他溶液中含有 Ca^{2+}的混合物添加至容器中。亦提供含有物品及活化劑之套組。

2. 雙腔室設備

用於本文中之所涵蓋之設備的一實例為雙腔室容器。一般而言，此設備具有兩個腔室或隔室，從而保持基質降解酵素與活化劑分開直至需要活化。設備可包括允許在自設備分配之前混合組份之混合腔室。或者，混合可藉由將活化劑自一個腔室噴射至含有可活化的基質降解酵素之第二腔室中來進行。舉例而言，可活化的基質降解酵素可以凍乾形式提供，且復水可藉由將諸如酸性緩衝溶液之活化劑自第一腔室噴射至該含有凍乾酵素之第二腔室中來達成。

在一具體實例中，雙腔室設備在其操作時使用機械泵機制。在該實例中，分配裝置使組份保持在分開的腔室中。

泵機制經操作以自各腔室取出內含物且置於混合腔室中，或自一個腔室取出置於第二腔室中。混合之後，藉由腔室中之組份的反應來活化經混合組成物。該泵機制可例如藉由活塞手動操作。該雙腔室設備之實例包括雙腔室注射器（參見例如，美國專利第 6,972,005 號、第 6,692,468 號、第 5,971,953 號、第 4,529,403 號、第 4,202,314 號、第 4,214,584 號、第 4,983,164 號、第 5,788,670 號、第 5,395,326 號；及國際專利申請案第 WO2007006030 號及第 WO2001047584 號）。

用於本文中之所涵蓋之雙腔室流體分配裝置的另一具體實例採用可壓縮瓶或管或其他類似裝置之形式。該裝置在其中具有保持組份分開之兩個隔室。裝置之蓋子可充當混合腔室，混合腔室可位於兩個腔室與該蓋子之間，或混合可在腔室之一者中達成。藉由壓縮將組份自分開的隔室推動至該混合腔室中。接著將其自混合腔室分配。舉例而言，可藉由使活塞/注射器設備連接於分配末端且經此取出內含物將混合之內含物自裝置移出。該等裝置為此項技術所已知（參見例如，國際專利申請案第 WO1994015848 號）。

3. 套組

所選基質降解酵素、活化劑及/或其製品亦可以套組形式提供。套組可包括本文所述之醫藥組成物及以製品形式提供之用於投藥的物品。舉例而言，所選基質降解酵素可由用於投藥之裝置供應，諸如注射器、吸入器、劑量杯、滴管或施藥器。組成物可含於用於投藥之物品中或可分開

提供以稍後添加。通常，套組含有具有基質降解酵素及含有活化條件之活化劑組成物之物品。該套組可視情況包括關於包括劑量、給藥方案之應用的說明書及關於投藥方式之說明書。套組亦可包括本文所述之醫藥組成物及用於診斷之物品。舉例而言，該等套組可包括用於量測個體體內之所選蛋白酶之濃度、量或活性的物品。

H. 評估基質降解酵素之活性的方法

1. 評估酵素活性之方法

可測試可活化的基質降解酵素之針對已知受質之酶促活性。可在活化劑存在或不存在之情況下執行活性評估。亦可於不同條件下執行活性評估，例如藉由改變用於活化之活化劑的量來執行。在一實例中，可執行 pH 值概況以測定於各種 pH 值條件下酵素之相對活性（參見例如，Dehrmann 等人 (1995) *Arch. Biochm. Biophys.*, 324:93-98）。可對條件培養基或其他上清液或經純化之蛋白質執行活性評估。

可藉由使用酵素之已知受質檢定受質裂解來評估酶促活性。該等受質可呈經純化之蛋白質的形式或以肽受質形式提供。舉例而言，組織蛋白酶 L 之酶促活性可藉由裂解經純化之蛋白質（如偶氮酪蛋白（Azocasein）、膠原蛋白、彈性蛋白、人類血清白蛋白及 rHuPH20），藉由將其個別地與 ADME 一起培養或以兩種或兩種以上經純化之蛋白質的混合物形式培養來評估。藉由酵素使經純化之蛋白質裂解可使用任何蛋白質偵測方法來評估，該方法包括（但不限

於）HPLC、CE、質譜法、SDS-PAGE 分析、ELISA、西方墨點法（Western blotting）、免疫組織化學、免疫沈澱、NH_2-末端定序及蛋白質標記。

使用受質上之螢光基團促進對裂解之偵測。舉例而言，受質可以肽受質之螢光標記四肽形式，諸如 ACC-或 7-胺基-4-甲基香豆素（AMC）-四肽提供。其他螢光基團為已知的且可使用並偶合於蛋白質或肽受質。其包括（例如）7-胺基-4-甲基-2-喹啉酮（AMeq）、2-萘胺（NHNap）及 7-胺基-4-甲基香豆素（NHMec）及螢光素-5-異硫氰酸酯（FITC）（Sarath 等人「Protease Assay Methods,」在 *Proteolytic Enzymes: A Practical Approach.* Robert J. Beynon 及 Judith S. Bond.編 Oxford University Press, 2001. 第 45-76 頁中）。肽受質為熟習此項技術者所已知，如例示性螢光肽受質。舉例而言，用於組織蛋白酶 B 之例示性受質包括 N-αBZ-Phe-Val-Arg-p-NA、DNA-Phe-Arg-Nph-Leu、Z-Ala-Arg-Arg-F^3MCA、Z-Arg-Arg-MBNA、Z-Arg-Arg-NHMec、Z-Phe-Arg-NHMec 及 Z-Leu-Arg-AMC 及其變化形式（諸如具有不同螢光基團）。在另一實例中，用於組織蛋白酶 L 之例示性受質包括 Z-Phe-Arg-NHMec 及 Z-Leu-Arg-AMC 及 Z-His-Arg-Tyr-Arg-AMC 及其變化形式（諸如具有不同螢光基團）。因此，因為組織蛋白酶 B 及組織蛋白酶 L 共用相同受質，例如 Z-Phe-Arg-NHMec 及 Z-Leu-Arg-AMC，所以組織蛋白酶 L 之活性評估可在組織蛋白酶 B 之特異性抑制劑

存在下執行。該抑制劑之實例為 CA-074。此在本文之實施例 9 中舉例說明。用於藉由螢光強度來量測酶促活性之酵素檢定為標準檢定，且典型地根據酵素及受質之培養時間來執行（參見例如，Dehrmann 等人 (1995) *Arch. Biochem. Biophys.*, 324:93-98; Barrett 等人 (1981) *Methods Enzymol.*, 80:536-561）。

雖然螢光化合物之偵測可使用螢光計完成，但偵測可藉由熟習此項技術者所熟知之多種其他方法來完成。因此，舉例而言，當螢光團發射可見波長時，偵測可簡單地藉由目測對光源激發作出反應之螢光來進行。偵測亦可藉助於使用連接於數位轉換器之視訊攝影機的圖像分析系統或其他圖像獲取系統來進行。偵測亦可藉由經由濾光器（如在螢光顯微鏡下）觀測來進行。該顯微鏡可提供由操作者簡單地觀測之信號。或者，該信號可記錄於感光膠片上或使用視訊分析系統來記錄。信號亦可簡單地使用圖像分析系統或光度計即時量化。

因此，舉例而言，用於樣品之酵素活性的基礎檢定涉及使該樣品懸浮或溶解於緩衝液中（於所檢定之特定蛋白酶的最佳 pH 值及離子強度下），將螢光酵素肽指示劑添加至該緩衝液中，且於用於培養之特定溫度下使用光譜螢光計監測產生之螢光變化，例如如 Harris 等人, (1998) *J Biol Chem* 273:27364 中所示。該光譜螢光計設定為於螢光團之激發波長下激發螢光團且於螢光團之發射波長下偵測信號。該螢光酵素指示劑為酵素之（例如蛋白酶之）由於蛋

白酶裂解指示劑而改變螢光之受質序列。酵素活性典型地根據用不同濃度之螢光受質所產生的校正曲線，以標準單位/毫升表示。

2. 評估 ECM 降解之方法

可在試管內或活體內評估基質降解酵素（包括（但不限於）上文所述者（諸如組織蛋白酶 L））對細胞外基質蛋白質之降解。用於該評估之檢定為熟習此項技術者所已知，且可用於測試多種基質降解酵素對多種細胞外基質蛋白質之活性，該等蛋白質包括（但不限於）膠原蛋白（I、II、III 及 IV）、纖維結合蛋白、玻璃連結蛋白及蛋白聚糖。

a. 試管內檢定

例示性試管內檢定包括在與基質降解酵素一起培養後評估細胞外基質蛋白質之降解產物的檢定。在一些實例中，該等檢定偵測單一特定降解產物。在其他實例中，檢定偵測多種降解產物，其一致性可能已知或可能未知。降解產物之評估可使用此項技術中熟知之方法執行，該等方法包括（但不限於）HPLC、CE、質譜法、SDS-PAGE 分析、ELISA、西方墨點法、免疫組織化學、免疫沈澱、NH_2-末端定序及蛋白質標記。細胞外基質降解產物可在與基質降解酵素一起於適當溫度下培養適量時間後例如藉由 SDS-PAGE 分析觀測。舉例而言，可將膠原蛋白與經活化之組織蛋白酶 L 一起培養且經受使用（例如）4-20% Tris/甘胺酸凝膠之 SDS-PAGE 以分離產物。對該凝膠之庫馬斯染色利於觀測與完整膠原蛋白相比較小之降解產物，或膠原

蛋白條帶之消失。使用（例如）對細胞外基質蛋白質具特異性之多株 Ig 的免疫墨點法亦可用於在用 SDS-PAGE 分離後觀測降解產物。

在降解細胞外基質蛋白質後特異性偵測單一產物之檢定亦為此項技術所已知且可用於評估基質降解酵素降解細胞外基質蛋白質之能力。舉例而言，羥基脯胺酸（HP）檢定可用於量測膠原蛋白之降解。4-羥基脯胺酸為佔膠原蛋白重量之約 12%的經修飾之亞胺基酸。HP 檢定藉由在與基質降解酵素（諸如經活化之組織蛋白酶 L）一起培養後測定上清液中之 HP 的量來量測溶解之膠原蛋白的量（參見例如以下實施例 2 及 Reddy 及 Enwemeka (1996) *Clinical Biochemistry* 29:225-229）。HP 之量測可藉由例如比色法、高效液相層析法、質譜法及酶促方法實現（參見例如，Edwards 等人, (1980) *Clin. Chim. Acta* 104:161-167；Green (1992) *Anal. Biochem.* 201:265-269；Tredget 等人, (1990) *Anal. Biochem.* 190:259-265; Ito 等人, (1985) *Anal. Biochem.* 151:510-514；Garnero 等人 (1998) *J. Biol. Chem* 273:32347-32352）。

用於該等試管內檢定中之膠原蛋白來源可包括（但不限於）市售經純化之膠原蛋白、骨顆粒、皮膚、軟骨及大鼠尾腱。諸如組織蛋白酶 L 之基質降解酵素之溶膠原活性可藉由將經活化之酵素與不溶性膠原蛋白懸浮液一起培養，接著諸如用 HCl 水解來評估。來源於溶解（降解）之膠原蛋白之羥基脯胺酸的量可在與艾利希試劑（Ehrlich's

reagent）一起培養後藉由光譜分析法來測定，諸如量測於550 nm下之吸光度。在一些實例中，膠原蛋白來源為以手術方式自麻醉動物移除且接著首先用酸性溶液且接著用基質降解酵素（諸如組織蛋白酶L）灌注之大鼠或豬皮膚外植體（參見例如以下實施例3-4）。接著可評估灌注液中之HP含量。在此方法之改良形式中，可評估例如組織蛋白酶L對外植體中之纖維中隔的作用（參見例如實施例5）。簡言之，在用基質降解酵素灌注後，將外植體切成小塊且包埋於石蠟中並在馬松三色染色（Masson's Trichrome staining）後藉由顯微術分析以觀測膠原蛋白。可觀測膠原蛋白纖維中隔之數目且與尚未用基質降解酵素處理之組織相比較。

偵測特定膠原蛋白之降解的檢定亦為此項技術所已知。該等檢定可使用免疫方法來偵測特定膠原蛋白獨有之降解產物。舉例而言，一些基質降解酵素對膠原蛋白I之降解釋放具有不同抗原決定基之端肽，其可使用免疫檢定來偵測。該等檢定偵測交聯N-端肽（NTx）及交聯C-端肽（CTx及ICTP），其中每一者均含有獨特抗原決定基。典型地，CTx檢定使用識別8個胺基酸之序列EKAHD-β-GGR八肽的CrossLaps（Nordic Biosciences）抗體，其中在α1鏈之C-末端端肽區域中天冬胺酸呈β-異構化構型（Eastell (2001) Bone Markers: Biochemical and Clinical Perspectives, 第40頁）。偵測ICTP之免疫檢定亦為此項技術所已知且可用於偵測膠原蛋白I之降解（美國專利第5,538,853號）。在其他實例中，諸如ELISA之免疫檢定可用於在將I型膠原蛋白

與蛋白酶（諸如組織蛋白酶 K、S、L 及 B）一起培養後偵測 NTx（Atley 等人, (2000) *Bone*, 26:241-247）。對於降解之膠原蛋白具特異性的其他抗體及檢定為此項技術所已知且可用於偵測由基質降解酵素進行之降解。其包括對於降解之膠原蛋白 I（Hartmann 等人 (1990) *Clin. Chem.* 36:421-426）、膠原蛋白 II（Hollander 等人 (1994) *J. Clin. Invest.* 93:1722-1732）、膠原蛋白 III（美國專利第 5,34,2756 號）及膠原蛋白 IV（Wilkinson 等人 (1990) *Anal. Biochem.* 185:294-6）具特異性的抗體及檢定。

b. 活體內檢定

偵測 ECM 之活體內降解的檢定亦為此項技術所已知。該等檢定可使用上述偵測生物樣品（諸如尿、血液、血清及組織）中之（例如）羥基脯胺酸及 N-端肽與 C-端肽及降解之膠原蛋白或其他 ECM 的方法。對降解之 ECM 的偵測可在向患者投予一或多種基質降解酵素後執行。對吡啶啉（PYD）及脫氧吡啶啉（DPYD）之偵測亦可用於評估膠原蛋白之降解。分別亦稱為羥基離胺醯基吡啶啉（hydroxylysylpyridinoline）及離胺醯基吡啶啉（lysylpyridinoline）之 PYD 及 DPYD 為兩種不可還原性三價交聯，其使 I 型膠原蛋白鏈穩定且在成熟膠原纖維之降解期間釋放。吡啶啉在骨及軟骨中豐富，而脫氧吡啶啉基本上侷限於骨中。III 型膠原蛋白於胺基末端處亦含有吡啶啉交聯。可在逆相 HPLC 後藉由螢光偵測來量測例如水解之尿樣品或血清中的總 PYD 及 DPYD（Hata 等人 (1995)

Clin.Chimica. Acta. 235:221-227)。

c. 非人類動物模型

可使用非人類動物模型來評估基質降解酵素之活性。舉例而言，非人類動物可用作疾病或病狀之模型。可在投予基質降解酵素之前給非人類動物注射疾病及/或表型誘導物質。遺傳模型亦適用。可藉由一或多種基因之過度表現、表現不足（underexpression）或剔除來產生模擬疾病或病狀之動物（諸如小鼠）。舉例而言，在此項技術中已知包括（但不限於）以下病狀之動物模型：帕榮雷氏病（Davila 等人 (2004) *Biol. Reprod.*, 71:1568-1577）、肌腱變性（Warden 等人，(2006) *Br. J. Sports Med.* 41:232-240）及硬皮病（Yamamoto (2005) *Cur. Rheum. Rev.* 1:105-109）。

亦可使用非人類動物來活體內測試非患病動物體內之基質降解酵素之活性。舉例而言，可向諸如小鼠、大鼠或豬之非人類動物投予基質降解酵素，且可測定 ECM 降解之程度。在一些實例中，使用該等動物獲得外植體以活體外評估 ECM 降解，諸如上文及以下實施例 3-5 中所述之該降解。在其他實例中，活體內評估 ECM 降解。在一實例中，評估經麻醉之大鼠之皮膚的膠原蛋白降解（參見例如以下實施例 6）。簡言之，經由將針插入尾部皮膚之真皮層中來灌注於具有 pH 5 之緩衝液中之基質降解酵素（諸如組織蛋白酶 L）。自尾部皮膚收集灌注液部分且藉由羥基脯胺酸分析來分析膠原蛋白降解。可使用其他方法來偵測降解，包括（但不限於）上述檢定中之任一者，諸如偵測特定降解

產物之免疫檢定。向皮膚投予促進最佳活性之酸性溶液（諸如含有組織蛋白酶 L 之緩衝液）之作用亦可在非人類動物模型中評估（參見例如實施例 7）。對 pH 值變化敏感之染料（諸如酚紅）可用於此等目的。

I. 治療 ECM 之疾病或缺陷的例示性方法

本文所提供之可活化的基質降解酵素可用於治療由任一或多種 ECM 組份介導之任何病狀。本部分提供可活化的基質降解酵素之例示性用途及投藥方法。此等所述療法為例示性的且並不限制酵素之應用。該等方法包括（但不限於）治療由任一或多種 ECM 組份之過量、異常或積累表現所引起的任何 ECM 病狀或疾病之方法。欲治療之疾病或病狀之實例為由膠原蛋白、彈性蛋白、纖維結合蛋白或葡糖胺聚糖（諸如蛋白聚糖）介導之任何疾病或病狀。舉例而言，膠原蛋白介導之疾病或病症之實例包括（但不限於）脂肪團、杜普宜特朗氏病（亦稱為杜普宜特朗氏攣縮）、帕榮雷氏病、凍肩、腱之慢性肌腱變性或瘢痕組織、局部硬皮病及淋巴水腫。其在治療醫師確定該等疾病或病狀之技能範圍內。

欲治療之特定疾病或病狀指定所選擇之可活化的基質降解酵素。舉例而言，膠原蛋白介導之疾病或病症的治療可藉由投予裂解膠原蛋白之基質降解酵素來實現。該等基質降解酵素列於上文表 3 中，且/或為熟習此項技術者所已知。因此可選擇可活化的基質降解酵素及用於活化之系統及方法以治療特定疾病或病狀。舉例而言，半胱胺酸及天

冬胺酸家族之組織蛋白酶可藉由如本文中所述之酸性pH值條件使得暫時具活性。因此，在一實例中，裂解膠原蛋白之組織蛋白酶（例如組織蛋白酶L）可在諸如酸性pH值之活化條件存在下投予以治療膠原蛋白介導之疾病或病狀。

用可活化的基質降解酵素治療疾病及病狀可藉由任何合適投藥途徑使用如本文中所述之合適調配物來實現，該等途徑包括（但不限於）皮下注射、肌肉內、皮內及表面與經皮投藥。如上文所述，典型地選擇使得在皮膚下方直接向受影響部位投予之可活化的基質降解酵素之投藥途徑。該等投藥途徑之實例包括（但不限於）皮下、肌肉內或皮內投藥。

必要時，特定劑量及持續時間及治療方案可憑經驗確定或推斷。舉例而言，重組及天然活性基質降解酵素或可活化的基質降解酵素之例示性劑量可用作確定適當劑量之起點。劑量水準可根據多種因素來確定，諸如個體之體重、一般健康情況、年齡、所用特定化合物之活性、性別、飲食、投藥時間、排泄速率、藥物組合、疾病之嚴重性及病程及患者患病之傾向及治療醫師之判斷。可與載劑物質組合以製備單一劑型之活性成份之量將視特定基質降解酵素、所治療之宿主、特定投藥方式及活化所需之活化條件及/或需要活化之預定時間或時間長度而不同。醫藥組成物典型地應提供約1 μg/ml至約20 mg/ml之劑量。通常，劑量為或約為每單劑量投藥10至1 mg/ml，典型地為約100 μg/ml。應瞭解投藥量將與所選可活化的基質降解酵素及活

化條件、所治療之適應症及將耐受之可能副作用有關。劑量可使用各病症之公認模型憑經驗確定。又，如本文其他地方所述，可活化的基質降解酵素可與其他藥劑組合依次、同時或間歇投予。該等藥劑之實例包括（但不限於）利多卡因、腎上腺素、諸如玻尿酸酶之分散劑及其組合。

在改善患者病狀之後，必要時可投予維持劑量之化合物或組成物；且可修改劑量、劑型、或投藥頻率或其組合。在一些情況下，在任何疾病症狀復發後，個體可能需要長期間歇治療。

以下作為ECM組份在不同疾病及病狀中之作用的實例提供對膠原蛋白與膠原蛋白介導之疾病或病狀之相關性的描述。該等描述意欲僅為例示性的且並不限於特定可活化的基質降解酵素或特定ECM介導之疾病或病狀。熟習此項技術者可根據特定酵素裂解或降解特定疾病或病狀所涉及之ECM組份之能力選擇可活化的基質降解酵素及用於其活化之活化條件，以用於治療任何所需ECM介導之疾病。特定治療及劑量可由熟習此項技術者確定。評估治療中之考慮因素包括（例如）欲治療之疾病、疾病所涉及之ECM組份、疾病之嚴重性及病程、出於預防性或治療性目的投予可活化的基質降解酵素、先前療法、患者之臨床病史及對療法之反應及主治醫師之判斷。

膠原蛋白介導之疾病或病狀

膠原蛋白為哺乳動物生物體之主要結構組份且佔皮膚及動物體之其他部分之總蛋白質含量的大部分。諸多疾病

及病狀與過量膠原蛋白沈積相關，例如由於富含膠原蛋白之纖維組織的錯誤積累或其他原因。膠原蛋白介導之疾病或病狀（亦稱為纖維變性組織病症）為熟習此項技術者所已知（參見例如，公開美國申請案第 20070224183 號；美國專利第 6,353,028 號；第 6,060,474 號；第 6,566,331 號；第 6,294,350 號）。過量膠原蛋白已與諸如（但不限於）以下疾病及病狀相關：導致瘢痕形成之纖維變性疾病或病狀、脂肪團、杜普宜特朗氏症候群、帕榮雷氏病、凍肩、局部硬皮病、淋巴水腫、間質性膀胱炎（Interstitial cystitis，IC）、毛細管擴張（Telangrectase）、巴瑞特氏化生（Barrett's metaplasia）、腸管囊腫樣氣腫（Pneumatosis cytoides intestinalis）、膠原性結腸炎。舉例而言，諸如皺紋、脂肪團形成及贅生性纖維變性之皮膚的損毀性病狀由過量膠原蛋白沈積引起，其產生正常組織結構之不當結合及變形。

可使用包括（但不限於）組織蛋白酶 L 之本文所述之可活化的基質降解酵素來治療膠原蛋白介導之疾病或病狀。用於治療本文所述之疾病及病狀之可活化的基質降解酵素之實例為於中性 pH 值下具活性且其活性需要持續酸性條件的彼等酵素。舉例而言，細胞外基質（諸如皮膚間質）之暫時性酸化可藉由於受影響部位處直接輸注經緩衝酸性溶液來達成。在一實例中，緩衝酸溶液可經由上皮下投藥（亦即皮膚下方）來投予，以使得直接於存在及積累 ECM 組份之部位處實現投藥。鑒於本文之描述，可使用其他活化方法，且其為熟習此項技術者所已知。

a. 脂肪團

諸如本文所述者之可活化的基質降解酵素（包括組織蛋白酶 L）可用於治療脂肪團。在正常脂肪組織中，血管及淋巴管之細孔供應組織必需營養物及氧，且負責代謝產物之移除。舉例而言，甘油三酯儲存於分組成富含毛細管之小葉的個別脂肪細胞中。各脂肪小葉由脂肪細胞構成。稱為纖維中隔之膠原纖維的垂直線分隔脂肪小葉且使上層淺筋膜拴連於下層肌肉。

脂肪團典型地特徵在於由血管完整性之破壞及皮膚之真皮及皮下層面中之毛細管網的損失引起之真皮退化。血管退化傾向於減少真皮代謝。此減少之代謝阻礙蛋白質合成及修復過程，其導致真皮變薄。該病狀進一步特徵在於脂肪細胞變得充滿脂質，腫脹且聚集在一起，以及過量流體滯留在皮膚之真皮及皮下區域中。脂肪小球或脂肪細胞之積累造成需要較大血液供應以提供額外營養。為了向組織提供血液，形成新毛細管，其釋放更多濾液，導致組織之間質液飽和，引起脂肪組織水腫。間質組織中豐富的網狀纖維在聚集之脂肪細胞附近積累且變厚；其形成囊或中隔，該等囊或中隔逐漸轉化為膠原纖維且感覺如節結。此等中隔之形成進一步滯留脂肪細胞。膠原纖維亦沈積於間質組織空間中，使得結締組織硬化（變硬）。

因此，當病狀進一步發展時，真皮區域中形成由中隔包圍之脂肪細胞之硬節結及脂肪之結塊。此導致皮膚表面顯示相當大的不均勻性且表徵為具有「乾酪」或「橘皮」

外觀。當使皮膚連接於真皮及較深組織層之纖維中隔收緊且拉入皮膚中時產生凹痕。因此，脂肪團之「橘皮」外觀係歸因於由對脂肪組織之外力引起的脂肪小葉之變形。脂肪小葉可例如大至 1 cm 寬，且容易突出至上層真皮中，引起皮膚表面上之明顯變形。最後結果為當將脂肪向上推時表皮出現波浪形外觀。當結締中隔在與此等向外力相同之方向上移動時，其會不提供反作用力來防止脂肪突出至真皮中。

脂肪團在女性中比在男性中更普遍。脂肪團之發生率估計在女性群體之 60%與 80%之間且其嚴重性傾向於隨肥胖惡化。最近，公開研究藉由活體內磁共振成像展示，患有脂肪團之女性的垂直纖維中隔之百分比高於未患脂肪團之女性或男性（Querleux 等人, (2002) *Skin Research and Technology*, 8:118-124）。脂肪團最常發生在臀部、大腿及上臂。舉例而言，停經前女性傾向於皮下積累脂肪，主要在脂肪團最常見之臀肌/大腿區域。臨床上，脂肪團伴隨有包括表皮變薄、導致流體皮下積累之微脈管系統的減少及破壞及脂肪組織之皮下聚集的症狀。

b. 杜普宜特朗氏病

諸如本文所述者之可活化的基質降解酵素可用於治療杜普宜特朗氏症候群（亦稱為杜普宜特朗氏攣縮）。杜普宜特朗氏攣縮（亦稱為杜普宜特朗病（Morbus Dupuytren））為手部固定性屈曲攣縮，其中手指彎向手掌且不能完全伸展。類似病變有時發生在腳部。手部之結締組織變得異常

厚且伴隨有存在含有纖維母細胞及膠原蛋白（尤其 III 型膠原蛋白）之節結。膠原蛋白之纖維索帶常常與脂肪組織之中隔樣排列交替。臨床上以不同尺寸之床墊型「團塊」存在且杜普宜特朗氏病中存在之此等物質稱為節結。此可引起手指捲曲，且會導致手指（尤其小指及無名指）之功能減弱。杜普宜特朗氏病主要在男性中出現。其通常見於中年及老年人，北歐血統者，及患有某些慢性疾病（諸如糖尿病、酒精中毒及吸煙）者中。

杜普宜特朗氏病為存在許多年之緩進型疾病，其引起手指之掌指（MP）及近端指間（PIP）關節的固定性屈曲畸形。小指及無名指最常受影響。該疾病經由三個階段進展（Luck 等人 (1959) *J. Bone Joint Surg.*, 41A:635-664）。初始增殖階段之特徵在於手掌筋膜中形成節結，其中稱為肌纖維母細胞之細胞出現且開始增殖。退化或中期疾病階段涉及肌纖維母細胞增生及活性 III 型膠原蛋白形成。在最後或剩餘階段中，節結消失，留下無細胞組織及膠原蛋白之厚條帶。III 型膠原蛋白與 I 型膠原蛋白之比率增大。用可活化的基質降解酵素治療杜普宜特朗氏病典型地在中期疾病及剩餘疾病階段中進行。

c. 帕榮雷氏病

諸如本文所述者之可活化的基質降解酵素可用於治療帕榮雷氏病。帕榮雷氏病為涉及陰莖軟組織中之纖維斑塊生長的結締組織病症，其影響多達 1-4%之男性。膠原蛋白為帕榮雷氏病中之斑塊的主要組份。具體言之，在白膜（包

圍陰莖海綿體之纖維包膜）中出現纖維化過程。與帕榮雷氏病相關之疼痛及損毀與陰莖之物理結構有關，其中發現兩個稱為海綿體（其為尿自膀胱所流經之管道（尿道））之勃起桿，及將海綿體與陰莖皮膚之外層分隔的被膜。展現帕雷榮氏病之人將在被膜與皮膚之此等外層之間（本申請案中稱為「皮下」）形成斑塊或瘢痕組織。膜之瘢痕形成或斑塊積累降低其彈性，使得在受影響區域中其不會伸展至與周圍未受影響之組織相同的程度（即使如此）。因此，勃起陰莖在瘢痕或斑塊積累之方向上彎曲，常常伴有一定程度之相關疼痛。在帕雷榮氏病之所有（但次要）表現中，患者具有一定程度之性功能障礙。在更嚴重情況下，無法進行性交，或者如此疼痛以致實際上受到阻礙。

實驗證據指示帕雷榮氏病發病率約為男性群體之 1%。儘管疾病主要出現在中年男性中，但較年輕及老年男性可患該病。約 30%患有帕雷榮氏病之男性亦在身體之其他彈性組織中（諸如手或腳上）發展纖維化（硬化細胞）。該等其他病狀之常見實例包括手部杜普宜特朗氏攣縮及腳部萊德豪斯纖維化（Ledderhose Fibrosis）。

d. 萊德豪斯纖維化

諸如本文所述者之可活化的基質降解酵素可用於治療萊德豪斯纖維化。萊德豪斯纖維化類似於杜普宜特朗氏病及帕榮雷氏病，其例外之處在於由纖維母細胞增生及膠原蛋白沈積引起之纖維化發生在腳部。萊德豪斯病之特徵在於遍及腳底內側之腳底纖維化，且有時稱為腳底纖維化。

e. 關節僵硬

諸如本文所述者之可活化的基質降解酵素可用於治療關節僵硬，例如凍肩。凍肩（黏連性關節囊炎）為關節囊之慢性纖維化病狀，其特徵在於肩部之疼痛及運動喪失或僵硬。其影響約 2%之普通群體。凍肩由纖維母細胞基質合成增加引起。該合成由導致細胞激素及生長因子過量產生之過量發炎性反應引起。纖維母細胞及肌纖維母細胞在肩部囊中沈積膠原蛋白（尤其 I 型及 III 型膠原蛋白）之稠密基質。此導致有瘢痕、收縮之肩部囊且引起關節僵硬。

關節僵硬之其他實例包括（但不限於）由囊攣縮、黏連性關節囊炎及關節纖維化引起者，其由肌肉骨骼手術引起。該等關節僵硬可發生在包括（例如）膝關節、肩關節、肘關節、踝關節及髖關節之關節。類似於凍肩，該等關節疾病由基質合成增加及瘢痕形成引起。關節僵硬不可避免地可引起異常高壓力傳輸至受影響區域之關節軟骨。隨時間，此等壓力導致發展退化性關節病及關節炎。舉例而言，在關節纖維化及囊攣縮中，纖維母細胞對局部創傷（諸如關節錯位）作出反應而形成過量基質。

f. 現有瘢痕

諸如本文所述者之可活化的基質降解酵素可用於治療現有瘢痕。膠原蛋白在創口癒合過程中及在自然老化之過程中尤其重要，其中其由成纖維細胞產生。然而，在一些情況下，過度癒合反應會導致產生大量癒合組織（基礎物質），亦稱為瘢痕組織。舉例而言，諸如灼傷、手術、感染、

創口及事故之各種皮膚創傷特徵常在於富含膠原蛋白之纖維組織的錯誤積累。常常亦存在蛋白聚糖內含物增加。除替換已損傷或破壞之正常組織外，有時在癒合過程期間形成新組織之過量及損毀性沈積。過量膠原蛋白沈積係歸因於膠原蛋白合成與膠原蛋白降解之間平衡的紊亂。瘢痕中包括（例如）腱之慢性肌腱變性或瘢痕組織、手術黏連、瘢痕瘤、肥厚性瘢痕及凹陷性瘢痕。

i. 手術黏連

手術黏連為經由瘢痕形成使器官或組織相互連接，其可引起嚴重臨床問題。手術或組織損傷後一些瘢痕組織之形成為正常的。然而，在一些情況下，瘢痕組織長滿損傷區域且造成手術黏連，其傾向於限制受影響身體部分之正常活動及功能。詳言之，纖維母細胞增生及基質合成在該軟組織損傷後局部增加。接著當身體試圖藉由誘導癒合反應來修復組織時形成黏連。舉例而言，此癒合過程可在兩種或兩種以上另外健康分開的結構之間（諸如在腹部手術後腸袢之間）發生。或者，在周邊神經局部創傷後，可形成纖維黏連，導致在正常運動期間產生劇痛。

ii. 瘢痕瘤

瘢痕瘤為含有增生塊之結締組織的瘢痕，其發生在真皮及相鄰皮下組織中，最通常在創傷後發生。瘢痕瘤通常為顏色可自粉紅色或紅色至深棕色變化之纖維狀節結。由於參與創口修復之膠原蛋白之過度生長，瘢痕組織中形成瘢痕瘤。當局部皮膚纖維母細胞對局部刺激作出反應而經

歷活躍增生及增殖時，形成瘢痕瘤病變。產生之病變會導致比初始瘢痕大許多倍之團塊。除由於創口或其他創傷而發生外，瘢痕瘤亦可因刺破、丘疹、刮傷、嚴重粉刺、水痘瘢痕形成、創口部位感染、一定區域之重複創傷或在創口閉合期間過度皮膚拉伸而形成。

iii. 肥厚性瘢痕

肥厚性瘢痕為形成於創傷部位之凸起瘢痕。其通常不會生長超過初始創口之邊界。類似於瘢痕瘤，肥厚性瘢痕為身體過度產生膠原蛋白之結果。

iv. 凹陷性瘢痕

凹陷性瘢痕通常由發炎性發作引起且特徵在於皮膚收縮，並留下美觀上不愉快及永久性之瘢痕。最常見實例為發炎性粉刺後發生之瘢痕形成。凹陷作為創口癒合之正常結果出現，且引起凹陷之瘢痕組織主要由自纖維母細胞增殖及代謝產生之膠原蛋白構成。

g. 硬皮病

諸如本文所述者之可活化的基質降解酵素可用於治療硬皮病。硬皮病之特徵在於膠原變厚。該疾病之較常見形式局部硬皮病僅影響皮膚，通常僅在少數位置，且有時在面部。其有時稱為 CREST 症候群。症狀包括皮膚硬化及相關瘢痕形成。皮膚亦呈現紅色或鱗片狀，且血管可更明顯。在更嚴重情況下，硬皮病可影響血管及內臟。彌漫性硬皮病由於心臟、腎、肺或腸道損傷而具致死性，此係歸因於肌肉骨骼、肺、胃腸、腎及其他併發症。

該病狀之特徵在於膠原蛋白累積，導致彈性喪失。膠原蛋白之過量產生係歸因於自體免疫功能障礙，導致 T 細胞積累及刺激膠原蛋白自纖維母細胞沈積之細胞激素與其他蛋白質的產生。

h. 淋巴水腫

諸如本文所述者之可活化的基質降解酵素可用於治療淋巴水腫。淋巴水腫為引起手臂及腿之腫脹的淋巴液之積累。淋巴水腫可進行至包括皮膚變化，諸如淋巴滯留性纖維化、硬化及乳頭瘤（良性皮膚腫瘤）及腫脹。與淋巴水腫相關之組織變化包括結締組織細胞（諸如纖維母細胞）之增殖、膠原纖維產生、脂肪沈積物增加及纖維變性變化。此等變化首先發生在下肢末端，亦即手指及腳趾。淋巴水腫可根據末端之腫大程度來鑑別。舉例而言，一種評估淋巴水腫之方法係根據鑑別所涉及與未涉及之末端的四個比較點之間的 2 cm 或 3 cm 差異。

i. 膠原性結腸炎

諸如本文所述者之可活化的基質降解酵素可用於治療膠原性結腸炎。膠原性結腸炎首先描述為慢性水瀉（Lindstrom 等人 (1976) Pathol. Eur., 11:87-89）。膠原性結腸炎之特徵在於膠原蛋白沈積，可能由黏膜纖維母細胞產生膠原蛋白與膠原蛋白降解之間的不平衡引起。其導致分泌性腹瀉。膠原性結腸炎之發病率類似於原發性膽汁性肝硬化。該疾病具有每 100,000 人 1.8 人之年發病率及每 100,000 人 15.7 人之發生率，其類似於原發性膽汁性肝硬化

（每 100,000 人 12.8 人）且低於潰瘍性結腸炎（每 100,000 人 234 人）、克羅恩氏病（Crohn's disease）（每 100,000 人 146 人）或乳糜瀉（每 100,000 人 5 人）。在患有慢性腹瀉之患者中，約 0.3%至 5%患有膠原性結腸炎。膠原性結腸炎為導致刺激纖維母細胞增殖之細胞激素及其他藥劑之產生增加、從而導致膠原蛋白積累增加的發炎性疾病。

J. 實施例

僅出於說明性目的包括以下實施例且其不欲限制本發明之範疇。

實施例 1

經活化之重組組織蛋白酶-L 之製備

經組胺酸（His）標籤標記之經純化重組人類組織蛋白酶-L 係購自 R&D systems（Minneapolis, MN.，目錄號 952-CY）且以 0.9 mg/mL 之濃度調配於 50 mM 乙酸鹽（pH 4.0）、100 mM NaCl 中。將 500 μL 之等分試樣儲存於-80℃下直至其使用。

在使用之前對所儲存之等分試樣執行濃縮及緩衝液交換。簡言之，將 2 mL 之 0.9 mg/mL 組織蛋白酶-L 於冰上解凍且將 500 μL 轉移至具有 30 KDa 截斷之 4 個 microcon 離心過濾膜管（Millipore；Bedford, MA，目錄號 42410）中。將該等 microcon 管於 9000 rpm 下旋轉 5 分鐘，產生 50 μl 之最終體積。將 450 μL 冷濃縮緩衝液（100 mM 甲酸鈉 pH 4、100 mM NaCl、5mM DTT、10 mM EDTA）添加至各微米管中。在加工期間添加 5 mM DTT 使組織蛋白酶-L 轉化

為如 SDS-PAGE 所評估之約 36 KDa 之單鏈蛋白質。濃縮及緩衝液交換步驟移除抑制性 10-16 KDa 前肽。另外，在濃縮及緩衝液交換期間添加之 DTT 及 EDTA 使組織蛋白酶-L 之蛋白水解降解降至最少。將離心程序重複三次。因為組織蛋白酶-L 對溫度敏感，所以冷卻管及濃縮溶液以使降解降至最少。最終旋轉後，倒置 microcon 管且藉由於 5000 rpm 下離心 5 分鐘將液體收集於保留物杯中。回收之最終體積為 400 μL，產生 5 倍濃縮。將濃縮之組織蛋白酶-L 以 67 μL 之體積等分，其含有約 300 μg 經活化之酵素。將等分試樣儲存於-80℃下，且在使用之前於冰上解凍。

在使用之前，藉由將一個等分試樣添加至 3 mL MES 緩衝溶液（2-(N-嗎啉基)乙烷磺酸）（pH 5）中來於其最佳 pH 值 5 下調配組織蛋白酶-L，產生 100 μg/mL 經活化組織蛋白酶-L 之最終濃度。作為對照，於 HEPES 緩衝液（pH 7.4）中調配組織蛋白酶-L，在該緩衝液中酵素活性最小。

實施例 2

羥基脯胺酸檢定

羥基脯胺酸檢定用於量測在用組織蛋白酶-L 灌注後皮膚樣品中之膠原蛋白含量變化。當其他蛋白質之羥基脯胺酸含量可忽略不計時，膠原蛋白含有濃度為 8%之羥基脯胺酸（TV. Burjanadze, Hydroxyproline content and location in relation to collagen thermal stability. Biopolymers 18: 4931-4938 (2002)）。所用之羥基脯胺酸（HP）檢定為 Reddy 及 Enwemeka（Clinical Biochemistry 29:225-229 (1996)）之

程序的修改形式。

詳言之，試劑之體積經修改以在 8 孔 0.2 mL 洗提管（Brandtech, Essex, CT）中於標準熱循環儀（Eppenforf Mastercycler, Westbury, NY）中完成反應。包括水解、酸化及用艾利希試劑偵測之所有步驟均在 0.2 mL 管中進行。所有化學品均購自 Sigma（St. Louis, MO）。簡言之，藉由用 5 體積之 200 標準酒度乙醇沈澱來萃取來自灌注實驗之灌注液樣品並加以離心。使用 1 mL 或 200 μL 移液管量測所收集之灌注液之體積。將該等灌注液轉移至經標記之 15 mL 錐形離心管中。將乙醇灌注液混合物儲存於中-80℃冷凍器中歷時 30 分鐘，隨後在 Eppendorf 吊桶式離心機中於 3000 rpm 下離心 10 分鐘。離心後，視離心塊之大小而定，將沈澱物溶解於 150-400 μL 2 N NaOH 中。將上清液在凍乾器中乾燥，且溶解於 150-200 μL 2 N NaOH 中。溶解於 NaOH 中後，將樣品以每管 200 μL 或 200 μL 以下之體積轉移至 8 孔洗提管中且於 99℃下在熱循環儀中水解 12 小時以使得膠原蛋白完全水解及羥基脯胺酸釋放。用濃 HCl 酸化樣品（每 25 μL 水解樣品 5.2 μL HCl）。將 60 μL 氯胺-T（Sigma；目錄號 C9887）添加至等體積之酸化水解物中以完成羥基脯胺酸氧化。完全氧化後，添加 120 μL 艾利希試劑（Sigma, Saint Louis, MO，目錄號 39070（Fluka））且於 65℃下培養 25 分鐘，產生紫色。顯色之強度視來源於釋放於灌注液中之膠原蛋白之羥基脯胺酸的量而定。在 Spectramax 2E 讀板器（Molecular Devices, Sunnyvale, CA）中於 550 nm 下在可見

光範圍內對樣品進行讀數。使用經純化之羥基脯胺酸溶液（Sigma, Saint Louis, MO，目錄號 H54409）建立標準曲線，且自該標準曲線確定皮膚樣品中之羥基脯胺酸含量。

實施例 3

藉由用經活化之組織蛋白酶-L 灌注活體外大鼠皮膚外植體來降解膠原蛋白

以手術方式自經 2%異氟醚麻醉之 3 月齡的雄性 Sprague-Dawley 大鼠（Harlan Sprague Dawley, Indianapolis, IN）之背外側部位移除皮膚外植體（2 cm×2 cm）。用針將外植體壓在膠合至 100 mm 皮氏培養皿（Petri dish）之聚苯乙烯發泡塑料（Styrofoam）墊上且用加熱板保持於 37℃下。首先使用輸注泵（Thermo Orion，型號 M361，Boston, MA）將 6 mL 含有 MES 緩衝液（2-(N-嗎啉基)-乙烷磺酸）（pH 5）及 2500 單位/毫升之 rHuPH20（rHuPH20 Halozyme 內部製造，批號 056-100；比活性：124,000 U/mL 且蛋白質含量為 1.05 mg/mL）之溶液經由插入外植體之真皮層中的 27 號蝶形針灌注穿過皮膚外植體歷時 35 分鐘。完成酸灌注後，用有或無 100 μg/mL 經活化組織蛋白酶-L 的 MES 緩衝液（pH 5）或有或無對照組織蛋白酶-L 之 HEPES 緩衝液（pH 7.4）將皮膚外植體灌注約 30 分鐘。藉由用 200 μL 微量移液管吸出且在整個灌注程序期間以 5-10 分鐘之時間間隔將內含物收集在 1.5 mL Eppendorf 管中來收集部分。將該等部分混合於 Eppendorf 管中且快速冷凍直至如實施例 2 中所述執行羥基脯胺酸（HP）分析。

三個不同實驗之結果展示 HP 含量僅在於最適 pH 值 5 下用經活化之組織蛋白酶-L 灌注的樣品中顯著增加。平均（n = 3）HP 含量自約 6 分鐘時之小於 1 μg/mL 灌注液增加至約 30 分鐘之大於 30 μg/mL 灌注液。在來自僅用 MES 緩衝液（pH 5）、僅用 HEPES 緩衝液（pH 7.4）及對照組織蛋白酶-L（pH 7.4）輸注之灌注液中量測到無 HP 或極少 HP。

實施例 4

藉由用經活化之組織蛋白酶-L 灌注活體外豬皮膚外植體來降解膠原蛋白

使 3 月齡的雌性約克夏（Yorkshire）豬（S 及 S Farm, Ramona, CA）禁食隔夜且藉由肌肉內注射氯胺酮（Ketamine）（20 mg/kg）/甲苯噻口井（Xylazine）（2 mg/kg）及阿托品（atropine）（0.04 mg/kg）麻醉。接著對動物插管且經吸入 2%於氧氣（Airgas, San Diego, CA）中之異氟烷（Baxter, Deerfield, IL）維持麻醉。以手術方式自動物背部移除完整皮膚外植體（5 cm×5 cm），於 4℃下將其置於磷酸鹽緩衝生理食鹽水（phosphate buffered saline，PBS）中，且在切除後 2 小時內使用。基本上如實施例 3 中所述進行外植體之灌注及羥基脯胺酸分析，其例外之處在於用 MES 緩衝液（pH 5）或含有 100 μg/ml 組織蛋白酶-L 而無 PH20 之 MES 緩衝液（pH 5）灌注豬皮膚外植體。起初，用 6 mL MES 緩衝液（pH 5）將外植體灌注約 30 分鐘，且每隔 5-10 分鐘收集部分。此後，用 3 mL 於 MES 緩衝液（pH 5）中之 100 μg/ml 組織蛋白酶-L 或作為對照之單獨緩衝液灌注

外植體，每隔 5 分鐘收集，歷時約 25 分鐘。HP 分析展示用組織蛋白酶-L 灌注之樣品中之 HP 含量的時間依賴性增加。在用無組織蛋白酶-L 之 MES 緩衝液（pH 5）灌注的樣品中未量測到可偵測的 HP。15 分鐘時間時量測到最高含量之 HP。25 分鐘時量測到之 HP 含量類似於 15 分鐘時量測到者。

實施例 5

藉由用經活化之組織蛋白酶-L 灌注豬外植體來減少皮下間隙中之纖維中隔

基本上如實施例 4 中所述，藉由以每分鐘 0.17 mL 之速率用含有 2500 U/mL rHuPH20 之 MES 緩衝液（pH 5）灌注 30 分鐘，接著以 0.12 mL/min 用 3 mL 於無 rHuPH20 之 MES 緩衝液（pH 5）中的 100 μg/ml 組織蛋白酶-L 灌注 25 分鐘來處理豬皮膚外植體。用組織蛋白酶-L 輸注後，將外植體修剪成小塊，將其固定於 4%緩衝福馬林（formalin）中隔夜。類似地處理對照未經處理之豬外植體。將組織於 PBS 中洗滌，於分級乙醇及二甲苯溶液中脫水，且包埋於石蠟中。將塊狀體切成 4 μm 薄的切片，將其轉移至載玻片上且用馬松三色染色進行染色以觀測膠原蛋白。簡言之，使切片脫石蠟，於蒸餾水中水合且於 56℃下用於波恩氏溶液（Bouin's solution）中之媒染劑（Sigma，目錄號 HT10-132）處理 15 至 30 分鐘。將該等切片冷卻且以流水洗滌直至黃色消失並以蒸餾水沖洗。接著以魏格特氏鐵蘇木素工作溶液（Weigert's Iron Hematoxylin Working solution）

（Sigma，目錄號 HT107 及 HT109）將切片染色 5 分鐘且以流水洗滌 10 分鐘。以去離子水將切片沖洗 5 分鐘且置於比布裏希猩紅-酸性品紅（Biebrich Scarlet-Acid Fuchsin）（Sigma，目錄號 HT151）中 5 分鐘。將切片轉移至工作磷鎢酸/磷鉬酸溶液（Phosphotungstic/Phosphomolybdic Acid solution）（Sigma，目錄號 HT152 及 HT153）中且最後以苯胺藍溶液（Aniline Blue Solution）（Sigma，目錄號 HT154）染色 5 分鐘並於 1%乙酸中區分 2 分鐘。將切片以蒸餾水沖洗，於 95%酒精及無水酒精中脫水，且以二甲苯清洗，變化兩次。固定切片且以 Nikon 倒置顯微鏡觀察。以 Nikon 螢光顯微鏡結合含有 SPOT 晚期成像程序之攝像掃描器（Diagnostic Instrument Inc., Sterling Heights, MI）使用 20× 物鏡獲得圖像。

下皮主要含有脂肪組織。由膠原蛋白纖維中隔組成之緻密結締組織條帶自真皮深處延伸至下皮中且使皮膚錨定於下層結構。組織學結果展示在未經處理之樣品中在整個下皮中可見分隔脂肪細胞腔室之纖維中隔。用於 MES 緩衝液（pH 5）中之組織蛋白酶-L 處理後，膠原蛋白纖維中隔之數目實質上低於未經處理之樣品，表明用組織蛋白酶-L 處理顯著改變下皮中之膠原蛋白網路結構。

實施例 6

A. 經麻醉之活大鼠之皮膚中的膠原蛋白降解

對以 2%異氟烷保持麻醉之 3 月齡的雄性 Sprague-Dawley 大鼠（Harlan Sprague-Dawley, Inc.

Indianapolis, IN)執行灌注實驗。使用組織蛋白酶-L在pH 5下執行灌注實驗，且作為特定性之對照，以pH 7.4之HEPES緩衝液執行灌注實驗。簡言之，首先使用輸注泵，將約15 mL含有25 mM MES緩衝液（pH 5）或25 mM HEPES緩衝液（pH 7.4）及2500單位/毫升rHuPH20（Halozyme內部製造批號056-100，比活性為124,000 U/mL且蛋白質含量為1.05 mg/mL）之溶液經由尾部皮膚使用27號插入皮膚之真皮層中的蝶形針灌注約60分鐘。此後，灌注3 mL含有組織蛋白酶-L或緩衝液對照之溶液歷時25分鐘。含有Cat-L之灌注溶液含有於5 mM MES中之處於最適pH值5的100 μg/mL經活化之Cat-L或於20 mM HEPES中之處於對照pH值7.4的100 μg/mL經活化之Cat-L。使pH 5緩衝液之離子強度自25 mM降至5 mM以促進藉由局部組織環境中和pH值且從而限制活性酵素之擴散。在於HEPES緩衝液(pH 7.4)中之Cat-L的情況下，維持至少20 mM之離子強度以確保於高離子強度緩衝液(pH 4)中活化及調配之所添加的Cat-L不會實質上改變HEPES緩衝液之pH值（pH 7.4)。用pH試紙檢查添加至20 mM HEPES(pH 7.4)中之Cat-L的小等分試樣以確保在已添加Cat-L後所得溶液之pH值實際上接近pH 7.4。用於灌注之緩衝液對照溶液為不添加酵素之5 mM MES（pH 5）或20 mM HEPES（pH 7.4)。以規律時間間隔，亦即在初始灌注期間於20、40及60分鐘時且在用Cat-L灌注期間於8及25分鐘時，自尾部皮膚收集灌注液部分。將該等部分彙集於Eppendorf管中且快速冷凍以防止

進一步酵素作用。如實施例 2 中所述執行羥基脯胺酸分析。結果展示僅在用經活化之組織蛋白酶-L 灌注的樣品中可量測到 HP。在 25 分鐘灌注液樣品中量測到最高含量之 HP。在僅用 MES 緩衝液（pH 5）或僅用 HEPES 緩衝液（pH 7.4）或用於 HEPES 緩衝液（pH 7.4）中之組織蛋白酶-L 灌注的樣品中不存在可偵測的 HP。

B. 組織蛋白酶-L 處理導致試管內 pH 值依賴性膠原蛋白降解

評估組織蛋白酶 B、D、L 及 S 及細菌膠原酶於 pH 5.0 及 pH 8.0 下對大鼠膠原蛋白之降解。組織蛋白酶 B、D、L 及 S 係購自 R&D systems 且根據來自酵素製造之個別說明書使每一酵素活化。細菌膠原酶係購自 Sigma Chemicals，且不需要活化。於 37℃下藉由於製造商指定緩衝液中或於 Tris（pH 8.0）緩衝生理食鹽水中與經活化之組織蛋白酶 B、D、L 或 S 或細菌膠原酶一起培養，使可溶性大鼠尾部 I 型膠原蛋白消化 1 小時，接著進行 SDS-Page 凝膠處理且庫馬斯藍染色。其他組織蛋白酶不於 pH 5 下進行測試，而以製造商指定 pH 值及緩衝液測試。結果展示組織蛋白酶-L 為於 pH 5.0 下而非於 pH 8.0 下具活性之唯一酵素。組織蛋白酶 B、D 及 S 於製造商指定 pH 值下展示大鼠膠原蛋白之一些略微降解及於 pH 8.0 下展示大鼠膠原蛋白無降解，而細菌膠原酶於 pH 5.0 與 pH 8.0 皆降解大鼠膠原蛋白。

實施例 7

A. 酸化活大鼠之皮膚後恢復至中性

當將稀酸水溶液注入皮膚間質中時，pH 值之變化為暫時性的且由於間質之顯著緩衝能力而快速恢復至中性皮膚 pH 值。使用酚紅作為間質 pH 值之觀測指示劑。酚紅之鈉鹽廣泛用於細胞培養基中以鑑別中性至酸性 pH 值之變化。酚紅溶液於 6.4 或 6.4 以下之 pH 值時具有黃色，於 pH 7.0 時具有橙色，於 pH 7.4 及以上時具有紅色，且於 pH 7.8 時具有紫色。

以 2%異氟烷使 3 月齡的雄性 Sprague-Dawley 大鼠（Harlan Sprague Dawley, Indianapolis, IN）保持麻醉。將皮膚刮去毛髮以便易於觀測酚紅染色。將 2-2.5mL 含有 500 U/ml rHuPH20 之 25 mM MES（pH 5）經由插入真皮層中之 27 號蝶形針灌注至尾部皮膚中。在此之後灌注 1-1.5 mL 0.05%酚紅（Sigma-Aldrich, St. Louis, MO，目錄號 P0290）於 10 mM、25 mM、50 mM 及 100 mM MES 緩衝液（pH 5）中之溶液。MES（2-(N-嗎啉基)-乙烷磺酸（C16H13NO4A））具有 195.2 之分子量。該酚紅溶液中不包括 rHuPH20。使用測微計，於不同時間點，以兩個維度量測酚紅前緣，且使用下式計算面積：面積=(D1×D2)×π/4。觀察到顏色變化且記錄恢復至中性之時間。表 4A 之結果總結恢復至中性之平均時間（以分鐘計）且指示恢復至中性可藉由緩衝液之離子強度來調節。

表 4A-恢復至中性之平均時間

以 mM id MES 計之緩衝溶液濃度	酚紅之初始面積	5 分鐘後之減少%	10 分鐘後之減少%	15 分鐘後之減少%	20 分鐘後之減少%	恢復至中性之平均時間以 min 計
10；n=3	80	71	86	98	-	10
25；n=3	123	59	78	91	-	10
50；n=2	115	38	100	100	-	10
100；n=2	191	15	38	55	71	20

B. 酸化小鼠皮膚後恢復至中性

恢復至中和之時期及隨後組織蛋白酶-L 之失活視所注射緩衝液之濃度而定。在裸鼠體內藉由於 pH 5.0 下在增加緩衝液濃度（10-100 mM MES）下使用酚紅指示劑染色量測恢復至中和之時間來評估間質之固有緩衝能力。給經麻醉之裸鼠注射 0.125 mL 含有酚紅之 MES 緩衝液（10 mM 至 100 mM）（pH 5）。肉眼量測在真皮中至酚紅中和之時間。結果描述於下表 4B 中。

表 4B：小鼠皮膚中之間質緩衝能力的量測

緩衝液	離子強度（mM）	pH 值	恢復至中和之時間（分鐘）	SD
磷酸鹽	10	7.4	0	-
MES	10	5.0	0	-
MES	25	5.0	0	-
MES	50	5.0	7.3	1.25
MES	100	5.0	7.8	2.1

SD：標準偏差

因此，藉由漸增之緩衝液濃度（10-100 mM MES，pH 5.0）經皮內注射 pH 值指示劑，確定可獲得來自 1-20 分鐘/100 平方公分注射之酸性時空細胞外環境。

實施例 8

重組人類肝組織蛋白酶-L 之工程化

使用根據人類腎組織蛋白酶原-L cDNA 之公開定序資料設計的引子將人類 Cat-L cDNA SEQ ID NO: 9(由 SEQ ID NO:10 中所闡明之核苷酸的序列編碼）及 Cat-L-His cDNA SEQ ID NO: 12（由 SEQ ID NO:13 中所闡明之核苷酸的序列編碼）自人類肝 cDNA（Clonetech QUICK-Clone cDNA 637205）進行 PCR 擴增。添加 5' NheI 及 3' BamHI 限制性位點作為 PCR 引子合成之部分。用於擴增之引子闡明於表 5 中。

表 5：引子

	引子	序列	SEQ ID NO	溫度	長度	匹配長度
人類 Cat-L	5'	5'-AAGGCCGCTAGCCACC ATGGATCCTACACTCATC CTTGCTGC-3'	16	64℃	42 mer	22
	3'（具有兩個終止密碼子）	5'-GAGCACGGATCCTCAT CACACAGTGGGGTAGCT GG-3'	17	65℃	35 mer	20
Cat-L-His	5'	5'-AAGGCCGCTAGCCACC ATGGATCCTACACTCATC CTTGCTGC-3'	16	64℃	42 mer	22
	3'（具有 6×His 標籤）	5'-CCTGCCGGATCCTCAA TGATGATGATGATGATGC ACAGTGGGGTAGCTG-3'	18	57℃	49 mer	16

兩種基於 cDNA 之構築體皆具有藉由單鹼基突變以形成一致 Kozak 序列的天然 Cat-L 分泌性前導肽之第二胺基酸，從而使該第二胺基酸自 N 變為 D（如 SEQ ID NO: 9 及

12 中所闡明）。藉由標準瓊脂糖凝膠電泳及 DNA 序列分析來驗證純系之一致性。

引入所得擴增產物以選殖入 HZ24（b/s）表現載體中。該表現載體為用於表現由來自腦心肌炎病毒之內部核糖體進入位點（IRES）分隔之組織蛋白酶-L 蛋白質與鼠類 DHFR 基因的基於 CMV 之雙順反子序列盒。所得 HZ24-Cat-L 表現載體之序列闡明於 SEQ ID NO:11 中。所得 HZ24-Cat-L-His 表現載體之序列闡明於 SEQ ID NO:14 中。

藉由轉染，使用 Genejuice 轉染試劑（EMD Biosciences, San Diego, CA，目錄號 70967）將 Cat-L 與 Cat-L-His 表現質體皆引入 CHO-S 細胞（適於無血清懸浮液培養之 CHO-K1 細胞，Invitrogen, Carlsbad, CA，目錄號 11619-012）中。亦藉由電穿孔將該等表現質體引入適於以懸浮液培養方式生長於化學界定之無動物產物培養基（Invitrogen，目錄號 10743-029）中的 DG44 CHO 細胞（藉由來自 Columbia University 之 Lawrence Chasin 博士的特許而獲得）中。對於電穿孔而言，每一質體之每次電穿孔使用大於 100 μg 之 ClaI 線性化質體。於 350 伏特恆定電壓下轉染每次電穿孔 2 千萬個 DG44 CHO 細胞。電穿孔緩衝液含有 2×HeBS（40 mM HEPES，pH 7.0；274 mM NaCl；10 mM KCl；1.4 mM Na_2HPO_4；12 mM 右旋糖）。在無次黃嘌呤鈉及胸苷之標準 CD-CHO 培養基（Invitrogen #12610-010）中電穿孔後 72 小時藉由限制稀釋法來選殖經轉染之細胞以選擇帶有 DHFR 質體之細胞。將在無次黃嘌呤鈉及胸苷情況下生長之

所選純系進一步次選殖，使用甲胺喋呤擴增以增加插入物複本數。模擬物轉染充當陰性對照。

轉染後 72 小時收集上清液且於 1500 rpm 下旋轉 5 分鐘。將來自經 his-Cat-L、Cat-L 及模擬物轉染之 CHO-S 及 CHO-DG44 細胞的無細胞上清液施加於 10 kDa 截斷微米離心濃縮器（Millipore；Bedford, MA.，目錄號 42407）上且藉由於 4℃下於 12000 rpm 下離心而濃縮約 10 倍。藉由捕捉 ELISA（Calbiochem 組織蛋白酶-L ELISA 套組#QIA94），西方墨點分析，如實施例 10 中所述使用單株 Mab 33/1（Bender MedSystems, Burlingame, CA）且對於酵素活性而言如實施例 9 中所述使用螢光肽受質（Z-L-R-AMC）篩選分泌至組織培養上清液中之重組人類組織蛋白酶-L。

實施例 9

使用螢光肽受質測定組織蛋白酶-L 之酶促活性

使用稱為 Z-Leu-Arg-AMC（Z=:N-苄氧羰基；AMC：7-胺基-4-甲基香豆素，R&D Systems, Minneapolis, MN，目錄號 ES008）之市售螢光受質檢定組織蛋白酶-L 之酶促活性。該肽受質含有高度螢光 7-胺基-4-甲基香豆素基團（AMC），其藉由形成於其胺基與 Arg 殘基之羧基之間的醯胺鍵淬滅。經活化之組織蛋白酶-L 裂解此醯胺鍵，使得釋放之螢光增加。雖然肽受質可由其他組織蛋白酶裂解，但其中主要為組織蛋白酶-B，組織蛋白酶-L 活性特定地藉由使用適合於組織蛋白酶-B 之特異性抑制劑且在抑制劑存在及不存在之情況下量測活性來確定。特定言之，使用最終濃度為 1

μM之選擇性組織蛋白酶-B抑制劑CA-074(Calbiochem, San Diego, CA，目錄號205530）且在CA-074存在及不存在之情況下檢定樣品。藉由添加pH 5之濃MES緩衝液將在CHO細胞中轉染後72小時之細胞培養物上清液調整至pH 5且於冰上培養30分鐘。此酸活化步驟裂解前肽且產生成熟組織蛋白酶-L。為稀釋為組織蛋白酶-L酵素活性之有效抑制劑的前肽片段（Carmona, E.等人 Potency and selectivity of the cathepsin-L propeptide as an inhibitor of cysteine proteases. Biochemistry 35: 8149-8157 (1996)），濃縮該等樣品且於30 KDa microcon管上用50 mM MES（pH 5）緩衝液進行緩衝液交換3次。接著藉由對Z-AMC受質進行螢光肽受質檢定來檢定樣品之酵素活性。

以類似於樣品之方式活化市售組織蛋白酶-L製劑（R&D Systems；目錄號952-CY），且藉由連續稀釋將其用作標準物。活化後，將樣品及標準物在不透明底微板中於含有5 mM DTT及10 mM EDTA之100 mM MES緩衝液（pH 5）中連續稀釋且於37℃下與螢光肽受質Z-AMC一起培養30分鐘。當與樣品或標準物組合時，使用總體積為200 μL、最終濃度為10 μM之Z-AMC受質。

在螢光板讀取器（Molecular Devices, SpectraMax 3, Sunnyvale, CA）中於受質之推薦最佳激發-發射（380 nm-460 nm）條帶下讀取所得螢光。樣品值來源於由自標準物之稀釋系列獲得的相對螢光單位（relative fluorescence unit，RFU）值所繪之標準曲線。用 Softmax®軟體（Molecular

Devices, SpectraMax 3, Sunnyvale, CA）進行 4 參數擬合後，該標準曲線在 10-100 ng/mL 之濃度範圍之間為假線性。結果展示於下表 6 中。來自經轉染之 CHO-S 細胞之組織蛋白酶-L 的活性比來自經模擬物轉染之宿主細胞且藉由在選擇性組織蛋白酶-B 抑制劑 CA-074 存在下檢定之背景活性高至少 10-20 倍。因此經組織蛋白酶-L 轉染之組織培養基中的酶促活性增加可歸因於 Cat-L 比活性。

表 6：轉染後 72 小時在經轉染之細胞中在組織蛋白酶-B 抑制劑存在下藉由 Z-AMC 檢定量測 Cat-L 酵素活性

純系描述	經模擬物轉染之 CHO-S	經 Cat-L 轉染之 CHO-S	經 His Cat-L 轉染之 CHO-S
Cat-L 活性之 ng/mL	20	723	248

實施例 10

所表現之人類重組組織蛋白酶-L 的西方墨點分析

如實施例 8 中所述表現及濃縮無細胞上清液後，執行西方墨點分析以證實表現。簡言之，對於 6 種不同樣品（來自 CHO-S 或 CHO-DG44 細胞每一者之 cat-L、cat-L-His 及模擬物）中之每一者而言，將 30 μL 濃縮上清液與用於 SDS-PAGE 之 10 μL 4×（替代凝膠加樣樣品緩衝液）（EMD Bioscience, San Diego, CA，目錄號 70607-3）及 2 μL 100 mM DTT 混合且於 80℃下培養 20 分鐘。作為陽性對照，包括於 30 μL 1× PBS 中之 750 ng 市售經純化之重組組織蛋白酶-L（R&D Systems）且同等處理。將總體積（42 μL）之樣品加樣於 4-20% Tris-甘胺酸凝膠（Invitrogen, Carlsbad, CA，目

錄號 EC6028BOX）上且於 Tris-甘胺酸 SDS 電泳緩衝液中進行電泳直至預染色之分子量標誌（Invitrogen，目錄號 LC5925）之染料前緣到達凝膠底部。藉由 I-Blot 半乾墨點設備（Invitrogen，目錄號 IB1001）根據製造商之說明書將蛋白質轉移至 PVDF 膜上。藉由凝膠上幾乎完全不存在預染色標誌條帶之顏色而驗證轉移。於室溫下於由於 PBS 中之 5%脫脂奶粉組成之阻斷劑緩衝液中阻斷該膜 2 小時。用以於阻斷劑中之 1 μg/mL 最終濃度使用之人類組織蛋白酶-L 之小鼠單株抗體（Mab 33/1）（Bender MedSystems, Burlingame, CA，目錄號 BMS 166）偵測組織蛋白酶-L 且於 4℃下培養隔夜，接著於室溫下用以於阻斷劑中之 33 ng/mL 濃度的 HRP 接合之抗-小鼠 IgG（Calbiochem, San Diego, CA，目錄號 DC02L）偵測 1 小時。藉由不溶性 TMB（Calbiochem，目錄號 613548）膜顯影液使 HRP 信號顯影且於室溫下 30 分鐘後停止反應。

西方墨點分析展示對 Cat-L 具特異性之蛋白質條帶。在經模擬物轉染之細胞中未偵測到特異性條帶。Cat-L 及 His-Cat-L 之表現量似乎在 CHO-S 細胞中比在 DG44 細胞中高，此可能歸因於兩種細胞系之轉染效率。西方墨點分析結果與使用如實施例 9 中所述用螢光肽受質進行之 Z-AMC 酵素活性檢定的結果一致。表現於 CHO-S 及 DG44 中之組織蛋白酶-L 的分子量為 44-45 KDa，其對應於仍含有前肽之蛋白質的預期大小。用作陽性對照之市售組織蛋白酶（R&D Systems）的分子量對成熟組織蛋白酶-L 而言為 36 KDa。表

現於經轉染之 CHO-S 及 CHO-DG44 細胞中之蛋白質與市售組織蛋白酶-L 之間的大小差異可能歸因於不同宿主細胞特異性糖基化或前肽自市售 Cat-L 移除。

實施例 11

合成組織蛋白酶-L 及組織蛋白酶-L-His 之產生

對於 CHO 細胞使用密碼子優化合成編碼成熟人類組織蛋白酶-L 之 DNA 構築體（GenBank 寄存編號 EAW62736 之胺基酸 18-333；SEQ ID NO:1）。密碼子優化係基於由 Blue Heron Biotech（www.blueheronbio.com）列出之用於黑線倉鼠（Cricetulus griseus）之密碼子優化表。合成含有自人類 κ IgG 基因家族（SEQ ID NO:2）設計之異源信號肽的構築體以允許將重組蛋白質分泌至組織培養上清液中。經優化之組織蛋白酶-L 構築體的序列闡明於 SEQ ID NO: 3 中且編碼 SEQ ID NO:4 中所闡明之多肽。添加 5' NheI 及 3' BamHI 限制性位點作為構築體合成之部分，且將該位點引入以選殖至 HZ24（b/s）表現載體中（如實施例 8 中所述）。合成 Cat-L 表現載體稱為 HZ24（B/S）-CAT-L 且闡明於 SEQ ID NO:5 中。亦合成含有由連接子（GGGGSG；SEQ ID NO:15）分隔之 C-末端 6 組胺酸標籤的類似合成構築體。合成之 Cat-L-His 構築體的序列闡明於 SEQ ID NO:6 中且編碼 SEQ ID NO:7 中所闡明之多肽。此構築體亦具有作為構築體合成之部分添加的 5' NheI 及 3' BamHI 限制性位點，且將該位點引入以供選殖至 HZ24（b/s）表現載體中。合成 Cat-L-His 表現載體稱為 HZ24(B/S)-Cat-L-His 且闡明於 SEQ ID NO:

8 中。

如實施例 8 中所述藉由電穿孔將 SEQ ID NO:5 中所闡明之合成 Cat-L 表現載體及 SEQ ID NO:8 中所闡明之合成 Cat-L-His 表現載體轉染至 CHO-DG44 細胞中。轉染後 72 小時收集上清液且如實施例 8 中所述進行處理（不進行 pH 值調整）以產生未活化之組織蛋白酶-L。亦經 pH 4 之調整來處理組織培養上清液以活化組織蛋白酶，接著於 30 KDa 膜上濃縮且藉由西方墨點分析來分析組織蛋白酶-L。簡言之，於低 pH 值下，裂解出組織蛋白酶-L 之前肽，使酵素活化。藉由以 1:10 之比率將濃縮酸性緩衝液（1000 mM 甲酸鹽 pH 4、1000 mM NaCl、50 mM DTT、100 mM EDTA）分別添加至來自經合成構築體轉染之細胞及未經轉染之對照細胞的上清液中而將該等上清液調整至 pH 4。將上清液於冰上培養 30 分鐘以使活化完成。藉由經由 30 KDa 分子量截斷離心濃縮裝置（Microcon 30, Millipore, Bedford, MA.，目錄號 42410）離心來使其濃縮。30 KDa 截斷尺寸允許經裂解之前肽（預測大小為約 12-14 KDa）穿過，而成熟蛋白質被保留（預測大小為約 36-40 kDa）。濃縮後，使經活化（B）及未經活化之上清液（A）於 4-12% SDS-PAGE 凝膠上電泳，接著如實施例 10 中所述藉由西方墨點法，使用單株 Mab 33/1 加以分析。在經轉染之細胞的組織培養上清液中偵測到類似含量之合成組織蛋白酶-L 及 Cat-His-L。未經活化之上清液的分子量為約 44 kDa，而對於經活化之上清液而言為約 36 至 40 kDa，此歸因於由於蛋白質於較低

pH 值下活化而不存在前肽。

亦如實施例 9 中所述使用螢光肽受質（Z-L-R-AMC）針對酶促活性篩選經活化之上清液。轉染後 72 小時在經轉染之 CHO-DG44 細胞中藉由 Z-AMC 檢定在組織蛋白酶-B 抑制劑存在下量測 Cat-L 酵素活性。結果闡述於下表 7 中。轉染後 72 小時來自經轉染之 CHO-DG44 細胞之組織蛋白酶-L 的活性比來自經模擬物轉染之宿主細胞且藉由在選擇性組織蛋白酶-B 抑制劑 CA-074 存在下檢定之背景活性高至少 5-10 倍，阻斷宿主組織蛋白酶-B 之作用（如酵素活性）。因此，在經組織蛋白酶-L 轉染之組織培養基中之酵素活性增加可歸因於自經轉染之 Cat-L 純系表現的 Cat-L 比活性。

表 7：

純系描述	經模擬物轉染	經 Cat-L 轉染	經 His Cat-L 轉染
Cat-L 活性之 ng/mL	小於 100	1700	600

實施例 12

可溶性重組人類 PH20（rHuPH20）表現細胞系之產生

使用 HZ24 質體（SEQ ID NO:224 中所示）轉染中國倉鼠卵巢（CHO 細胞）。編碼可溶性 rHuPH20 構築體之 DNA 含有在編碼人類 PH20 玻尿酸酶之天然信號前導序列的胺基酸位置 1 處之甲硫胺酸的 DNA 之前的 NheI 位點及 Kozak 一致序列，及在編碼人類 PH20 玻尿酸酶之胺基酸位置 482 處的酪胺酸之後的 DNA 終止密碼子，接著為 BamHI 限制性位點。因此，構築體 pCI-PH20-IRES-DHFR-SV40pa(HZ-24)

產生由 CMV 啟動子驅動之編碼由內部核糖體進入位點（IRES）分隔之 PH20 之胺基酸 1-482（SEQ ID NO:225 中所示）及二氫葉酸還原酶之胺基酸 1-187（SEQ ID NO:261 中所示）的單一 mRNA 物質。

使未經轉染之 DG44 CHO 細胞生長於補充有 4 mM Glutamax^{Tm} 及 18 ml Plurionic F68/L（Gibco）之用於 DHFR(-) 細胞的 GIBCO 改良型 CD-CHO 培養基，且以 0.5×10^6 個細胞/毫升接種於搖瓶中以為轉染作準備。使細胞於 37℃、5% CO_2 下在濕潤恆溫箱中生長，於 120 rpm 下震盪。在轉染之前測試按指數規律生長之未經轉染之 DG44 CHO 細胞的生存力。

將未經轉染之 DG44 CHO 細胞培養物中的 6 千萬個活細胞粒化且再懸浮於 0.7 mL 2×轉染緩衝液（2× HeBS：40 mM Hepes（pH 7.0）、274 mM NaCl、10 mM KCl、1.4 mM Na_2HPO_4、12 mM 右旋糖）中至 2×10^7 個細胞之密度。向再懸浮細胞之每一等分試樣中添加 0.09 mL（250 μg）線性 HZ24 質體（藉由用 Cla I（New England Biolabs）消化隔夜而線性化；SEQ ID NO: 19 中所闡明之線性 HZ24 質體），且於室溫下將細胞/DNA 溶液轉移至 0.4 cm 間隙 BTX（Gentronics）電穿孔比色管中。在無與細胞混合之 DNA 情況下執行陰性對照電穿孔。用 330 V 之電容器放電及 960 μF 或於 350 V 及 960 μF 下對細胞/質體混合物進行電穿孔。

電穿孔後將細胞自比色管移出且轉移至補充有 4 mM 麩胺醯胺及 18 ml Plurionic F68/L（Gibco）之 5 mL 用於

DHFR(-)細胞的改良型 CD-CHO 培養基中，且在無選擇情況下使其於 37℃、5% CO_2 下在濕潤恆溫箱中生長於 6 孔組織培養板之孔中。

電穿孔後兩天，自各孔移出 0.5 mL 組織培養基且測試玻尿酸酶活性之存在（參見實施例 16）。結果闡述於下表 8 中。

表 8：轉染後 40 小時時經 HZ24 轉染之 DG44 CHO 細胞的初始玻尿酸酶活性

	稀釋度	活性 單位/毫升
轉染 1 330 V	1 至 10	0.25
轉染 2 350 V	1 至 10	0.52
陰性對照	1 至 10	0.015

自組織培養孔收集來自轉染 2（350 V）之細胞，對其進行計數且稀釋至每毫升 1×10^4 個至 2×10^4 個活細胞。將細胞懸浮液之 0.1 mL 等分試樣轉移至 5 個 96 孔圓底組織培養板之各孔中。將 100 微升含有 4 mM GlutaMAX™-1 補充劑（GIBCO™, Invitrogen Corporation）且無次黃嘌呤及胸苷補充劑之 CD-CHO 培養基（GIBCO）添加至含有細胞之孔中（最終體積為 0.2 mL）。

鑑別來自 5 個培養板之在無甲胺喋呤情況下生長的 10 個純系（參見表 9）。

表 9

培養板/孔編號	相對玻尿酸酶
1C3	261
2C2	261
3D3	261
3E5	243
3C6	174
2G8	103
1B9	304
2D9	273
4D10	302

在培養物中擴增 6 個 HZ24 純系且以單細胞懸浮液形式轉移至搖瓶中。使用二維無限稀釋策略將純系 3D3、3E5、2G8、2D9、1E11 及 4D10 塗鋪於 96 孔圓底組織培養板中，其中將細胞沿培養板向下 1:2 稀釋，且沿培養板橫向 1:3 稀釋，在頂部左手孔中以 5000 個細胞開始。使經稀釋之純系生長於每孔 500 個未經轉染之 DG44 CHO 細胞的背景中，以提供必需生長因子歷時培養最初數天。每個次純系製作 10 個培養板，其中 5 個培養板含有 50 nM 甲胺喋呤且 5 個培養板無甲胺喋呤。

純系 3D3 產生 24 個可見次純系(13 個來自無甲胺喋呤處理，且 11 個來自 50 nM 甲胺喋呤處理)。在來自 24 個次純系中之 8 個的上清液中量測到顯著玻尿酸酶活性（大於 50 單位/毫升)，且適當時在 50 nM 甲胺喋呤存在下將此等 8 個次純系擴增至 T-組織培養燒瓶中。使純系 3D3 50 nM 進一步在 500 nM 甲胺喋呤中擴增，在搖瓶中得到產生超過

1,000 單位/毫升之純系(純系 3D35M;1 代或 Gen1 3D35M)。

實施例 13

Gen1 人類 sPH20 之製備及純化

A. 5 L 生物反應器製程

將一小瓶 3D35M 解凍且自搖瓶經由 1 L 旋轉燒瓶在補充有 100 nM 甲胺喋呤及 GlutaMAX™-1 (Invitrogen) 之 CD-CHO 培養基 (Invitrogen, Carlsbad Calif.) 中擴增。將細胞以每毫升 4×10^5 個活細胞之接種密度自旋轉燒瓶轉移至 5 L 生物反應器 (Braun) 中。參數為溫度設定點 37℃、pH 7.2 (起始設定點)、溶解氧設定點 25%及 0-100 cc/min 之空氣覆蓋。168 小時時,添加 250 ml 1 號饋料培養基 (具有 50 g/L 葡萄糖之 CD CHO)。216 小時時,添加 250 ml 2 號饋料培養基 (具有 50 g/L 葡萄糖及 10 mM 丁酸鈉之 CD CHO),且 264 小時時添加 250 ml 2 號饋料培養基。此製程產生每毫升 1600 單位之最終生產力及 6×10^6 個細胞/毫升之最大細胞密度。丁酸鈉之添加用於在製備之最後階段顯著增強可溶性 rHuPH20 之產生。

藉由深部過濾及切向流動透濾至 10 mM Hepes (pH 7.0) 中來使來自 3D35M 純系之條件培養基澄清。接著藉由依次於 Q 瓊脂糖 (Pharmacia) 離子交換管柱層析、苯基瓊脂糖 (Pharmacia) 疏水性相互作用層析法、硼酸苯酯 (Prometics) 及羥基磷灰石層析法 (Biorad, Richmond, CA) 來純化可溶性 rHuPH20。

使可溶性 rHuPH20 與 Q 瓊脂糖結合且於相同緩衝液中

以 400 mM NaCl 溶離。用 2 M 硫酸銨將溶離液稀釋至 500 mM 硫酸銨之最終濃度且通過苯基瓊脂糖（低取代）管柱，接著於相同條件下與硼酸苯酯樹脂結合。於 pH 9.0 下以 50 mM 無硫酸銨之二甘胺酸（bicine）洗滌後，將可溶性 rHuPH20 以 Hepes（pH 6.9）自苯基瓊脂糖樹脂溶離。將溶離液以 5 mM 磷酸鉀及 1 mM $CaCl_2$ 加樣於 pH 6.9 之陶瓷羥基磷灰石樹脂上且用具有 0.1 mM $CaCl_2$ 之 80 mM 磷酸鉀（pH 7.4）溶離。

所得經純化之可溶性 rHuPH20 具有經由使用 USP 參考標準之微濁度檢定（實施例 16）得出超過 65,000 USP 單位/毫克蛋白質之比活性。經純化之 sPH20 自 24 至 26 分鐘時自 Pharmacia 5RPC 苯乙烯二乙烯基苯管柱以介於 0.1% TFA/H_2O 與 0.1% TFA/90%乙腈/10% H_2O 之間的梯度以單一峰溶離且藉由 SDS 電泳以單一寬峰 61 kDa 條帶解析，在用 PNGASE-F 處理後減小為尖的 51 kDa 條帶。N-末端胺基酸序列揭示已有效地移除前導肽。

B. 達到 100 L 生物反應器細胞培養之上游細胞培養物擴增製程

使用按比例擴大製程分別純化來自四個不同小瓶之 3D35M 細胞的可溶性 rHuPH20 以產生 4 批分開的 sHuPH20；HUA0406C、HUA0410C、HUA0415C 及 HUA0420C。分別擴增每一小瓶且經由 125 L 生物反應器培養，接著使用管柱層析法純化。在整個製程中採集樣品以酵素產量形式評估該等參數。以下所提供之對製程之描述

陳述諸如生物反應器起始及饋料培養基體積、轉移細胞密度及洗滌與溶離體積之情況的代表性規格。精確數目隨各批次略有變化，且詳述於表 3 至 10 中。

將四個小瓶之 3D35M 細胞於 37℃水浴中解凍，添加含有 100 nM 甲胺喋呤及 40 mL/L GlutaMAX 之 CD CHO 且將該等細胞離心。將細胞再懸浮於 125 mL 具有 20 mL 新鮮培養基之搖瓶中且置於 37℃、7% CO_2 恆溫箱中。使細胞在該 125 mL 搖瓶中擴增至 40 mL。當細胞密度達到 1.5-2.5×10^6 個細胞/毫升時，使培養物以 100 mL 培養體積擴增至 125 mL 旋轉燒瓶中。於 37℃、7% CO_2 下培養該燒瓶。當細胞密度達到 1.5-2.5×10^6 個細胞/毫升時，使培養物以 200 mL 培養體積擴增至 250 mL 旋轉燒瓶中，且於 37℃、7% CO_2 下培養該燒瓶。當細胞密度達到 1.5-2.5×10^6 個細胞/毫升時，使培養物以 800 mL 培養體積擴增至 1 L 旋轉燒瓶中且於 37℃、7% CO_2 下培養。當細胞密度達到 1.5-2.5×10^6 個細胞/毫升時，使培養物以 5 L 培養體積擴增至 6 L 旋轉燒瓶中且於 37℃、7% CO_2 下培養。當細胞密度達到 1.5-2.5×10^6 個細胞/毫升時，使培養物以 20 L 培養體積擴增至 36 L 旋轉燒瓶中且於 37℃、7% CO_2 下培養。

於 121℃、20 PSI 下用蒸汽使 125 L 反應器滅菌且添加 65 L CD CHO 培養基。在使用之前，檢查反應器之污染情況。當 36 L 旋轉燒瓶中之細胞密度達到 1.8-2.5×10^6 個細胞/毫升時，將 20 L 細胞培養物自 36 L 旋轉燒瓶轉移至 125 L 生物反應器（Braun）中，得到 85 L 之最終體積及約 4×10^5

個細胞/毫升之接種密度。參數為溫度設定點 37℃；pH 值：7.2；溶解氧：25%±10%；葉輪速度 50 rpm；容器壓力 3 psi；空氣噴射 1 L/min；空氣覆蓋：1 L/min。每日對反應器進行取樣以用於細胞計數、pH 值驗證、培養基分析、蛋白質產生及滯留。在運作期間添加營養物饋料。第 6 天時，添加 3.4 L 1 號饋料培養基（CD CHO + 50 g/L 葡萄糖+ 40 mL/L GlutaMAX™-1），且使培養溫度變為 36.5℃。第 9 天時，添加 3.5 L 2 號饋料（CD CHO + 50 g/L 葡萄糖+ 40 mL/L GlutaMAX™-1 + 1.1 g/L 丁酸鈉），且使培養溫度變為 36℃。第 11 天時，添加 3.7 L 3 號饋料（CD CHO + 50 g/L 葡萄糖+ 40 mL/L GlutaMAX™-1 + 1.1 g/L 丁酸鈉），且使培養溫度變為 35.5℃。第 14 天時或當細胞之生存力下降至 50% 以下時對反應器進行收集。該製程使得產生具有 1600 單位/毫升之酶促活性的可溶性 rHuPH20 及 8 百萬個細胞/毫升之最大細胞密度。收集時，對培養物進行取樣以測定黴漿菌（mycoplasma）、生物負荷、內毒素，及進行病毒試管內及活體內透射電子顯微術（transmission electron microscopy，TEM）以測定病毒顆粒，及測定酵素活性。

將 100 公升生物反應器細胞培養收集物經由一系列具有聚醚碸介質之拋棄式囊式過濾器（Sartorius）過濾：首先經由 8.0 μm 深囊（depth capsule）、0.65 μm 深囊、0.22 μm 囊，且最後經由 0.22 μm Sartopore 2000 cm^2 過濾器且過濾至 100 L 無菌儲存袋中。使用兩個具有螺旋聚醚碸 30 kDa MWCO 過濾器（Millipore）之 TFF 使培養物濃縮 10 倍，接

著用 10 mM HEPES、25 mM Na_2SO_4（pH 7.0）進行 6×緩衝液交換至 0.22 μm 終濾器中進入 20 L 無菌儲存袋中。表 10 提供與細胞培養、收集、濃縮及緩衝液交換步驟有關之監測資料。

表 10. 關於細胞培養、收集、濃縮及緩衝液交換步驟之監測資料。

參數	HUA0406C	HUA04010C	HUA0415C	HUA0420C
解凍至接種 100 L 生物反應器之時間（天）	21	19	17	18
100 L 接種密度（×10^6 個細胞/毫升）	0.45	0.33	0.44	0.46
對數生長之加倍時間（小時）	29.8	27.3	29.2	23.5
最大細胞密度（×10^6 個細胞/毫升）	5.65	8.70	6.07	9.70
收集物生存力（%）	41	48	41	41
收集物效價（U/ml）	1964	1670	991	1319
在 100 L 生物反應器中之時間（天）	13	13	12	13
澄清之收集物體積（mL）	81800	93300	91800	89100
澄清之收集物酵素檢定（U/mL）	2385	1768	1039	1425
濃縮物酵素檢定（U/mL）	22954	17091	8561	17785
經緩衝液交換之濃縮物酵素檢定（U/mL）	15829	11649	9915	8679
經過濾、緩衝液交換之濃縮物酵素檢定（U/mL）	21550	10882	9471	8527
經緩衝液交換之濃縮物體積（mL）	10699	13578	12727	20500
酵素單位濃縮/收集比率	0.87	0.96	1.32	1.4

製備 Q 瓊脂糖（Pharmacia）離子交換柱（3 L 樹脂，高度＝20 cm，直徑＝14 cm）。收集洗滌樣品以測定 pH 值、

傳導率及內毒素(LAL檢定)。用5管柱體積之10 mM Tris、20 mM Na_2SO_4(pH 7.5)使該管柱平衡。將經濃縮、透濾之收集物以100 cm/hr之流速加樣於該Q管柱上。用5管柱體積之10 mM Tris、20 mM Na_2SO_4(pH 7.5)及10 mM Hepes、50 mM NaCl(pH 7.0)洗滌管柱。用10 mM Hepes、400 mM NaCl(pH 7.0)溶離蛋白質且經由0.22 μm終濾器過濾至無菌袋中。

隨後執行苯基-瓊脂糖(Pharmacia)疏水性相互作用層析法。製備苯基-瓊脂糖(PS)管柱(9.1 L樹脂,高度= 29 cm,直徑= 20 cm)。用5管柱體積之5 mM磷酸鉀、0.5 M硫酸銨、0.1 mM $CaCl_2$(pH 7.0)使該管柱平衡。分別用2 M硫酸銨、1 M磷酸鉀及1 M $CaCl_2$儲備溶液將來自上文之蛋白質溶離液補充至5 mM、0.5 M及0.1 mM之最終濃度。將蛋白質以100 cm/hr之流速加樣於PS管柱上。以100 cm/hr添加5 mM磷酸鉀、0.5 M硫酸銨及0.1 mM $CaCl_2$(pH 7.0)。使流過物質通過0.22 μm終濾器至無菌袋中。

將經PS純化之蛋白質加樣於已用5管柱體積之5 mM磷酸鉀、0.5 M硫酸銨平衡的硼酸胺基苯酯管柱(ProMedics)6.3 L樹脂,高度= 20 cm,直徑= 20 cm)上。使蛋白質以100 cm/hr之流速通過該管柱,且用5 mM磷酸鉀、0.5 M硫酸銨(pH 7.0)洗滌管柱。接著用20 mM二甘胺酸、100 mM NaCl(pH 9.0)洗滌管柱且經由無菌過濾器用50 mM Hepes、100 mM NaCl(pH 6.9)溶離蛋白質且溶離至20 L無菌袋中。測試溶離液之生物負荷、蛋白質濃度及酵素活

性。

用 5 mM 磷酸鉀、100 mM NaCl、0.1 mM $CaCl_2$(pH 7.0)使羥基磷灰石(HAP)管柱(BioRad)(1.6 L 樹脂，高度= 10 cm，直徑= 14 cm)平衡。收集洗滌樣品且測試 pH 值、傳導率及內毒素(LAL 檢定)。用磷酸鉀及 $CaCl_2$ 補充經硼酸胺基苯酯純化之蛋白質以得到 5 mM 磷酸鉀及 0.1 mM $CaCl_2$ 之最終濃度且以 100 cm/hr 之流速加樣於 HAP 管柱上。用 5 mM 磷酸鉀(pH 7.0)、100 mM NaCl、0.1 mM $CaCl_2$ 接著 10 mM 磷酸鉀(pH 7.0)、100 mM NaCl、0.1 mM $CaCl_2$ (pH)洗滌管柱。用 70 mM 磷酸鉀(pH 7.0)溶離蛋白質且經由 0.22 μm 過濾器過濾至 5L 無菌儲存袋中。測試溶離液之生物負荷、蛋白質濃度及酵素活性。

接著經由壓力槽將經 HAP 純化之蛋白質抽汲通過 20 nM 病毒移除過濾器。將蛋白質添加至 DV20 壓力槽及過濾器(Pall Corporation)中，通過具有 20 nm 孔之 Ultipor DV20 過濾器(Pall Corporation)至無菌 20 L 儲存袋中。測試濾液之蛋白質濃度、酵素活性、寡醣、單醣及唾液酸概況，及製程相關雜質。接著使用 10 kD 分子量截斷(molecular weight cut off，MWCO) Sartocon Slice 切向流動過濾(tangential flow filtration，TFF)系統(Sartorius)使濾液中之蛋白質濃縮至 1 mg/mL。首先藉由用 Hepes/生理食鹽水溶液(10 mM Hepes、130 mM NaCl，pH 7.0)洗滌來準備過濾器且對滲透物進行取樣以測定 pH 值及傳導率。濃縮後，對經濃縮之蛋白質進行取樣且測試蛋白質濃度及酵素

活性。對經濃縮之蛋白質執行 6×緩衝液交換至最終緩衝液中：10 mM Hepes、130 mM NaCl（pH 7.0）。使經濃縮之蛋白質通過 0.22 μm 過濾器至 20 L 無菌儲存袋中。對蛋白質進行取樣且測試蛋白質濃度、酵素活性、游離巰基、寡醣概況及滲透壓度。

表 11 至 17 提供每一 3D35M 細胞批號的與上述純化步驟中之每一者有關的監測資料。

表 11. Q 瓊脂糖管柱資料

參數	HUA0406C	HUA0410C	HUA0415C	HUA0420C
加樣體積（mL）	10647	13524	12852	20418
加樣體積/樹脂體積比	3.1	4.9	4.5	7.3
管柱體積（mL）	2770	3840	2850	2880
溶離液體積（mL）	6108	5923	5759	6284
溶離液之蛋白質濃度（mg/mL）	2.8	3.05	2.80	2.86
溶離液酵素檢定（U/mL）	24493	26683	18321	21052
酵素產率（%）	65	107	87	76

表 12. 苯基瓊脂糖管柱資料

參數	HUA0406C	HUA0410C	HUA0415C	HUA0420C
添加儲備溶液之前的體積（mL）	5670	5015	5694	6251
加樣體積（mL）	7599	6693	7631	8360
管柱體積（mL）	9106	9420	9340	9420
加樣體積/樹脂體積比	0.8	0.71	0.82	0.89
溶離液體積（mL）	16144	18010	16960	17328
溶離液之蛋白質濃度（mg/mL）	0.4	0.33	0.33	0.38
溶離液酵素檢定（U/mL）	8806	6585	4472	7509
蛋白質產率（%）	41	40	36	37
酵素產率（%）	102	88	82	96

表 13. 硼酸胺基苯酯管柱資料

參數	HUA0406C	HUA0410C	HUA0415C	HUA0420C
加樣體積（mL）	16136	17958	16931	17884
加樣體積/樹脂體積比	2.99	3.15	3.08	2.98
管柱體積（mL）	5400	5700	5500	5300
溶離液體積（mL）	17595	22084	20686	19145
溶離液之蛋白質濃度（mg/mL）	0.0	0.03	0.03	0.04
經過濾溶離液之蛋白質濃度（mg/mL）	未測試	0.03	0.00	0.04
溶離液酵素檢定（U/mL）	4050	2410	1523	4721
蛋白質產率（%）	0	11	11	12
酵素產率（%）	未測定	41	40	69

表 14. 羥基磷灰石管柱資料

參數	HUA0406C	HUA0410C	HUA0415C	HUA0420C
添加儲備溶液之前的體積（mL）	16345	20799	20640	19103
加樣體積/樹脂體積比	10.95	13.58	14.19	12.81
管柱體積（mL）	1500	1540	1462	1500
加樣體積（mL）	16429	20917	20746	19213
溶離液體積（mL）	4100	2415	1936	2419
溶離液之蛋白質濃度（mg/mL）	未測試	0.24	0.17	0.23
經過濾溶離液之蛋白質濃度（mg/mL）	NA	NA	0.17	NA
溶離液酵素檢定（U/mL）	14051	29089	20424	29826
蛋白質產率（%）	未測試	93	53	73
酵素產率（%）	87	118	140	104

表 15. DV20 過濾資料

參數	HUA0406C	HUA0410C	HUA0415C	HUA0420C
起始體積（mL）	4077	2233	1917	2419
濾液體積（mL）	4602	3334	2963	3504
濾液之蛋白質濃度（mg/mL）	0.1	NA	0.09	NA
經過濾溶離液之蛋白質濃度（mg/mL）	NA	0.15	0.09	0.16
蛋白質產率（%）	未測試	93	82	101

表 16. 最終濃縮資料

參數	HUA0406C	HUA0410C	HUA0415C	HUA0420C
起始體積（mL）	4575	3298	2963	3492
濃縮物體積（mL）	562	407	237	316
濃縮物之蛋白質濃度（mg/mL）	0.9	1.24	1.16	1.73
蛋白質產率（%）	111	102	103	98

表 17. 緩衝液交換為最終調配物資料

參數	HUA0406C	HUA0410C	HUA0415C	HUA0420C
起始體積（mL）	562	407	237	316
經緩衝液交換之濃縮物的最終體積（U/mL）	594	516	310	554
濃縮物之蛋白質濃度（mg/mL）	1.00	0.97	0.98	1.00
經過濾濃縮物之蛋白質濃度（mg/mL）	0.95	0.92	0.95	1.02
蛋白質產率（%）	118	99	110	101

將經純化及濃縮之可溶性 rHuPH20 蛋白質無菌填充至具有 5 mL 及 1 mL 填充體積之無菌小瓶中。使該蛋白質通過 0.22 μm 過濾器至用於使用重量分析讀數器填充小瓶之操作者控制的泵中。用塞子封閉小瓶且用螺紋蓋緊固。對

封閉之小瓶目測檢查外來顆粒且接著加以標記。標記後，藉由浸入液氮中不長於 1 分鐘將小瓶急驟冷凍且儲存於≤15℃（-20±5℃）下。

實施例 14

含有可溶性人類 PH20（rHuPH20）之 Gen2 細胞之製備

使實施例 12 中所述之 Gen1 3D35M 細胞系適應於較高甲胺喋呤含量以產生 2 代（Gen2）純系。將 3D35M 細胞自所建立之含有甲胺喋呤之培養物接種至含有 4 mM GlutaMAX-1™及 1.0 μM 甲胺喋呤之 CD CHO 培養基中。藉由經 46 天時期使細胞在 37℃、7% CO_2 濕潤恆溫箱中生長及繼代 9 次而使其適應於較高甲胺喋呤含量。在含有具有 2.0 μM 甲胺喋呤之培養基的 96 孔組織培養板中藉由限制稀釋法來選殖出擴增之細胞群。約 4 週後，鑑別純系且選擇純系 3E10B 用於擴增。使 3E10B 細胞生長於含有 4 mM GlutaMAX-1™及 2.0 μM 甲胺喋呤之 CD CHO 培養基中達 20 次繼代。產生 3E10B 細胞系之主細胞庫（master cell bank，MCB）且將其冷凍並用於隨後研究。

藉由將 3E10B 細胞培養於含有 4 mM GlutaMAX-1™及 4.0 μM 甲胺喋呤之 CD CHO 培養基中繼續細胞系之擴增。第 12 次繼代後，將細胞冷凍於小瓶中作為研究細胞庫（research cell bank，RCB）。將一小瓶 RCB 解凍且培養於含有 8.0 μM 甲胺喋呤之培養基中。5 天後，使培養基中之甲胺喋呤濃度增加至 16.0 μM，接著 18 天後增加至 20.0 μM。在含有 4 mM GlutaMAX-1™及 20.0 μM 甲胺喋呤之 CD CHO

培養基的 96 孔組織培養板中藉由限制稀釋法選殖出含有 20.0 μM 甲胺喋呤之培養基中之來自第 8 次繼代的細胞。5-6 週後鑑別純系且選擇純系 2B2 用於在含有 20.0 μM 甲胺喋呤之培養基中擴增。第 11 次繼代後，將 2B2 細胞冷凍於小瓶中作為研究細胞庫（RCB）。

所得 2B2 細胞為表現可溶性重組人類 PH20(rHuPH20)之二氫葉酸還原酶缺陷型（dhfr-）DG44 CHO 細胞。該可溶性 PH20 以約 206 個複本/細胞之複本數存在於 2B2 細胞中。使用 rHuPH20 特異性探針對經 Spe I-、Xba I-及 BamH I/Hind III 消化之基因組 2B2 細胞 DNA 進行南方墨點法分析揭示以下限制性消化特徵：在用 Spe I 消化之 DNA 情況下一個約 7.7 kb 之主要雜交條帶及四個次要雜交條帶（約 13.9、約 6.6、5.7 及約 4.6 kb）；在用 Xba I 消化之 DNA 情況下一個約 5.0 kb 之主要雜交條帶及兩個次要雜交條帶（約 13.9 及 6.5 kb）；及使用用 BamH I/Hind III 消化之 2B2 DNA 觀察到一個約 1.4 kb 之單一雜交條帶。

實施例 15

A. 在 300 L 生物反應器細胞培養中製備 Gen2 可溶性 rHuPH20

將一小瓶 HZ24-2B2 解凍且自搖瓶經由 36 L 旋轉燒瓶在補充有 20 μM 甲胺喋呤及 GlutaMAX-1™(Invitrogen)之 CD-CHO 培養基（Invitrogen, Carlsbad, CA）中擴增。簡言之，將一小瓶細胞於 37℃水浴中解凍，添加培養基且將該等細胞離心。將細胞再懸浮於 125 mL 具有 20 mL 新鮮培養

基之搖瓶中且置於 37℃、7% CO_2 恆溫箱中。使細胞在該 125 mL 搖瓶中擴增至 40 mL。當細胞密度達到大於 1.5×10^6 個細胞/毫升時，使培養物以 100 mL 培養體積擴增至 125 mL 旋轉燒瓶中。於 37℃、7% CO_2 下培養該燒瓶。當細胞密度達到大於 1.5×10^6 個細胞/毫升時，使培養物以 200 mL 培養體積擴增至 250 mL 旋轉燒瓶中，且於 37℃、7% CO_2 下培養該燒瓶。當細胞密度達到大於 1.5×10^6 個細胞/毫升時，使培養物以 800 mL 培養體積擴增至 1 L 旋轉燒瓶中且於 37℃、7% CO_2 下培養。當細胞密度達到大於 1.5×10^6 個細胞/毫升時，使培養物以 5000 mL 培養體積擴增至 6 L 旋轉燒瓶中且於 37℃、7% CO_2 下培養。當細胞密度達到大於 1.5×10^6 個細胞/毫升時，使培養物以 32 L 培養體積擴增至 36 L 旋轉燒瓶中且於 37℃、7% CO_2 下培養。

將 400 L 反應器滅菌且添加 230 mL CD-CHO 培養基。在使用之前，檢查反應器之污染情況。將約 30 L 細胞以每毫升 4.0×105 個活細胞之接種密度及 260 L 之總體積自 36 L 旋轉燒瓶轉移至 400 L 生物反應器（Braun）。參數為溫度設定點 37℃；葉輪速度 40-55 RPM；容器壓力：3 psi；空氣噴射 0.5-1.5 L/Min；空氣覆蓋：3 L/min。每日對反應器進行取樣以進行細胞計數、pH 值驗證、培養基分析、蛋白質產生及滯留。又，在運作期間添加營養物饋料。120 小時（第 5 天）時，添加 10.4 L 1 號饋料培養基（4×CD-CHO + 33 g/L 葡萄糖+ 160 mL/L GlutaMAX-1™ + 83 mL/L Yeastolate + 33 mg/L rHuInsulin）。168 小時（第 7 天）時，添加 10.8 L 2

號饋料（2×CD-CHO + 33 g/L 葡萄糖 + 80 mL/L GlutaMAX-1™ + 167 mL/L Yeastolate + 0.92 g/L 丁酸鈉），且使培養溫度變為 36.5℃。216 小時（第 9 天）後，添加 10.8 L 3 號饋料（1×CD-CHO + 50 g/L 葡萄糖 + 50 mL/L GlutaMAX-1™ + 250 mL/L Yeastolate + 1.80 g/L 丁酸鈉），且使培養溫度變為 36℃。264 小時（第 11 天）後，添加 10.8 L 4 號饋料（1×CD-CHO + 33 g/L 葡萄糖 + 33 mL/L GlutaMAX-1 + 250 mL/L Yeastolate + 0.92 g/L 丁酸鈉），且使培養溫度變為 35.5℃。在製備之最後階段觀察到饋料培養基之添加顯著增強可溶性 rHuPH20 之產生。第 14 天或第 15 天時或當細胞之生存力下降至 40%以下時對反應器進行收集。該製程產生每毫升 17,000 單位之最終生產力及 1 千萬個細胞/毫升之最大細胞密度。收集時，對培養物進行取樣以測定徵漿菌、生物負荷、內毒素及病毒試管內及活體內透射電子顯微術（TEM）以測定病毒顆粒及測定酵素活性。

藉由螺形壓縮泵經由並聯的四個各含有一層屬於 4-8 μm 等級之矽藻土及一層屬於 1.4-1.1 μm 等級之矽藻土、接著纖維素膜的 Millistak 過濾系統模組（Millipore），隨後經由含有一層屬於 0.4-0.11 μm 等級之矽藻土及一層屬於小於 0.1 μm 等級之矽藻土的第二單一 Millistak 過濾系統（Millipore），且接著經由 0.22 μm 終濾器將培養物抽汲至具有 350 L 容量之無菌單一用途可撓性袋中。用 10 mM EDTA 及 10 mM Tris 補充所收集之細胞培養液至 7.5 之 pH 值。用

切向流動過濾（TFF）設備使用四個 Sartoslice TFF 30 kDa 分子量截斷（MWCO）聚醚碸（PES）過濾器（Sartorious）使培養物濃縮 10 倍，接著用 10 mM Tris、20 mM Na_2SO_4（pH 7.5)進行 10×緩衝液交換至 0.22 μm 終濾器中進入 50 L 無菌儲存袋中。

使經濃縮、透濾之收集物中之病毒失活。在病毒失活之前，製備 10% Triton X-100、3%三(正丁基)磷酸鹽（tri(n-butyl) phosphate，TNBP）之溶液。使經濃縮、透濾之收集物在 36 L 玻璃反應容器中暴露於 1% Triton X-100、0.3% TNBP 歷時 1 小時，緊接著隨後於 Q 管柱上純化。

B. Gen2 可溶性 rHuPH20 之純化

製備 Q 瓊脂糖（Pharmacia）離子交換柱（9 L 樹脂，H = 29 cm，D = 20 cm)。收集洗滌樣品以測定 pH 值、傳導率及內毒素(LAL 檢定)。用 5 管柱體積之 10 mM Tris、20 mM Na2SO4（pH 7.5）使該管柱平衡。病毒失活後，將經濃縮、透濾之收集物以 100 cm/hr 之流速加樣於 Q 管柱上。用 5 管柱體積之 10 mM Tris、20 mM Na_2SO_4（pH 7.5）及 10 mM Hepes、50 mM NaCl（ph7.0）洗滌管柱。用 10 mM Hepes、400 mM NaCl（pH 7.0）將蛋白質溶離至 0.22 μm 終濾器中進入無菌袋中。測試溶離液樣品之生物負荷、蛋白質濃度及玻尿酸酶活性。在交換之開始及結束時進行 A_{280} 吸光度讀數。

隨後執行苯基-瓊脂糖（Pharmacia）疏水性相互作用層析。製備苯基-瓊脂糖(PS)管柱(19-21 L 樹脂，H = 29 cm，

D = 30 cm)。收集洗液且進行取樣以測定 pH 值、傳導率及內毒素（LAL 檢定）。用 5 管柱體積之 5 mM 磷酸鉀、0.5 M 硫酸銨、0.1 mM $CaCl_2$（pH 7.0）使該管柱平衡。分別用 2 M 硫酸銨、1 M 磷酸鉀及 1 M $CaCl_2$ 儲備溶液補充來自 Q 瓊脂糖管柱之蛋白質溶離液以得到 5 mM、0.5 M 及 0.1 mM 之最終濃度。將蛋白質以 100 cm/hr 之流速加樣於 PS 管柱上且收集管柱流過物質。用 5 mM 磷酸鉀、0.5 硫酸銨及 0.1 mM $CaCl_2$（pH 7.0）以 100 cm/hr 洗滌管柱且將洗液添加至所收集之流過物質中。與管柱洗液合併，使流過物質通過 0.22 μm 終濾器至無菌袋中。對流過物質進行取樣以測定生物負荷、蛋白質濃度及酵素活性。

製備硼酸胺基苯酯管柱（Promtics）。收集洗液且進行取樣以測定 pH 值、傳導率及內毒素（LAL 檢定）。用 5 管柱體積之 5 mM 磷酸鉀、0.5 M 硫酸銨使該管柱平衡。將含有經純化之蛋白質的 PS 流過物質以 100 cm/hr 之流速加樣於硼酸胺基苯酯管柱上。用 5 管柱體積之 5 mM 磷酸鉀、0.5 M 硫酸銨（pH 7.0）洗滌管柱。用 20 mM 二甘胺酸、0.20 M 硫酸銨（pH 9.0）洗滌管柱。用 20 mM 二甘胺酸、100 mM 氯化鈉（pH 9.0）洗滌管柱。用 50 mM Hepes、100 mM NaCl（pH 6.9）溶離蛋白質且使其通過無菌過濾器至無菌袋中。測試經溶離之樣品的生物負荷、蛋白質濃度及酵素活性。

製備羥基磷灰石（HAP）管柱（Biorad）。收集洗液且測試 pH 值、傳導率及內毒素（LAL 檢定）。用 5 mM 磷酸鉀、100 mM NaCl、0.1 mM $CaCl_2$（pH 7.0）使該管柱平衡。

將經硼酸胺基苯酯純化之蛋白質補充至 5 mM 磷酸鉀及 0.1 mM $CaCl_2$ 之最終濃度且以 100 cm/hr 之流速加樣於 HAP 管柱上。用 5 mM 磷酸鉀（pH 7）、100 mM NaCl、0.1 mM $CaCl_2$ 洗滌管柱。隨後用 10 mM 磷酸鉀（pH 7）、100 mM NaCl、0.1 mM $CaCl_2$ 洗滌管柱。用 70 mM 磷酸鉀（pH 7.0）溶離蛋白質且使其通過 0.22 μm 無菌過濾器至無菌袋中。測試經溶離之樣品的生物負荷、蛋白質濃度及酵素活性。

接著使經 HAP 純化之蛋白質通過病毒移除過濾器。首先藉由用 2 L 70 mM 磷酸鉀（pH 7.0）洗滌來製備經滅菌之 Viosart 過濾器（Sartorius）。在使用之前，對經過濾之緩衝液進行取樣以測定 pH 值及傳導率。經由壓力槽經由 20 nM 病毒移除過濾器抽汲經 HAP 純化之蛋白質。使於 70 mM 磷酸鉀（pH 7.0）中之經過濾之蛋白質通過 0.22 μm 終濾器至無菌袋中。測試經過濾病毒之樣品的蛋白質濃度、酵素活性、寡醣、單醣及唾液酸概況。亦測試該樣品之製程相關雜質。

接著使用 10 kD 分子量截斷（MWCO）Sartocon Slice 切向流動過濾（TFF）系統（Sartorius）使濾液中之蛋白質濃縮至 10 mg/mL。首先藉由用 10 mM 組胺酸、130 mM NaCl（pH 6.0）洗滌來製備過濾器且對滲透物進行取樣以測定 pH 值及傳導率。濃縮後，對經濃縮之蛋白質進行取樣且測試蛋白質濃度及酵素活性。對經濃縮之蛋白質執行 6×緩衝液交換至最終緩衝液中：10 mM 組胺酸、130 mM NaCl（pH 6.0）。緩衝液交換後，使經濃縮之蛋白質通過 0.22 μm 過濾

器至20 L無菌儲存袋中。對蛋白質進行取樣且測試蛋白質濃度、酵素活性、游離巯基、寡醣概況及滲透壓度。

接著將經無菌過濾之塊狀蛋白質以20 mL無菌分配於30 mL無菌鐵氟龍（Teflon）小瓶（Nalgene）中。接著將該等小瓶急驟冷凍且儲存於-20±5℃下。

C. Gen1可溶性rHuPH20與Gen2可溶性rHuPH20之製備及純化的比較

在300 L生物反應器細胞培養中Gen2可溶性rHuPH20之製備及純化在方案方面與在100 L生物反應器細胞培養中Gen1可溶性rHuPH20之製備及純化（實施例13.B中所述）相比含有一些變化。表18陳述除簡單按比例擴大變化外該等方法之間的例示性差異。

表18

製程差異	Gen1可溶性rHuPH20	Gen2可溶性rHuPH20
細胞系	3D35M	2B2
用於擴增細胞接種物之培養基	含有0.10 μM甲胺喋呤（0.045 mg/L）	含有20 μM甲胺喋呤（9 mg/L）
在6 L向前培養中之培養基	含有0.10 μM甲胺喋呤	不含甲胺喋呤
36 L旋轉燒瓶	無儀器 20 L操作體積	配備有監測及控制pH值、溶解氧、噴射及覆蓋氣體流速之儀器。 32 L操作體積
在生物反應器中之最終操作體積	在125 L生物反應器中約100 L（初始培養體積+65 L）	在400 L生物反應器中約300 L（初始培養體積+260 L）
在最終生物反應器中之培養基	無rHuInsulin	5.0 mg/L rHuInsulin
培養基饋料體積	以4%之生物反應器細胞培養體積按比例擴大，亦即3.4、3.5及3.7 L，產生約92 L之目標	以4%之生物反應器細胞培養體積按比例擴大，亦即10.4、10.8、11.2及11.7 L，產生約303 L之

	生物反應器體積。	目標生物反應器體積。
培養基饋料	1 號饋料培養基：CD CHO +50 g/L 葡萄糖+ 8 mM GlutaMAX™-1 2 號饋料（CD CHO + 50 g/L 葡萄糖+ 8 mM GlutaMAX + 1.1 g/L 丁酸鈉 3 號饋料：CD CHO + 50 g/L 葡萄糖+ 8 mM GlutaMAX + 1.1 g/L 丁酸鈉	1 號饋料培養基：4×CD CHO + 33 g/L 葡萄糖 + 32 mM Glutamax + 16.6 g/L Yeastolate + 33 mg/L rHuInsulin 2 號饋料：2×CD CHO + 33 g/L 葡萄糖+ 16 mM Glutamax + 33.4 g/L Yeastolate + 0.92 g/L 丁酸鈉 3 號饋料：1×CD CHO + 50 g/L 葡萄糖+ 10 mM Glutamax + 50 g/L Yeastolate + 1.80 g/L 丁酸鈉 饋料 4 號：1×CD CHO + 33 g/L 葡萄糖+ 6.6 mM Glutamax + 50 g/L Yeastolate + 0.92 g/L 丁酸鈉
生物反應器細胞培養物之過濾	串聯的四個聚醚碸過濾器（8.0 μm、0.65 μm、 0.22 μm 及 0.22 μm） 100 L 儲存袋	第一階段-並聯的四個模組，各具有一層屬於 4-8 μm 等級之矽藻土及一層屬於 1.4-1.1 μm 等級之矽藻土，接著為纖維素膜。 第二階段-單一模組，其含有一層屬於 0.4-0.11 μm 等級之矽藻土及一層屬於小於 0.1 μm 等級之矽藻土，接著為纖維素膜。 第三階段-0.22 μm 聚醚碸過濾器 300 L 儲存袋 用 10 mM EDTA、10 mM Tris 補充所收集之細胞培養物至 7.5 之 pH 值。
在層析前之濃縮及緩衝液交換	用 2 個具有 Millipore 螺旋聚醚碸 30K MWCO 過濾器之 TFF 濃縮 用 10 mM Hepes、25 mM NaCl（pH 7.0）對濃縮物 6×進行緩衝液交換 20 L 無菌儲存袋	使用四個 Sartorius Sartoslice TFF 30K MWCO 過濾器進行濃縮 用 10 mM Tris、20 mM Na_2SO_4（pH 7.5）對濃縮物 10×進行緩衝液交換 50 L 無菌儲存袋
在層析前之病毒失活	無	在添加 1% Triton X-100、0.3% 磷酸三丁酯（pH 7.5）的同時執行病毒失活

第一純化步驟 （Q瓊脂糖）	無吸光度讀數	在開始及結束時進行 A_{280} 量測
在層析後之病毒過濾	Pall DV-20 過濾器（20 nm）	Sartorius Virosart 過濾器 （20 nm）
在層析後之濃縮及 緩衝液交換	Hepes/生理食鹽水（pH 7.0） 緩衝液 使蛋白質濃縮至 1 mg/mL	組胺酸/生理食鹽水（pH 6.0） 緩衝液 使蛋白質濃縮至 10 mg/mL

實施例 16

可溶性 rHuPH20 之玻尿酸酶活性的測定

使用比濁檢定測定諸如細胞培養物、純化部分及經純化溶液之樣品中之可溶性 rHuPH20 的玻尿酸酶活性，該檢定係根據當玻尿酸與血清白蛋白結合時形成不溶性沈澱物。藉由將可溶性 rHuPH20 與透明質酸鈉（玻尿酸）一起培養規定時期（10 分鐘）且接著在添加酸化血清白蛋白下使未經消化之透明質酸鈉沈澱來量測該活性。30 分鐘發展時期後於 640 nm 下量測所得樣品之混濁度。由於酵素對透明質酸鈉受質之活性而使混濁度降低為可溶性 rHuPH20 酶促活性之量度。使用以可溶性 rHuPH20 檢定工作參考標準之稀釋液產生的校正曲線運作該方法，且相對於此校正曲線進行樣品活性量測。

於酵素稀釋劑溶液中製備樣品之稀釋液。該酵素稀釋劑溶液係藉由將 33.0±0.05 mg 經水解之明膠溶解於 25.0 mL 50 mM PIPES 反應緩衝液（140 mM NaCl、50 mM PIPES，pH 5.5）及 25.0 mL SWFI 中且將 0.2 mL 25% Buminate 溶解於混合物中並渦旋 30 秒來製備。在 2 小時使用時間內執行此步驟且儲存於冰上直至需要時。將樣品稀釋至估算的 1-2

U/mL。通常，每步驟之最大稀釋度不超過 1:100 且用於首次稀釋之初始樣品體積不小於 20 μL。執行檢定所需之最小樣品體積為：處理中樣品，FPLC 部分：80 μL；組織培養上清液：1 mL；經濃縮之物質 80 μL；經純化或最後步驟之物質：80 μL。在低蛋白質結合 96 孔板中以一式三份方式製備稀釋液，且將各 30 μL 稀釋液轉移至 Optilux 黑色/透明底培養板（BD BioSciences）。

於酵素稀釋劑溶液中製備濃度為 2.5 U/mL 之已知可溶性 rHuPH20 的稀釋液以產生標準曲線且將其以一式三份方式添加至 Optilux 培養板中。該等稀釋液包括 0 U/mL、0.25 U/mL、0.5 U/mL、1.0 U/mL、1.5 U/mL、2.0 U/mL 及 2.5 U/mL。該培養板中包括作為陰性對照之含有 60 μL 酵素稀釋劑溶液的「試劑空白」孔。接著覆蓋培養板且於 37℃下於加熱塊上加溫 5 分鐘。移除覆蓋物且將培養板震盪 10 秒。震盪後，將培養板放回至該加熱塊上且給 MULTIDROP 384 液體操作裝置裝填溫熱 0.25 mg/mL 透明質酸鈉溶液（藉由將 100 mg 透明質酸鈉（LifeCore Biomedical）溶解於 20.0 mL SWFI 中來製備。藉由輕輕地旋轉且/或於 2-8℃下搖動 2-4 小時將其混合，或直至完全溶解）。將反應培養板轉移至 MULTIDROP 384 且藉由按啟動鍵來起始反應以將 30 μL 透明質酸鈉分配於各孔中。接著將培養板自 MULTIDROP 384 移出且震盪 10 秒，隨後在更換培養板覆蓋物之情況下轉移至加熱塊。將培養板於 37℃下培養 10 分鐘。

藉由給機器裝填血清工作溶液且將體積設定變為 240

μL 來使 MULTIDROP 384 準備停止反應。(於 75 mL 500 mM 乙酸鹽緩衝溶液中之 25 mL 血清儲備溶液[用 9 體積之 500 mM 乙酸鹽緩衝溶液稀釋 1 體積之馬血清（Sigma）且用鹽酸將 pH 值調整至 3.1])。自加熱塊移出培養板且置於 MULTIDROP 384 上並將 240 μL 血清工作溶液分配於孔中。移出培養板且於讀板器上震盪 10 秒。再過 15 分鐘後，於 640 nm 下量測樣品之混濁度且藉由擬合標準曲線來測定各樣品之酵素活性（以 U/mL 計）。

藉由將酵素活性（U/ml）除以蛋白質濃度（mg/mL）來計算比活性（U/mg）。

實施例 17

組織蛋白酶-L 充當 Zucker 大鼠之皮下間隙中的纖維中隔

藉由投予於 MES 緩衝液（pH 5.3）中之 90 μg/ml 組織蛋白酶-L 來處理 Zucker 大鼠且對皮膚切片執行組織學以觀測纖維中隔。作為對照，單獨用 MES 緩衝液（pH 5.3）處理大鼠。如實施例 5 中所述固定切片且用馬松三色染色來染色以觀測膠原蛋白。亦用蘇木素（Hemotoxylin）及伊紅（Eosin）對切片進行染色。簡言之，使切片脫石蠟且與水水合。若切片經 Zenker 固定，則用碘移除氯化汞晶體且用硫代硫酸鈉清洗。用邁爾蘇木素（Mayer's hematoxylin）將樣品染色 15 分鐘，接著以流動自來水洗滌 20 分鐘。用伊紅將切片對比染色 15 秒至 2 分鐘，其視伊紅之老化及所需對比染色深度而定。為得到均勻染色結果，將載玻片浸漬若

干次，隨後使其固定於伊紅中。使切片於 95%酒精及無水酒精中脫水，兩分鐘變化兩次（一分鐘一次），直至移除過量伊紅。於顯微鏡下檢驗載玻片，隨後以二甲苯清洗，兩分鐘變化兩次（一分鐘一次）。將切片置於 Permount 或 Histoclad 中。結果展示在僅用酸性緩衝液處理之對照動物體內，皮下脂肪小葉由垂直地延伸至皮膚表面之膠原蛋白纖維中隔的複雜網分隔。用組織蛋白酶-L 處理大鼠使得下皮纖維中隔降解。

在用無組織蛋白酶-L 之 MES 緩衝液（pH 5.3）、用 90 μg/ml 組織蛋白酶-L 或用於 50 mM HEPES 緩衝液（pH 7.4）中之 90 μg/ml 細菌膠原酶處理後，進一步用兔抗-膠原蛋白抗體觀測纖維中隔之組織。結果展示在僅用酸性 MES 緩衝液處理之對照大鼠體內的正常膠原蛋白分布。用組織蛋白酶-L 處理大鼠展示膠原蛋白染色減少，從而證明膠原蛋白降解。然而，藉由用細菌膠原酶處理大鼠使膠原蛋白之降解更顯著。此等結果表明組織蛋白酶-L 與細菌膠原酶相比對膠原蛋白降解具有更強暫時性控制。

實施例 18

在 Zucker 大鼠真皮中組織蛋白酶-L 之酶促作用的持續時間

在 Zucker 大鼠之真皮中使用兩種互補方法評估組織蛋白酶-L 之酶促作用的持續時間：西方墨點法及酶促活性。給大鼠在真皮中注射 1 mL 含有腎上腺素（2.5 μg/mL）之 1200 單位/毫升 rHuPH20（pH 5.3）以誘導血管收縮。此後緊接著注射 1 mL 於 50 mM MES 緩衝液中之 100 μg/mL 重

組組織蛋白酶-L（pH 5.3）。在注射部位處製造切口且注射後3至70分鐘用20 μL及200 μL Eppendorf移液管收集間質灌注液。如實施例10中所述藉由西方墨點分析及如實施例9中所述藉由經一個小時量測組織蛋白酶-L之酶促活性（如自稱為Z-Leu-Arg-AMC之市售螢光受質的水解速率所測定）來分析流體之膠原蛋白降解，該活性以相對螢光單位（relative fluorescence unit，RFU）/分鐘表示。使用pH值指示條（EMD Chemicals, Inc., Gibbstown, NJ，目錄號9588）記錄間質液灌注液之pH值。資料展示於表19中。

在處理後10分鐘內量測到最大酶促活性。在真皮中投藥後，活性在30 min時降低約50%且在60 min時降低約70%。

表19. 投予100 μg/mL重組組織蛋白酶-L（pH 5.3）後與組織蛋白酶-L活性及間質流體之pH值有關的投藥後時間。

時間（注射後之分鐘數）	組織蛋白酶-L活性（RFU/min）	灌注液之pH值
9	1930	5 - 5.5
12	1917	5 - 5.5
15	1759	5 - 5.5
18	1261	5 - 5.5
21	1165	5 - 5.5
25	1115	5.5
30	950	5.5 - 6
40	669	5.5 - 6
60	636	6

實施例19

組織蛋白酶-L對Zucker大鼠真皮中之膠原蛋白降解的劑量-反應作用

在 Zucker 大鼠之真皮中投予 1 ml 1200 U/ml rHuPH20（pH 5.3）後，向 Zucker 大鼠之真皮中投予 1 ml 範圍為 1 μg/mL 至 500 μg/mL 之組織蛋白酶-L 劑量。注射後 20 分鐘，收集活組織檢查，將其固定於波恩氏固定劑（Bouin's fixative）中，且經處理以供組織學分析。用蘇木素及伊紅對切片進行染色，且如實施例 5 中所述用馬松三色染色以觀測膠原蛋白。在注射部位用解剖刀製造切口且收集間質流體。

分別如實施例 5 及 10 中所述進行經處理之皮膚之組織學分析及灌注液之西方墨點分析。將 25 μL 間質之等分試樣與 5 μL 6x 凝膠加樣樣品緩衝液混合以供 SDS-PAGE。將總體積之樣品加樣於 4-20% Tris-甘胺酸凝膠（Invitrogen, Carlsbad, CA，目錄號 EC6038）上且於 Tris-甘胺酸 SDS 電泳緩衝液中進行電泳直至預染色之分子量標誌（Invitrogen，目錄號 LC5925）之染色前緣到達凝膠底部。於 4℃下使用 XCell II 墨點模組（Invitrogen，目錄號 IB1001）於 20V 下以 20%甲醇、25 mM Tris 及 220 mM 甘胺酸之緩衝液將蛋白質轉移至硝基纖維素膜（Invitrogen，目錄號 LC2001）上歷時 1.5 小時。藉由凝膠上幾乎完全不存在預染色標誌條帶之顏色而證實轉移。於室溫下將該膜在由 2% 於 PBST（磷酸鹽緩衝生理食鹽水（PBS）溶液（137 mM NaCl、2.7 mM KCl、10 mM 磷酸鹽，pH 7.4），以及用作 ELISA 之洗滌緩衝液及稀釋劑的清潔劑 Tween 20（0.05% v/v））中之脫脂奶粉組成之緩衝液中阻斷 30 分鐘。於室溫下用以於

PBST 中之 1 μg/mL 最終濃度使用且於室溫下培養 1 小時的人類膠原蛋白 I 之兔多株抗體（Abcam, Cambridge, MA，目錄號 ab34710），接著用以於 PBST 中之 33 ng/mL 濃度使用的 HRP 接合之山羊抗-兔 IgG（Calbiochem, San Diego, CA，目錄號 DC03L）偵測膠原蛋白 I 歷時 1 小時。藉由不溶性 TMB（Calbiochem，目錄號 613548）膜顯影液使 HRP 信號顯影且於室溫下 5-10 分鐘後藉由以 ddH_2O 沖洗來停止反應。

組織學及西方墨點分析展示組織蛋白酶-L 之劑量增加產生劑量依賴性膠原蛋白降解。西方墨點分析指示如藉由用 100 μg/mL 處理之樣品中存在諸多低分子量條帶所判斷，組織蛋白酶-L 之濃度愈高使得膠原蛋白降解規模愈大。

實施例 20

組織蛋白酶-L 對纖維中隔破壞之劑量依賴性作用

投予 1 mL 於 50 mM MES、150 mM NaCl（pH 5.3）中之 1200 U/ml rHuPH20 後，向 Zucker 大鼠之真皮投予 1 mL 範圍為於 MES 緩衝液（pH 5.3）中之 1、10、50、100、250 及 500 μg/mL 的人類重組組織蛋白酶-L 劑量。作為對照，單獨用 MES 緩衝液（pH 5.3）處理大鼠。注射後 20 分鐘，如實施例 18 中所述自注射部位收集間質灌注液。收集皮膚活組織，將其固定於波恩氏固定劑中且經處理以供組織學分析。用蘇木素及伊紅對脫蠟之切片進行染色，如實施例 5 中所述用馬松三色染色以觀測膠原蛋白。如實施例 10 中所述進行西方墨點法。

來自組織學及西方墨點分析之結果展示 Zucker 大鼠中之膠原蛋白的重組組織蛋白酶-L 降解具劑量依賴性。纖維中隔之破壞在用 10 μg/mL 組織蛋白酶-L 處理之皮膚中明顯可見。

實施例 21

離子強度對 Zucker 大鼠真皮中之組織蛋白酶-L 之作用的作用

根據緩衝液及腎上腺素之離子強度研究注射於真皮中之組織蛋白酶-L 酵素活性的時期。

給 Zucker 大鼠注射 1 mL 之 1200 U/ml rHuPH20，接著注射 1 mL 於 1、5、10 及 50 mM MES 緩衝液、150 mM NaCl（pH 5.3）中之 25 μg/mL 組織蛋白酶-L。投藥後 20 分鐘時收集間質灌注液。使用 pH 值指示條（EMD Chemicals, Inc., Gibbstown, NJ，目錄號 9588）記錄間質液灌注液之 pH 值且如實施例 9 中所述量測真皮中之組織蛋白酶-L 酶促活性。對於低離子緩衝液濃度（1、5 及 10 mM MES，pH 5.3）而言真皮灌注液之 pH 值為 7.5。當以 50 mM MES（pH 5.3）傳遞組織蛋白酶-L 時，真皮灌注液之 pH 值為 6.5。當以低離子緩衝液濃度（1、5 及 10 mM MES）傳遞組織蛋白酶-L 時，未偵測到可量測之酶促活性。在投予以 50 mM MES 調配之組織蛋白酶-L 之注射部位的灌注液中偵側到穩定的酶促活性。此等結果指示組織蛋白酶-L 之酶促活性可受到緩衝液離子強度之嚴格調節。

實施例 22

注入 Zucker 大鼠皮下層之組織蛋白酶-L 對纖維中隔之破壞

在投予於 50 mM MES、150 mM NaCl（pH 5.3）中之 1200 U/ml rHuPH20 後用於 50 mM MES 緩衝液、150 mM NaCl（pH 5.3）中之 10 μg/mL 或 100 μg/mL 組織蛋白酶-L 處理的 22 隻雄性 Zucker 大鼠體內評估注入 Zucker 大鼠之皮下層中之一個單劑量的組織蛋白酶-L 之作用。每週進行活組織檢查一次歷時 20 週之時期且如實施例 5 中所述進行組織學分析。如實施例 17 中所述用 10 μg/ml 或 100 μg/ml 劑量之組織蛋白酶-L 的單一處理導致纖維中隔之快速破壞。第 4 週時進行之組織學分析指示纖維中隔之數目在經處理之區域中比在未經處理之區域中少。自第 20 週起，在經處理之區域中未見纖維中隔之典型垂直取向。相反地，下皮中之膠原蛋白的取向為水平的且平行於皮膚表面，此與組織重塑一致。

實施例 23

投予組織蛋白酶-L 與副作用無關

對經血管內注射之組織蛋白酶 L 的安全性研究展示無明顯副作用。向 25 g 雄性 balb/c 小鼠（Charles River）及 200 g 雄性 Sprague Dawley 大鼠（Harlan Laboratories）之尾部靜脈中投予濃度達 12 mg/kg 之於 50 mM MES、150 mM NaCl（pH 5.3）中之重組組織蛋白酶 L。針對副作用觀察動物歷時一週。藉由籠側觀察未記錄到副作用。

實施例 24

組織蛋白酶-L 改變豬下皮中之纖維中隔微結構之結構

經由插入側腹之下皮中的 23 號蝶形針(Terumo, Leuven, Belgium，目錄號 CE0197)使經麻醉之約克夏豬(SNS 農場，Ramona, Ca)接受 5 mL 含有 1200 U/mL rHuPH20 之 50 mM MES、150 mM NaCl 緩衝液（pH 5.3)，緊接著隨後接受：i) 5 mL 於 50 mM MES、150 mM NaCl 緩衝液（pH 5.3）中之 50 μg/ml 組織蛋白酶-L；或 ii) 50 μg 於 50 mM HEPES、150 mM NaCl 緩衝液（pH 7.4）中之細菌膠原酶。對照為 50 mM MES 緩衝液、150 mM NaCl(pH 5.3)；單獨 rHuPH20(pH 5.3) 及組織蛋白酶-L（pH 7.4)。處理後 2 小時、24 小時及 7 天時收集全厚度活組織且將其固定於波恩氏固定劑中。切割 6 mm 組織切片且用蘇木素及伊紅或用馬松三色膠原蛋白染色進行染色。在膠原酶注射部位觀察到特徵為強烈棕色褪色之總體變化，但在經組織蛋白酶-L 處理之部位程度小得多。在注射對照之部位或在未經處理之皮膚中未見總體變化。此等結果展示用組織蛋白酶-L 處理與細菌膠原酶注射相比伴有最小限度的出血。

總體變化典型地與用膠原酶之實質皮下注射部位出血的組織學發現有關，但用組織蛋白酶-L 出血最少。纖維中隔之微結構的特徵在於與僅經 MES 緩衝液處理之皮膚中之緻密包裝的膠原蛋白中隔相比，注射組織蛋白酶-L 及細菌膠原酶之皮膚中之膠原纖維縱向分裂、崩解及形成角度。然而，組織學結果展示與經組織蛋白酶-L 處理之部位相

比，經膠原酶處理之部位中之中隔的微結構之變化更嚴重，此與出血結果一致。另外，用低至 5 μg/ mL 之劑量的細菌膠原酶處理導致嚴重橫紋肌溶解。此等結果證明雖然組織蛋白酶-L 降解膠原蛋白且改變纖維中隔之結構，但其作用比細菌膠原酶更受控制，因為組織蛋白酶-L 於生理學 pH 值下快速失活，而膠原酶於生理學 pH 值下在較長時期內具活性。

在另一研究中，使豬接受 5 mL 之 120 U/ml rHuPH20（pH 5.3），隨後接受 5 mL 於 50 mM MES、150 mM NaCl（pH 5.3）中之劑量範圍為 5 μg/mL 至 1000 μg/mL（5、25、50、100、200、500 及 1000 μg/mL）重組組織蛋白酶-L。處理後 2 小時及 24 小時時收集全厚度皮膚活組織，將其固定於波恩氏固定劑中且經處理以供 H&E 染色或如實施例 5 中所述用馬松三色處理以用於膠原蛋白染色。對注射後 2 小時及 24 小時時切下之皮膚的目測檢查展示用 25 μg/mL 及 25 μg/mL 以上劑量處理之注射部位存在中度出血。僅在 500 μg/mL 及 1000 μg/mL 之高劑量的重組組織蛋白酶-L 情況下在注射部位區域中觀察到橫紋肌溶解。

因為修改形式對於熟習此項技術者將顯而易見，所以預期本發明僅由隨附申請專利範圍之範疇限制。

【圖式簡單說明】

無

【主要元件符號說明】

無

序列表

<110> 吉伯特　凱樂
葛傑瑞　芙羅斯

<120> 可活化的基質降解酵素之活體內暫時性控制

<130> 0119374-00110/ 3056TW

<140> 尚未指定
<141> 同此

<150> 61/068,667
<151> 2008-03-06

<150> 61/127,725
<151> 2008-05-14

<160> 308

<170> 適用　Windows 4.0　版的　FastSEQ

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<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶L

<220>
<223> 組織蛋白酶L1重鏈 1-175

<220>
<223> 組織蛋白酶L1輕鏈 179-220

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Ala	Leu	Glu	Gly	Gln	Met	Phe	Arg	Lys	Thr	Gly	Arg	Leu	Ile	Ser	Leu
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Ser	Glu	Gln	Asn	Leu	Val	Asp	Cys	Ser	Gly	Pro	Gln	Gly	Asn	Glu	Gly
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Cys	Asn	Gly	Gly	Leu	Met	Asp	Tyr	Ala	Phe	Gln	Tyr	Val	Gln	Asp	Asn
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				85					90					95	
Ser	Cys	Lys	Tyr	Asn	Pro	Lys	Tyr	Ser	Val	Ala	Asn	Asp	Thr	Gly	Phe
			100					105					110		
Val	Asp	Ile	Pro	Lys	Gln	Glu	Lys	Ala	Leu	Met	Lys	Ala	Val	Ala	Thr
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Val	Gly	Pro	Ile	Ser	Val	Ala	Ile	Asp	Ala	Gly	His	Glu	Ser	Phe	Leu
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Phe	Tyr	Lys	Glu	Gly	Ile	Tyr	Phe	Glu	Pro	Asp	Cys	Ser	Ser	Glu	Asp
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Met	Asp	His	Gly	Val	Leu	Val	Val	Gly	Tyr	Gly	Phe	Glu	Ser	Thr	Glu
				165					170					175	
Ser	Asp	Asn	Asn	Lys	Tyr	Trp	Leu	Val	Lys	Asn	Ser	Trp	Gly	Glu	Glu
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Trp	Gly	Met	Gly	Gly	Tyr	Val	Lys	Met	Ala	Lys	Asp	Arg	Arg	Asn	His
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<211> 22
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<213> 現代人

<220>
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Leu Pro Gly Ala Arg Gly
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<210> 3
<211> 1032
<212> DNA
<213> 現代人

<220>
<223> 具有異源信號序列及Nhe1與BamHI限制性位點之經優化的合成Cat-L構築體

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<212> PRT
<213> 現代人

<220>
<223> 具有異源信號序列之經優化的合成Cat-L構築體

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35 40 45

Glu Glu Gly Trp Arg Arg Ala Val Trp Glu Lys Asn Met Lys Met Ile
50 55 60

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Ala Met Asn Ala Phe Gly Asp Met Thr Ser Glu Glu Phe Arg Gln Val
                85                  90                  95
Met Asn Gly Phe Gln Asn Arg Lys Pro Arg Lys Gly Lys Val Phe Gln
            100                 105                 110
Glu Pro Leu Phe Tyr Glu Ala Pro Arg Ser Val Asp Trp Arg Glu Lys
        115                 120                 125
Gly Tyr Val Thr Pro Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp
    130                 135                 140
Ala Phe Ser Ala Thr Gly Ala Leu Glu Gly Gln Met Phe Arg Lys Thr
145                 150                 155                 160
Gly Arg Leu Ile Ser Leu Ser Glu Gln Asn Leu Val Asp Cys Ser Gly
                165                 170                 175
Pro Gln Gly Asn Glu Gly Cys Asn Gly Gly Leu Met Asp Tyr Ala Phe
            180                 185                 190
Gln Tyr Val Gln Asp Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro
        195                 200                 205
Tyr Glu Ala Thr Glu Glu Ser Cys Lys Tyr Asn Pro Lys Tyr Ser Val
    210                 215                 220
Ala Asn Asp Thr Gly Phe Val Asp Ile Pro Lys Gln Glu Lys Ala Leu
225                 230                 235                 240
Met Lys Ala Val Ala Thr Val Gly Pro Ile Ser Val Ala Ile Asp Ala
                245                 250                 255
Gly His Glu Ser Phe Leu Phe Tyr Lys Glu Gly Ile Tyr Phe Glu Pro
            260                 265                 270
Asp Cys Ser Ser Glu Asp Met Asp His Gly Val Leu Val Val Gly Tyr
        275                 280                 285
Gly Phe Glu Ser Thr Glu Ser Asp Asn Asn Lys Tyr Trp Leu Val Lys
    290                 295                 300
Asn Ser Trp Gly Glu Glu Trp Gly Met Gly Gly Tyr Val Lys Met Ala
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Lys Asp Arg Arg Asn His Cys Gly Ile Ala Ser Ala Ala Ser Tyr Pro
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Thr Val
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<211> 6201
<212> DNA
<213> 人造序列

<220>
<223> 具有異源信號序列之合成Cat-L HZ24表現載體

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<223> 具有異源信號序列及限制性位點之經優化的合成Cat-L His構築體

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ggaaacgagg ggtgcaatgg agggctcatg gactatgcat ttcagtacgt gcaggacaat 600
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aaatactggt tggtgaaaaa ctcctggggg gaggagtggg gcatgggcgg atacgtgaag 960
atggccaaag acagaaggaa tcactgtgga atcgcatctg ctgccagcta tccaactgta 1020
ggaggaggcg gttcaggtca ccaccaccat caccactagt gaggatcc 1068

<210> 7
<211> 350
<212> PRT
<213> 現代人

<220>
<223> 具有異源信號序列之經優化的合成Cat-L-His構築體

<400> 7
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
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Leu Pro Gly Ala Arg Gly Thr Leu Thr Phe Asp His Ser Leu Glu Ala
            20   25   30

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

<210> 8
<211> 6237
<212> DNA
<213> 人造序列

<220>
<223> 具有異源信號序列之合成Cat-L-His表現載體

<400> 8

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aatatgaccg ccatgttggc attgattatt gactagttat taatagtaat caattacggg 180
gtcattagtt catagcccat atatggagtt ccgcgttaca taacttacgg taaatggccc 240
gcctggctga ccgcccaacg acccccgccc attgacgtca ataatgacgt atgttcccat 300
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ccacttggca gtacatcaag tgtatcatat gccaagtccg ccccctattg acgtcaatga 420
cggtaaatgg cccgcctggc attatgccca gtacatgacc ttacgggact ttcctacttg 480
gcagtacatc tacgtattag tcatcgctat taccatggtg atgcggtttt ggcagtacac 540
caatgggcgt ggatagcggt ttgactcacg gggatttcca agtctccacc ccattgacgt 600
caatgggagt ttgttttggc accaaaatca acgggacttt ccaaaatgtc gtaataaccc 660
cgccccgttg acgcaaatgg gcggtaggcg tgtacggtgg gaggtctata taagcagagc 720
tcgtttagtg aaccgtcaga tcactagaag ctttattgcg gtagtttatc acagttaaat 780
tgctaacgca gtcagtgctt ctgacacaac agtctcgaac ttaagctgca gaagttggtc 840
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```

<210> 9
<211> 333
<212> PRT
<213> 現代人

<220>
<223> 含有異源分泌信號之人類Cat-L蛋白質

<400> 9

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

Glu Ser Cys Lys Tyr Asn Pro Lys Tyr Ser Val Ala Asn Asp Thr Gly
```

```
    210                 215                 220
Phe Val Asp Ile Pro Lys Gln Glu Lys Ala Leu Met Lys Ala Val Ala
225                 230                 235                 240
Thr Val Gly Pro Ile Ser Val Ala Ile Asp Ala Gly His Glu Ser Phe
                245                 250                 255
Leu Phe Tyr Lys Glu Gly Ile Tyr Phe Glu Pro Asp Cys Ser Ser Glu
            260                 265                 270
Asp Met Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Ser Thr
        275                 280                 285
Glu Ser Asp Asn Asn Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Glu
    290                 295                 300
Glu Trp Gly Met Gly Gly Tyr Val Lys Met Ala Lys Asp Arg Arg Asn
305                 310                 315                 320
His Cys Gly Ile Ala Ser Ala Ala Ser Tyr Pro Thr Val
                325                 330
```

<210> 10
<211> 1002
<212> DNA
<213> 現代人

<220>
<223> 經定序之Cat-L插入物（BATJ）的cDNA

<400> 10

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ctgcacaatc aggaatacag ggaagggaaa cacagcttca caatggccat gaacgccttt 240
ggagacatga ccagtgaaga attcaggcag gtgatgaatg gctttcaaaa ccgtaagccc 300
aggaagggga aagtgttcca ggaacctctg ttttatgagg cccccagatc tgtggattgg 360
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tttagtgcta ctggtgctct tgaaggacag atgttccgga aaactgggag gcttatctca 480
ctgagtgagc agaatctggt agactgctct gggcctcaag gcaatgaagg ctgcaatggt 540
ggcctaatgg attatgcttt ccagtatgtt caggataatg gaggcctgga ctctgaggaa 600
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aatgacaccg gctttgtgga catccctaag caggagaagg ccctgatgaa ggcagttgca 720
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gaaggcattt attttgagcc agactgtagc agtgaagaca tggatcatgg tgtgctggtg 840
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<210> 11
<211> 6190
<212> DNA
<213> 人造序列

<220>
<223> 含有Cat-L cDNA之HZ24表現載體

<400> 11

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gtcattagtt catagcccat atatggagtt ccgcgttaca taacttacgg taaatggccc 240
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caatgggcgt ggatagcggt ttgactcacg gggatttcca agtctccacc ccattgacgt 600
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<212> PRT
<213> 現代人

<220>
<223> 含有異源分泌信號之人類-Cat-L-His

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Thr Val Gly Pro Ile Ser Val Ala Ile Asp Ala Gly His Glu Ser Phe
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Asp Met Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Ser Thr
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Glu Ser Asp Asn Asn Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Glu
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<213> 現代人

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<211> 6205
<212> DNA
<213> 人造序列

<220>
<223> 含有Cat-L-His cDNA之HZ24表現載體

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<211> 6
<212> PRT
<213> 人造序列

<220>
<223> 連接子

<400> 15
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<210> 16
<211> 42
<212> DNA
<213> 人造序列

<220>
<223> 人類Cat-L 5'引子

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<210> 17
<211> 35
<212> DNA

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<223> 人類Cat-L 3'引子

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<210> 18
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<212> DNA
<213> 人造序列

<220>
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<210> 19
<211> 952
<212> DNA
<213> 現代人

<220>
<223> 胰腺彈性蛋白酶（PE1；彈性蛋白酶-1）前驅體

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tgtccagccg gggctgtaat gtctccagga agcctacagt cttcacccag gtctctgctt 780
acatctcctg gataaataat gtcatcgcct ccaactgaac attttcctga gtccaacgac 840
cttcccaaaa tggttcttag atctgcaata ggacttgcga tcaaaaagta aaacacattc 900
tgaaagacta ttgagccatt gatagaaaag caaataaaac tagatataca tt 952

<210> 20
<211> 258
<212> PRT
<213> 現代人

<220>
<223> 胰腺彈性蛋白酶（PE1；彈性蛋白酶-1）前驅體

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

65 70 75 80
Ser Gln Asn Asp Gly Thr Glu Gln Tyr Val Ser Val Gln Lys Ile Val
85 90 95
Val His Pro Tyr Trp Asn Ser Asp Asn Val Ala Ala Gly Tyr Asp Ile
100 105 110
Ala Leu Leu Arg Leu Ala Gln Ser Val Thr Leu Asn Ser Tyr Val Gln
115 120 125
Leu Gly Val Leu Pro Gln Glu Gly Ala Ile Leu Ala Asn Asn Ser Pro
130 135 140
Cys Tyr Ile Thr Gly Trp Gly Lys Thr Lys Thr Asn Gly Gln Leu Ala
145 150 155 160
Gln Thr Leu Gln Gln Ala Tyr Leu Pro Ser Val Asp Tyr Ala Ile Cys
165 170 175
Ser Ser Ser Ser Tyr Trp Gly Ser Thr Val Lys Asn Thr Met Val Cys
180 185 190
Ala Gly Gly Asp Gly Val Arg Ser Gly Cys Gln Gly Asp Ser Gly Gly
195 200 205
Pro Leu His Cys Leu Val Asn Gly Lys Tyr Ser Val His Gly Val Thr
210 215 220
Ser Phe Val Ser Ser Arg Gly Cys Asn Val Ser Arg Lys Pro Thr Val
225 230 235 240
Phe Thr Gln Val Ser Ala Tyr Ile Ser Trp Ile Asn Asn Val Ile Ala
245 250 255

Ser Asn

<210> 21
<211> 239
<212> PRT
<213> 現代人

<220>
<223> 胰腺彈性蛋白酶(PE1;彈性蛋白酶-1)前蛋白

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

165 170 175
Asp Gly Val Arg Ser Gly Cys Gln Gly Asp Ser Gly Gly Pro Leu His
180 185 190
Cys Leu Val Asn Gly Lys Tyr Ser Val His Gly Val Thr Ser Phe Val
195 200 205
Ser Ser Arg Gly Cys Asn Val Ser Arg Lys Pro Thr Val Phe Thr Gln

```
    210                 215                 220
Val Ser Ala Tyr Ile Ser Trp Ile Asn Asn Val Ile Ala Ser Asn
225                 230                 235
```

<210> 22
<211> 979
<212> DNA
<213> 現代人

<220>
<223> 彈性蛋白酶-2A前驅體

<400> 22
cttacagaac tcccacggac acaccatgat aaggacgctg ctgctgtcca ctttggtggc 60
tggagccctc agttgtgggg accccactta cccaccttat gtgactaggg tggttggcgg 120
tgaagaagcg aggcccaaca gctggccctg gcaggtctcc ctgcagtaca gctccaatgg 180
caagtggtac cacacctgcg gagggtccct gatagccaac agctgggtcc tgacggctgc 240
ccactgcatc agctcctcca ggacctaccg cgtggggctg ggccggcaca acctctacgt 300
tgcggagtcc ggctcgctgg cagtcagtgt ctctaagatt gtggtgcaca aggactggaa 360
ctccaaccaa atctccaaag ggaacgacat tgccctgctc aaactggcta accccgtctc 420
cctcaccgac aagatccagc tggcctgcct ccctcctgcc ggcaccattc tacccaacaa 480
ctacccctgc tacgtcacgg gctggggaag gctgcagacc aacggggctg ttcctgatgt 540
cctgcagcag ggccggttgc tggttgtgga ctatgccacc tgctccagct ctgcctggtg 600
gggcagcagc gtgaaaacca gtatgatctg tgctgggggt gatggcgtga tctccagctg 660
caacggagac tctggcgggc cactgaactg tcaggcgtct gacggccggt ggcaggtgca 720
cggcatcgtc agcttcgggt ctcgcctcgg ctgcaactac taccacaagc cctccgtctt 780
cacgcgggtc tccaattaca tcgactggat caattcggtg attgcaaata actaaccaaa 840
agaagtccct gggactgttt cagacttgga aaggtcacag aaggaaaata atataataaa 900
gtgacaacta tgcaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaata aaaaaaaaaa 960
aaaaaaaaaa aaaaaaaaa   979

<210> 23
<211> 269
<212> PRT
<213> 現代人

<220>
<223> 彈性蛋白酶-2A前驅體

<400> 23
```
Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu Ser
 1               5                  10                  15
Cys Gly Asp Pro Thr Tyr Pro Pro Tyr Val Thr Arg Val Val Gly Gly
            20                  25                  30
Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln Tyr
        35                  40                  45
Ser Ser Asn Gly Lys Trp Tyr His Thr Cys Gly Gly Ser Leu Ile Ala
    50                  55                  60
Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Arg Thr
65                  70                  75                  80
Tyr Arg Val Gly Leu Gly Arg His Asn Leu Tyr Val Ala Glu Ser Gly
                85                  90                  95
Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp Asn
            100                 105                 110
Ser Asn Gln Ile Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu Ala
        115                 120                 125
Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro Pro
    130                 135                 140
Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr Val Thr Gly Trp
145                 150                 155                 160
Gly Arg Leu Gln Thr Asn Gly Ala Val Pro Asp Val Leu Gln Gln Gly
                165                 170                 175
Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser Ser Ala Trp Trp
            180                 185                 190
```

```
Gly Ser Ser Val Lys Thr Ser Met Ile Cys Ala Gly Gly Asp Gly Val
        195                 200                 205
Ile Ser Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln Ala
    210                 215                 220
Ser Asp Gly Arg Trp Gln Val His Gly Ile Val Ser Phe Gly Ser Arg
225                 230                 235                 240
Leu Gly Cys Asn Tyr Tyr His Lys Pro Ser Val Phe Thr Arg Val Ser
                245                 250                 255

Asn Tyr Ile Asp Trp Ile Asn Ser Val Ile Ala Asn Asn
            260                 265
```

<210> 24
<211> 241
<212> PRT
<213> 現代人

<220>
<223> 成熟彈性蛋白酶-2A

<400> 24

```
Val Val Gly Gly Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu Gln Tyr Ser Ser Asn Gly Lys Trp Tyr His Thr Cys Gly Gly
            20                  25                  30
Ser Leu Ile Ala Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser
        35                  40                  45
Ser Ser Arg Thr Tyr Arg Val Gly Leu Gly Arg His Asn Leu Tyr Val
    50                  55                  60
Ala Glu Ser Gly Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His
65                  70                  75                  80
Lys Asp Trp Asn Ser Asn Gln Ile Ser Lys Gly Asn Asp Ile Ala Leu
                85                  90                  95

Leu Lys Leu Ala Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala
            100                 105                 110
Cys Leu Pro Pro Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr
        115                 120                 125
Val Thr Gly Trp Gly Arg Leu Gln Thr Asn Gly Ala Val Pro Asp Val
    130                 135                 140
Leu Gln Gln Gly Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser
145                 150                 155                 160
Ser Ala Trp Trp Gly Ser Ser Val Lys Thr Ser Met Ile Cys Ala Gly
                165                 170                 175
Gly Asp Gly Val Ile Ser Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu
            180                 185                 190
Asn Cys Gln Ala Ser Asp Gly Arg Trp Gln Val His Gly Ile Val Ser
        195                 200                 205
Phe Gly Ser Arg Leu Gly Cys Asn Tyr Tyr His Lys Pro Ser Val Phe
    210                 215                 220
Thr Arg Val Ser Asn Tyr Ile Asp Trp Ile Asn Ser Val Ile Ala Asn
225                 230                 235                 240
Asn
```

<210> 25
<211> 941
<212> DNA
<213> 現代人

<220>
<223> 彈性蛋白酶-2B前驅體

<400> 25
cttacagaac tcccacggac acaccatgat taggaccctg ctgctgtcca ctttggtggc 60
tggagccctc agttgtgggg tctccactta cgcgcctgat atgtctagga tgcttggagg 120
tgaagaagcg aggcccaaca gctggccctg gcaggtctcc ctgcagtaca gctccaatgg 180
ccagtggtac cacacctgcg gagggtccct gatagccaac agctgggtcc tgacggctgc 240
ccactgcatc agctcctccg ggatctaccg cgtgatgctg ggccagcata acctctacgt 300
tgcagagtcc ggctcgctgg ccgtcagtgt ctctaagatt gtggtgcaca aggactggaa 360
ctccgaccag gtctccaaag ggaacgacat tgccctgctc aaactggcta accccgtctc 420
cctcaccgac aagatccagc tggcctgcct ccctcctgcc ggcaccattc tacccaacaa 480
ctacccctgc tacgtcacgg gctggggaag gctgcagacc aacggggctc tccctgatga 540
cctgaagcag ggccggttgc tggttgtgga ctatgccacc tgctccagct ctggctggtg 600
gggcagcacc gtgaagacga atatgatctg tgctgggggt gatggcgtga tatgcacctg 660
caacggagac tccggtgggc cgctgaactg tcaggcatct gacggccggt gggaggtgca 720
tggcatcggc agcctcacgt cggtccttgg ttgcaactac tactacaagc cctccatctt 780
cacgcgggtc tccaactaca acgactggat caattcggtg attgcaaata actaaccaaa 840
agaagtccct gggactgttt cagacttgga aaggtcacag aaggaaaata atattatata 900
aagtgacaac tatgcaaatc acaaaaaaaa aaaaaaaaaa a 941

<210> 26
<211> 269
<212> PRT
<213> 現代人

<220>
<223> 彈性蛋白酶-2B前驅體

<400> 26
Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu Ser
 1   5   10   15
Cys Gly Val Ser Thr Tyr Ala Pro Asp Met Ser Arg Met Leu Gly Gly
            20   25   30
Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln Tyr
        35   40   45
Ser Ser Asn Gly Gln Trp Tyr His Thr Cys Gly Gly Ser Leu Ile Ala
    50   55   60
Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Arg Ile
65   70   75   80
Tyr Arg Val Met Leu Gly Gln His Asn Leu Tyr Val Ala Glu Ser Gly
                85   90   95
Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp Asn
            100   105   110
Ser Asn Gln Val Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu Ala
        115   120   125
Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro Pro
    130   135   140
Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr Val Thr Gly Trp
145   150   155   160
Gly Arg Leu Gln Thr Asn Gly Ala Leu Pro Asp Asp Leu Lys Gln Gly
                165   170   175
Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser Ser Gly Trp Trp
            180   185   190
Gly Ser Thr Val Lys Thr Asn Met Ile Cys Ala Gly Gly Asp Gly Val
        195   200   205
Ile Cys Thr Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln Ala
    210   215   220
Ser Asp Gly Arg Trp Glu Val His Gly Ile Gly Ser Leu Thr Ser Val
225   230   235   240
Leu Gly Cys Asn Tyr Tyr Tyr Lys Pro Ser Ile Phe Thr Arg Val Ser
                245   250   255
Asn Tyr Asn Asp Trp Ile Asn Ser Val Ile Ala Asn Asn
            260   265

<210> 27
<211> 241

<212> PRT
<213> 現代人

<220>
<223> 成熟彈性蛋白酶-2B

<400> 27
Met Leu Gly Gly Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val
 1   5   10   15
Ser Leu Gln Tyr Ser Ser Asn Gly Gln Trp Tyr His Thr Cys Gly Gly
            20   25   30
Ser Leu Ile Ala Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser
        35   40   45
Ser Ser Arg Ile Tyr Arg Val Met Leu Gly Gln His Asn Leu Tyr Val
    50   55   60
Ala Glu Ser Gly Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His
65   70   75   80
Lys Asp Trp Asn Ser Asn Gln Val Ser Lys Gly Asn Asp Ile Ala Leu
                85   90   95
Leu Lys Leu Ala Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala
            100   105   110
Cys Leu Pro Pro Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr
        115   120   125
Val Thr Gly Trp Gly Arg Leu Gln Thr Asn Gly Ala Leu Pro Asp Asp
    130   135   140
Leu Lys Gln Gly Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser
145   150   155   160
Ser Gly Trp Trp Gly Ser Thr Val Lys Thr Asn Met Ile Cys Ala Gly
                165   170   175
Gly Asp Gly Val Ile Cys Thr Cys Asn Gly Asp Ser Gly Gly Pro Leu
            180   185   190
Asn Cys Gln Ala Ser Asp Gly Arg Trp Glu Val His Gly Ile Gly Ser
        195   200   205
Leu Thr Ser Val Leu Gly Cys Asn Tyr Tyr Tyr Lys Pro Ser Ile Phe
    210   215   220
Thr Arg Val Ser Asn Tyr Asn Asp Trp Ile Asn Ser Val Ile Ala Asn
225   230   235   240
Asn

<210> 28
<211> 938
<212> DNA
<213> 現代人

<220>
<223> 嗜中性白血球彈性蛋白酶前驅體

<400> 28
gcacggaggg gcagagaccc cggagcccca gccccaccat gaccctcggc cgccgactcg 60
cgtgtctttt cctcgcctgt gtcctgccgg ccttgctgct gggggggcacc gcgctggcct 120
cggagattgt gggggggccgg cgagcgcggc cccacgcgtg gcccttcatg gtgtccctgc 180
agctgcgcgg aggccacttc tgcggcgcca ccctgattgc gcccaacttc gtcatgtcgg 240
ccgcgcactg cgtggcgaat gtaaacgtcc gcgcggtgcg ggtggtcctg ggagcccata 300
acctctcgcg gcgggagccc acccggcagg tgttcgccgt gcagcgcatc ttcgaaaacg 360
gctacgaccc cgtaaacttg ctcaacgaca tcgtgattct ccagctcaac gggtcggcca 420
ccatcaacgc caacgtgcag gtggcccagc tgccggctca gggacgccgc ctgggcaacg 480
gggtgcagtg cctggccatg ggctggggcc ttctgggcag gaaccgtggg atcgccagcg 540
tcctgcagga gctcaacgtg acggtggtga cgtccctctg ccgtcgcagc aacgtctgca 600
ctctcgtgag gggccggcag gccggcgtct gtttcgggga ctccggcagc cccttggtct 660
gcaacgggct aatccacgga attgcctcct tcgtccgggg aggctgcgcc tcagggctct 720
accccgatgc ctttgccccg gtggcacagt ttgtaaactg gatcgactct atcatccaac 780
gctccgagga caacccctgt ccccaccccc gggacccgga cccggccagc aggacccact 840
gagaagggct gcccgggtca cctcagctgc ccacacccac actctccagc atctggcaca 900

ataaacattc tctgttttgt agaaaaaaaa aaaaaaaa 938

<210> 29
<211> 267
<212> PRT
<213> 現代人

<220>
<223> 嗜中性白血球彈性蛋白酶前驅體

<400> 29

```
Met Thr Leu Gly Arg Arg Leu Ala Cys Leu Phe Leu Ala Cys Val Leu
 1               5                  10                  15
Pro Ala Leu Leu Leu Gly Gly Thr Ala Leu Ala Ser Glu Ile Val Gly
            20                  25                  30
Gly Arg Arg Ala Arg Pro His Ala Trp Pro Phe Met Val Ser Leu Gln
        35                  40                  45
Leu Arg Gly Gly His Phe Cys Gly Ala Thr Leu Ile Ala Pro Asn Phe
    50                  55                  60
Val Met Ser Ala Ala His Cys Val Ala Asn Val Asn Val Arg Ala Val
65                  70                  75                  80
Arg Val Val Leu Gly Ala His Asn Leu Ser Arg Arg Glu Pro Thr Arg
                85                  90                  95
Gln Val Phe Ala Val Gln Arg Ile Phe Glu Asn Gly Tyr Asp Pro Val
            100                 105                 110
Asn Leu Leu Asn Asp Ile Val Ile Leu Gln Leu Asn Gly Ser Ala Thr
        115                 120                 125
Ile Asn Ala Asn Val Gln Val Ala Gln Leu Pro Ala Gln Gly Arg Arg
    130                 135                 140
Leu Gly Asn Gly Val Gln Cys Leu Ala Met Gly Trp Gly Leu Leu Gly
145                 150                 155                 160
Arg Asn Arg Gly Ile Ala Ser Val Leu Gln Glu Leu Asn Val Thr Val
                165                 170                 175
Val Thr Ser Leu Cys Arg Arg Ser Asn Val Cys Thr Leu Val Arg Gly
            180                 185                 190
Arg Gln Ala Gly Val Cys Phe Gly Asp Ser Gly Ser Pro Leu Val Cys
        195                 200                 205
Asn Gly Leu Ile His Gly Ile Ala Ser Phe Val Arg Gly Gly Cys Ala
    210                 215                 220
Ser Gly Leu Tyr Pro Asp Ala Phe Ala Pro Val Ala Gln Phe Val Asn
225                 230                 235                 240
Trp Ile Asp Ser Ile Ile Gln Arg Ser Glu Asp Asn Pro Cys Pro His
                245                 250                 255
Pro Arg Asp Pro Asp Pro Ala Ser Arg Thr His
            260                 265
```

<210> 30
<211> 238
<212> PRT
<213> 現代人

<220>
<223> 成熟嗜中性白血球彈性蛋白酶

<400> 30

```
Ile Val Gly Gly Arg Arg Ala Arg Pro His Ala Trp Pro Phe Met Val
 1               5                  10                  15
Ser Leu Gln Leu Arg Gly Gly His Phe Cys Gly Ala Thr Leu Ile Ala
            20                  25                  30
Pro Asn Phe Val Met Ser Ala Ala His Cys Val Ala Asn Val Asn Val
        35                  40                  45
Arg Ala Val Arg Val Val Leu Gly Ala His Asn Leu Ser Arg Arg Glu
    50                  55                  60
```

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

<210> 31
<211> 1001
<212> DNA
<213> 現代人

<220>
<223> 蛋白酶-3前驅體

<400> 31

```
cgtgggtgca ccctggaccc caccatggct caccggcccc ccagccctgc cctggcgtcc 60
gtgctgctgg ccttgctgct gagcggtgct gcccgagctg cggagatcgt gggcgggcac 120
gaggcgcagc cacactcccg gccctacatg gcctccctgc agatgcgggg gaacccgggc 180
agccacttct gcggaggcac cttgatccac cccagcttcg tgctgacggc cgcgcactgc 240
ctgcgggaca taccccagcg cctggtgaac gtggtgctcg gagcccacaa cgtgcggacg 300
caggagccca cccagcagca cttctcggtg gctcaggtgt ttctgaacaa ctacgacgcg 360
gagaacaaac tgaacgacgt tctcctcatc cagctgagca gcccagccaa cctcagtgcc 420
tccgtcgcca cagtccagct gccacagcag gaccagccag tgccccacgg cacccagtgc 480
ctggccatgg gctggggccg cgtgggtgcc cacgaccccc cagcccaggt cctgcaggag 540
ctcaatgtca ccgtggtcac cttcttctgc cggccacata acatttgcac tttcgtccct 600
cgccgcaagg ccggcatctg cttcggagac tcaggtggcc ccctgatctg tgatggcatc 660
atccaaggaa tagactcctt cgtgatctgg ggatgtgcca cccgcctttt ccctgacttc 720
ttcacgcggg tagccctcta cgtggactgg atccgttcca cgctgcgccg tgtggaggcc 780
aagggccgcc cctgaaccgc ccctcccaca gcgctggccg ggaccccgag cctggctcca 840
aaccctcgag gcggatcttt ggacagaagc agctcttccc cgaacactgt ggcgtccggg 900
acggccccac ccgtcccccc acactccctc ccacggggct ccgggagaca ggccggccct 960
gcacctcacc ccaccgtgac ctcaataaac gttgaaactc c                    1001
```

<210> 32
<211> 256
<212> PRT
<213> 現代人

<220>
<223> 蛋白酶-3前驅體

<400> 32

```
Met Ala His Arg Pro Pro Ser Pro Ala Leu Ala Ser Val Leu Leu Ala
 1               5                  10                  15
Leu Leu Leu Ser Gly Ala Ala Arg Ala Ala Glu Ile Val Gly Gly His
            20                  25                  30
Glu Ala Gln Pro His Ser Arg Pro Tyr Met Ala Ser Leu Gln Met Arg
```

```
         35                  40                  45
Gly Asn Pro Gly Ser His Phe Cys Gly Gly Thr Leu Ile His Pro Ser
     50                  55                  60
Phe Val Leu Thr Ala Ala His Cys Leu Arg Asp Ile Pro Gln Arg Leu
65                  70                  75                  80
Val Asn Val Val Leu Gly Ala His Asn Val Arg Thr Gln Glu Pro Thr
                85                  90                  95
Gln Gln His Phe Ser Val Ala Gln Val Phe Leu Asn Asn Tyr Asp Ala
            100                 105                 110
Glu Asn Lys Leu Asn Asp Val Leu Leu Ile Gln Leu Ser Ser Pro Ala
        115                 120                 125
Asn Leu Ser Ala Ser Val Ala Thr Val Gln Leu Pro Gln Gln Asp Gln
    130                 135                 140
Pro Val Pro His Gly Thr Gln Cys Leu Ala Met Gly Trp Gly Arg Val
145                 150                 155                 160
Gly Ala His Asp Pro Pro Ala Gln Val Leu Gln Glu Leu Asn Val Thr
                165                 170                 175
Val Val Thr Phe Phe Cys Arg Pro His Asn Ile Cys Thr Phe Val Pro
            180                 185                 190
Arg Arg Lys Ala Gly Ile Cys Phe Gly Asp Ser Gly Gly Pro Leu Ile
        195                 200                 205
Cys Asp Gly Ile Ile Gln Gly Ile Asp Ser Phe Val Ile Trp Gly Cys
    210                 215                 220
Ala Thr Arg Leu Phe Pro Asp Phe Phe Thr Arg Val Ala Leu Tyr Val
225                 230                 235                 240
Asp Trp Ile Arg Ser Thr Leu Arg Arg Val Glu Ala Lys Gly Arg Pro
                245                 250                 255
```

<210> 33
<211> 221
<212> PRT
<213> 現代人

<220>
<223> 成熟蛋白酶-3

<400> 33

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

210 215 220

<210> 34
<211> 846
<212> DNA
<213> 鼠屬

<220>
<223> 內源性血管彈性蛋白酶

<400> 34
atgcacagct ccgtgtacct cgtggctctg gtggtcctgg aggcggctgt atgtgttgcg 60
cagccccgag gtcggattct gggtggccag gaggccatgg cccatgctcg gccctacatg 120
gcttcagtgc aagtgaatgg cacgcacgtg tgcggtggca ccctggtgga tgagcagtgg 180
gtgctgagcg ccgcgcactg catggatgga gtgaccaagg atgaggttgt gcaggtgctc 240
ctgggtgccc actccctgtc cagtcctgaa ccctacaagc atttgtatga tgtgcaaagt 300
gtagtgcttc acccgggcag ccggcctgac agcgttgagg acgacctcat gctctttaag 360
ctctcccaca atgcctcact gggtccccat gtgagacccc tgcccttgca acgcgaggac 420
cgggaggtga aacccggcac gctctgcgat gtggccggtt ggggcgtggt cactcatgcg 480
ggacgcaggc ccgatgtcct gcagcaactg acagtgtcaa tcatggaccg gaacacctgc 540
aatctgcgca cgtaccatga tggggcaatc accaagaaca tgatgtgtgc agagagcaac 600
cgcagggaca cttgcagggg cgactccggc ggtcctctgg tgtgcgggga tgcggtcgaa 660
gctgtggtta cgtggggatc tcgagtctgt ggcaaccgga gaaagccagg tgtctttacc 720
cgcgtggcaa cctacgtgcc gtggattgaa aacgttctga gtggtaacgt gagtgttaac 780
gtgacggcct gaggggacac cggagaccgt gactcacaat aaatgcatgc atctaaaaaa 840
aaaaaa 846

<210> 35
<211> 262
<212> PRT
<213> 鼠屬

<220>
<223> 內源性血管彈性蛋白酶前驅體

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

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

```
    210                 215                 220
Gly Ser Arg Val Cys Gly Asn Arg Arg Lys Pro Gly Val Phe Thr Arg
225                 230                 235                 240
Val Ala Thr Tyr Val Pro Trp Ile Glu Asn Val Leu Ser Gly Asn Val
                245                 250                 255
Ser Val Asn Val Thr Ala
            260
```

<210> 36
<211> 238
<212> PRT
<213> 鼠屬

<220>
<223> 成熟內源性血管彈性蛋白酶

<400> 36

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

<210> 37
<211> 924
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶G前驅體

<400> 37

```
gcacagcagc aactgactgg gcagcctttc aggaaagatg cagccactcc tgcttctgct 60
ggcctttctc ctacccactg gggctgaggc aggggagatc atcggaggcc gggagagcag 120
gccccactcc cgcccctaca tggcgtatct tcagatccag agtccagcag gtcagagcag 180
atgtggaggg ttcctggtgc gagaagactt tgtgctgaca gcagctcatt gctggggaag 240
caatataaat gtcaccctgg gcgcccacaa tatccagaga cgggaaaaca cccagcaaca 300
catcactgcg cgcagagcca tccgccaccc tcaatataat cagcggacca tccagaatga 360
```

catcatgtta ttgcagctga gcagaagagt cagacggaat cgaaacgtga acccagtggc 420
tctgcctaga gcccaggagg gactgagacc cgggacgctg tgcactgtgg ccggctgggg 480
cagggtcagc atgaggaggg gaacagatac actccgagag gtgcagctga gagtgcagag 540
ggataggcag tgcctccgca tcttcggttc ctacgacccc cgaaggcaga tttgtgtggg 600
ggaccggcgg gaacggaagg ctgccttcaa gggggattcc ggaggccccc tgctgtgtaa 660
caatgtggcc cacggcatcg tctcctatgg aaagtcgtca ggggttcctc cagaagtctt 720
caccagggtc tcaagtttcc tgccctggat aaggacaaca atgagaagct tcaaactgct 780
ggatcagatg gagacccccc tgtgactgac tcttcttctc ggggacacag gccagctcca 840
cagtgttgcc agagccttaa taaacgtcca cagagtataa ataaccaatt cctcatttgt 900
tcattaaacg tcattcagta ctta 924

<210> 38
<211> 255
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶G前驅體

<400> 38
Met Gln Pro Leu Leu Leu Leu Leu Ala Phe Leu Leu Pro Thr Gly Ala
 1   5   10   15
Glu Ala Gly Glu Ile Ile Gly Gly Arg Glu Ser Arg Pro His Ser Arg
            20   25   30
Pro Tyr Met Ala Tyr Leu Gln Ile Gln Ser Pro Ala Gly Gln Ser Arg
        35   40   45
Cys Gly Gly Phe Leu Val Arg Glu Asp Phe Val Leu Thr Ala Ala His
    50   55   60
Cys Trp Gly Ser Asn Ile Asn Val Thr Leu Gly Ala His Asn Ile Gln
65   70   75   80
Arg Arg Glu Asn Thr Gln Gln His Ile Thr Ala Arg Arg Ala Ile Arg
                85   90   95
His Pro Gln Tyr Asn Gln Arg Thr Ile Gln Asn Asp Ile Met Leu Leu
            100   105   110
Gln Leu Ser Arg Arg Val Arg Arg Asn Arg Asn Val Asn Pro Val Ala
        115   120   125
Leu Pro Arg Ala Gln Glu Gly Leu Arg Pro Gly Thr Leu Cys Thr Val
    130   135   140
Ala Gly Trp Gly Arg Val Ser Met Arg Arg Gly Thr Asp Thr Leu Arg
145   150   155   160
Glu Val Gln Leu Arg Val Gln Arg Asp Arg Gln Cys Leu Arg Ile Phe
                165   170   175
Gly Ser Tyr Asp Pro Arg Arg Gln Ile Cys Val Gly Asp Arg Arg Glu
            180   185   190
Arg Lys Ala Ala Phe Lys Gly Asp Ser Gly Gly Pro Leu Leu Cys Asn
        195   200   205
Asn Val Ala His Gly Ile Val Ser Tyr Gly Lys Ser Ser Gly Val Pro
    210   215   220
Pro Glu Val Phe Thr Arg Val Ser Ser Phe Leu Pro Trp Ile Arg Thr
225   230   235   240
Thr Met Arg Ser Phe Lys Leu Leu Asp Gln Met Glu Thr Pro Leu
                245   250   255

<210> 39
<211> 235
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶G

<400> 39
Ile Ile Gly Gly Arg Glu Ser Arg Pro His Ser Arg Pro Tyr Met Ala
 1   5   10   15

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

<210> 40
<211> 784
<212> DNA
<213> 現代人

<220>
<223> 肥大細胞凝乳酶前驅體

<400> 40

```
agcatttgct caggcagcct ctctgggaag atgctgcttc ttcctctccc cctgctgctc 60
tttctcttgt gctccagagc tgaagctggg gagatcatcg ggggcacaga atgcaagcca 120
cattcccgcc cctacatggc ctacctggaa attgtaactt ccaacggtcc ctcaaaattt 180
tgtggtggtt tccttataag acggaacttt gtgctgacgg ctgctcattg tgcaggaagg 240
tctataacag tcacccttgg agcccataac ataacagagg aagaagacac atggcagaag 300
cttgaggtta taaagcaatt ccgtcatcca aaatataaca cttctactct tcaccacgat 360
atcatgttac taaagttgaa ggagaaagcc agcctgaccc tggctgtggg gacactcccc 420
ttcccatcac aattcaactt tgtcccacct gggagaatgt gccgggtggc tggctgggga 480
agaacaggtg tgttgaagcc gggctcagac actctgcaag aggtgaagct gagactcatg 540
gatccccagg cctgcagcca cttcagagac tttgaccaca atcttcagct gtgtgtgggc 600
aatcccagga agacaaaatc tgcatttaag ggagactctg ggggccctct tctgtgtgct 660
ggggtggccc agggcatcgt atcctatgga cggtcggatg caaagccccc tgctgtcttc 720
acccgaatct cccattaccg gccctggatc aaccagatcc tgcaggcaaa ttaatcctgg 780
atcc                                                              784
```

<210> 41
<211> 247
<212> PRT
<213> 現代人

<220>
<223> 肥大細胞凝乳酶前驅體

<400> 41

```
Met Leu Leu Leu Pro Leu Pro Leu Leu Leu Phe Leu Leu Cys Ser Arg
 1               5                  10                  15
```

```
Ala Glu Ala Gly Glu Ile Ile Gly Gly Thr Glu Cys Lys Pro His Ser
            20                  25                  30
Arg Pro Tyr Met Ala Tyr Leu Glu Ile Val Thr Ser Asn Gly Pro Ser
        35                  40                  45
Lys Phe Cys Gly Gly Phe Leu Ile Arg Arg Asn Phe Val Leu Thr Ala
    50                  55                  60
Ala His Cys Ala Gly Arg Ser Ile Thr Val Thr Leu Gly Ala His Asn
65                  70                  75                  80
Ile Thr Glu Glu Glu Asp Thr Trp Gln Lys Leu Glu Val Ile Lys Gln
                85                  90                  95
Phe Arg His Pro Lys Tyr Asn Thr Ser Thr Leu His His Asp Ile Met
            100                 105                 110
Leu Leu Lys Leu Lys Glu Lys Ala Ser Leu Thr Leu Ala Val Gly Thr
        115                 120                 125
Leu Pro Phe Pro Ser Gln Phe Asn Phe Val Pro Pro Gly Arg Met Cys
    130                 135                 140
Arg Val Ala Gly Trp Gly Arg Thr Gly Val Leu Lys Pro Gly Ser Asp
145                 150                 155                 160
Thr Leu Gln Glu Val Lys Leu Arg Leu Met Asp Pro Gln Ala Cys Ser
                165                 170                 175
His Phe Arg Asp Phe Asp His Asn Leu Gln Leu Cys Val Gly Asn Pro
            180                 185                 190
Arg Lys Thr Lys Ser Ala Phe Lys Gly Asp Ser Gly Gly Pro Leu Leu
        195                 200                 205
Cys Ala Gly Val Ala Gln Gly Ile Val Ser Tyr Gly Arg Ser Asp Ala
    210                 215                 220
Lys Pro Pro Ala Val Phe Thr Arg Ile Ser His Tyr Arg Pro Trp Ile
225                 230                 235                 240
Asn Gln Ile Leu Gln Ala Asn
                245
```

<210> 42
<211> 226
<212> PRT
<213> 現代人

<220>
<223> 成熟肥大細胞凝乳酶

<400> 42

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

```
Gln Gly Ile Val Ser Tyr Gly Arg Ser Asp Ala Lys Pro Pro Ala Val
        195                 200                 205
Phe Thr Arg Ile Ser His Tyr Arg Pro Trp Ile Asn Gln Ile Leu Gln
    210                 215                 220
Ala Asn
225
```

<210> 43
<211> 855
<212> DNA
<213> 現代人

<220>
<223> 肥大細胞類胰蛋白酶前驅體

<400> 43
aggcccacga tgctcctcct tgctccccag atgctgagcc tgctgctgct ggcgctgccc 60
gtcctggcga gcccggccta cgtggccccc gccccaggcc aggccctgca gcaaacgggc 120
attgttgggg ggcaggaggc ccccaggagc aagtggccct ggcaggtgag cctgagagtc 180
cgcggcccat actggatgca cttctgcggg ggctccctca tccaccccca gtgggtgcta 240
accgcggcgc actgcgtgga accggacatc aaggatctgg ccgccctcag ggtgcaactg 300
cgggagcagc acctctacta ccaggaccag ctgctgccgg tcagcaggat catcgtgcac 360
ccacagttct acatcatcca gaccggggcg gacatcgccc tgctggagct ggaggagccc 420
gtgaacatct ccagccacat ccacacggtc acgctgcccc ctgcctcgga gaccttcccc 480
ccggggatgc cgtgctgggt cactggctgg ggcgacgtgg acaataatgt gcacctgccg 540
ccgccatacc cgctgaagga ggtggaagtc cccgtagtgg aaaaccacct ttgcaacgcg 600
gaatatcaca ccggcctcca tacgggccac agctttcaaa tcgtccgcga tgacatgctg 660
tgtgcgggga gcgaaaatca cgactcctgc cagggtgact ctggagggcc cctggtctgc 720
aaggtgaatg gcacctaact gcaggcgggc gtggtcagct gggaggagag ctgtgcccag 780
cccaaccggc ctggcatcta cacccgtgtc acctactact tggactggat ccaccactat 840
gtccccaaga agccc 855

<210> 44
<211> 242
<212> PRT
<213> 現代人

<220>
<223> 肥大細胞類胰蛋白酶前驅體

<400> 44
```
Met Leu Leu Leu Ala Pro Gln Met Leu Ser Leu Leu Leu Leu Ala Leu
 1               5                  10                  15
Pro Val Leu Ala Ser Pro Ala Tyr Val Ala Pro Ala Pro Gly Gln Ala
            20                  25                  30
Leu Gln Gln Thr Gly Ile Val Gly Gly Gln Glu Ala Pro Arg Ser Lys
        35                  40                  45
Trp Pro Trp Gln Val Ser Leu Arg Val Arg Gly Pro Tyr Trp Met His
    50                  55                  60
Phe Cys Gly Gly Ser Leu Ile His Pro Gln Trp Val Leu Thr Ala Ala
65                  70                  75                  80
His Cys Val Glu Pro Asp Ile Lys Asp Leu Ala Ala Leu Arg Val Gln
                85                  90                  95
Leu Arg Glu Gln His Leu Tyr Tyr Gln Asp Gln Leu Leu Pro Val Ser
            100                 105                 110
Arg Ile Ile Val His Pro Gln Phe Tyr Ile Ile Gln Thr Gly Ala Asp
        115                 120                 125
Ile Ala Leu Leu Glu Leu Glu Glu Pro Val Asn Ile Ser Ser His Ile
    130                 135                 140
His Thr Val Thr Leu Pro Pro Ala Ser Glu Thr Phe Pro Pro Gly Met
145                 150                 155                 160
Pro Cys Trp Val Thr Gly Trp Gly Asp Val Asp Asn Asn Val His Leu
                165                 170                 175
Pro Pro Pro Tyr Pro Leu Lys Glu Val Glu Val Pro Val Val Glu Asn
```

```
            180                 185                 190
His Leu Cys Asn Ala Glu Tyr His Thr Gly Leu His Thr Gly His Ser
        195                 200                 205
Phe Gln Ile Val Arg Asp Asp Met Leu Cys Ala Gly Ser Glu Asn His
    210                 215                 220
Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Lys Val Asn
225                 230                 235                 240
Gly Thr
```

<210> 45
<211> 205
<212> PRT
<213> 現代人

<220>
<223> 成熟肥大細胞類胰蛋白酶

<400> 45

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

<210> 46
<211> 2732
<212> DNA
<213> 現代人

<220>
<223> 纖溶酶前驅體

<400> 46

```
aacaacatcc tgggattggg acccactttc tgggcactgc tggccagtcc caaaatggaa 60
cataaggaag tggttcttct acttctttta tttctgaaat caggtcaagg agagcctctg 120
gatgactatg tgaataccca gggggcttca ctgttcagtg tcactaagaa gcagctggga 180
gcaggaagta tagaagaatg tgcagcaaaa tgtgaggagg acgaagaatt cacctgcagg 240
gcattccaat atcacagtaa agagcaacaa tgtgtgataa tggctgaaaa caggaagtcc 300
tccataatca ttaggatgag agatgtagtt ttatttgaaa agaaagtgta tctctcagag 360
tgcaagactg ggaatggaaa gaactacaga gggacgatgt ccaaaacaaa aaatggcatc 420
acctgtcaaa aatggagttc cacttctccc cacagaccta gattctcacc tgctacacac 480
```

ccctcagagg gactggagga gaactactgc aggaatccag acaacgatcc gcaggggccc 540
tggtgctata ctactgatcc agaaaagaga tatgactact gcgacattct tgagtgtgaa 600
gaggaatgta tgcattgcag tggagaaaac tatgacggca aaatttccaa gaccatgtct 660
ggactggaat gccaggcctg ggactctcag agcccacacg ctcatggata cattccttcc 720
aaatttccaa acaagaacct gaagaagaat tactgtcgta accccgatag ggagctgcgg 780
ccttggtgtt tcaccaccga ccccaacaag cgctgggaac tttgcgacat cccccgctgc 840
acaacacctc caccatcttc tggtcccacc taccagtgtc tgaagggaac aggtgaaaac 900
tatcgcggga atgtggctgt taccgtttcc gggcacacct gtcagcactg gagtgcacag 960
acccctcaca cacataacag gacaccagaa aacttccccc gcaaaaattt ggatgaaaac 1020
tactgccgca atcctgacgg aaaaagggcc ccatggtgcc atacaaccaa cagccaagtg 1080
cggtgggagt actgtaagat accgtcctgt gactcctccc cagtatccac ggaacaattg 1140
gctcccacag caccacctga gctaacccct gtggtccagg actgctacca tggtgatgga 1200
cagagctacc gaggcacatc ctccaccacc accacaggaa agaagtgtca gtcttggtca 1260
tctatgacac cacaccggca ccagaagacc ccagaaaact acccaaatgc tggcctgaca 1320
atgaactact gcaggaatcc agatgccgat aaaggccccc ggtgttttac cacagacccc 1380
agcgtcaggt gggagtactg caacctgaaa aaatgctcag gaacagaagc gagtgttgta 1440
gcacctccgc ctgttgtcct gcttccagat gtagagactc cttccgaaga agactgtatg 1500
tttgggaatg ggaaaggata ccgaggcaag agggcgacca ctgttactgg gacgccatgc 1560
caggactggg ctgcccagga gccccataga cacagcattt tcactccaga gacaaatcca 1620
cgggcgggtc tggaaaaaaa ttactgccgt aaccctgatg gtgatgtagg tggtccctgg 1680
tgctacacga caaatccaag aaaactttac gactactgtg atgtccctca gtgtgcggcc 1740
ccttcatttg attgtgggaa gcctcaagtg gagccgaaga aatgtcctgg aagggttgtg 1800
gggggtgtg tggcccaccc acattcctgg ccctggcaag tcagtcttag aacaaggttt 1860
ggaatgcact tctgtggagg caccttgata tccccagagt gggtgttgac tgctgcccac 1920
tgcttggaga agtccccaag gccttcatcc tacaaggtca tcctgggtgc acaccaagaa 1980
gtgaatctcg aaccgcatgt tcaggaaata gaagtgtcta ggctgttctt ggagcccaca 2040
cgaaaagata ttgccttgct aaagctaagc agtcctgccg tcatcactga caaagtaatc 2100
ccagcttgtc tgccatcccc aaattatgtg gtcgctgacc ggaccgaatg tttcatcact 2160
ggctggggag aaacccaagg tacttttgga gctggccttc tcaaggaagc ccagctccct 2220
gtgattgaga ataaagtgtg caatcgctat gagtttctga atggaagagt ccaatccacc 2280
gaactctgtg ctgggcattt ggccggaggc actgacagtt gccagggtga cagtggaggt 2340
cctctggttt gcttcgagaa ggacaaatac attttacaag gagtcacttc ttggggtctt 2400
ggctgtgcac gccccaataa gcctggtgtc tatgttcgtg tttcaaggtt tgttacttgg 2460
attgagggag tgatgagaaa taattaattg gacgggagac agagtgacgc actgactcac 2520
ctagaggctg ggacgtgggt agggatttag catgctggaa ataactggca gtaatcaaac 2580
gaagacactg tccccagcta ccagctacgc caaacctcgg catttttttgt gttattttct 2640
gactgctgga ttctgtagta aggtgacata gctatgacat ttgttaaaaa taaactctgt 2700
acttaacttt gatttgagta aattttggtt tt 2732

<210> 47
<211> 810
<212> PRT
<213> 現代人

<220>
<223> 纖溶酶前驅體

<400> 47

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

```
    130                 135                 140
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln
145                 150                 155                 160
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys
                165                 170                 175
Asp Ile Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn
            180                 185                 190
Tyr Asp Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala
        195                 200                 205
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe
    210                 215                 220
Pro Asn Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu
225                 230                 235                 240
Leu Arg Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu
                245                 250                 255
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr
            260                 265                 270
Tyr Gln Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala
        275                 280                 285
Val Thr Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro
    290                 295                 300
His Thr His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp
305                 310                 315                 320
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His
                325                 330                 335
Thr Thr Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys
            340                 345                 350
Asp Ser Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro
        355                 360                 365
Glu Leu Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser
    370                 375                 380
Tyr Arg Gly Thr Ser Ser Thr Thr Thr Thr Gly Lys Lys Cys Gln Ser
385                 390                 395                 400
Trp Ser Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr
                405                 410                 415
Pro Asn Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp
            420                 425                 430
Lys Gly Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
        435                 440                 445
Cys Asn Leu Lys Lys Cys Ser Gly Thr Glu Ala Ser Val Val Ala Pro
    450                 455                 460
Pro Pro Val Val Leu Leu Pro Asp Val Glu Thr Pro Ser Glu Glu Asp
465                 470                 475                 480
Cys Met Phe Gly Asn Gly Lys Gly Tyr Arg Gly Lys Arg Ala Thr Thr
                485                 490                 495
Val Thr Gly Thr Pro Cys Gln Asp Trp Ala Ala Gln Glu Pro His Arg
            500                 505                 510
His Ser Ile Phe Thr Pro Glu Thr Asn Pro Arg Ala Gly Leu Glu Lys
        515                 520                 525
Asn Tyr Cys Arg Asn Pro Asp Gly Asp Val Gly Gly Pro Trp Cys Tyr
    530                 535                 540
Thr Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Val Pro Gln Cys
545                 550                 555                 560
Ala Ala Pro Ser Phe Asp Cys Gly Lys Pro Gln Val Glu Pro Lys Lys
                565                 570                 575
Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala His Pro His Ser Trp
            580                 585                 590
Pro Trp Gln Val Ser Leu Arg Thr Arg Phe Gly Met His Phe Cys Gly
        595                 600                 605
Gly Thr Leu Ile Ser Pro Glu Trp Val Leu Thr Ala Ala His Cys Leu
    610                 615                 620
Glu Lys Ser Pro Arg Pro Ser Ser Tyr Lys Val Ile Leu Gly Ala His
625                 630                 635                 640
Gln Glu Val Asn Leu Glu Pro His Val Gln Glu Ile Glu Val Ser Arg
                645                 650                 655
```

```
Leu Phe Leu Glu Pro Thr Arg Lys Asp Ile Ala Leu Leu Lys Leu Ser
            660                 665                 670
Ser Pro Ala Val Ile Thr Asp Lys Val Ile Pro Ala Cys Leu Pro Ser
        675                 680                 685
Pro Asn Tyr Val Val Ala Asp Arg Thr Glu Cys Phe Ile Thr Gly Trp
    690                 695                 700
Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Leu Leu Lys Glu Ala Gln
705                 710                 715                 720
Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Tyr Glu Phe Leu Asn
                725                 730                 735
Gly Arg Val Gln Ser Thr Glu Leu Cys Ala Gly His Leu Ala Gly Gly
            740                 745                 750
Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Phe Glu
        755                 760                 765
Lys Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu Gly Cys
    770                 775                 780
Ala Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg Phe Val
785                 790                 795                 800
Thr Trp Ile Glu Gly Val Met Arg Asn Asn
                805                 810
```

<210> 48
<211> 713
<212> PRT
<213> 現代人

<220>
<223> 成熟纖溶酶

<400> 48

```
Val Tyr Leu Ser Glu Cys Lys Thr Gly Asn Gly Lys Asn Tyr Arg Gly
 1                5                  10                  15
Thr Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser Ser
            20                  25                  30
Thr Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser Glu
        35                  40                  45
Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln Gly
    50                  55                  60
Pro Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys Asp
65                  70                  75                  80
Ile Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn Tyr
                85                  90                  95
Asp Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala Trp
            100                 105                 110
Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe Pro
        115                 120                 125
Asn Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu Leu
    130                 135                 140
Arg Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu Cys
145                 150                 155                 160
Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr Tyr
                165                 170                 175
Gln Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala Val
            180                 185                 190
Thr Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro His
        195                 200                 205
Thr His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp Glu
    210                 215                 220
Asn Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His Thr
225                 230                 235                 240
Thr Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys Asp
                245                 250                 255
Ser Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro Glu
            260                 265                 270
```

```
Leu Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser Tyr
        275                 280                 285
Arg Gly Thr Ser Ser Thr Thr Thr Thr Gly Lys Lys Cys Gln Ser Trp
    290                 295                 300
Ser Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr Pro
305                 310                 315                 320
Asn Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp Lys
                325                 330                 335
Gly Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys
            340                 345                 350
Asn Leu Lys Lys Cys Ser Gly Thr Glu Ala Ser Val Val Ala Pro Pro
        355                 360                 365
Pro Val Val Leu Leu Pro Asp Val Glu Thr Pro Ser Glu Glu Asp Cys
    370                 375                 380
Met Phe Gly Asn Gly Lys Gly Tyr Arg Gly Lys Arg Ala Thr Thr Val
385                 390                 395                 400
Thr Gly Thr Pro Cys Gln Asp Trp Ala Ala Gln Glu Pro His Arg His
                405                 410                 415
Ser Ile Phe Thr Pro Glu Thr Asn Pro Arg Ala Gly Leu Glu Lys Asn
            420                 425                 430
Tyr Cys Arg Asn Pro Asp Gly Asp Val Gly Gly Pro Trp Cys Tyr Thr
        435                 440                 445
Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Val Pro Gln Cys Ala
    450                 455                 460
Ala Pro Ser Phe Asp Cys Gly Lys Pro Gln Val Glu Pro Lys Lys Cys
465                 470                 475                 480
Pro Gly Arg Val Val Gly Gly Cys Val Ala His Pro His Ser Trp Pro
                485                 490                 495
Trp Gln Val Ser Leu Arg Thr Arg Phe Gly Met His Phe Cys Gly Gly
            500                 505                 510
Thr Leu Ile Ser Pro Glu Trp Val Leu Thr Ala Ala His Cys Leu Glu
        515                 520                 525
Lys Ser Pro Arg Pro Ser Ser Tyr Lys Val Ile Leu Gly Ala His Gln
    530                 535                 540
Glu Val Asn Leu Glu Pro His Val Gln Glu Ile Glu Val Ser Arg Leu
545                 550                 555                 560
Phe Leu Glu Pro Thr Arg Lys Asp Ile Ala Leu Leu Lys Leu Ser Ser
                565                 570                 575
Pro Ala Val Ile Thr Asp Lys Val Ile Pro Ala Cys Leu Pro Ser Pro
            580                 585                 590
Asn Tyr Val Val Ala Asp Arg Thr Glu Cys Phe Ile Thr Gly Trp Gly
        595                 600                 605
Glu Thr Gln Gly Thr Phe Gly Ala Gly Leu Leu Lys Glu Ala Gln Leu
    610                 615                 620
Pro Val Ile Glu Asn Lys Val Cys Asn Arg Tyr Glu Phe Leu Asn Gly
625                 630                 635                 640
Arg Val Gln Ser Thr Glu Leu Cys Ala Gly His Leu Ala Gly Gly Thr
                645                 650                 655
Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Phe Glu Lys
            660                 665                 670
Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu Gly Cys Ala
        675                 680                 685
Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg Phe Val Thr
    690                 695                 700
Trp Ile Glu Gly Val Met Arg Asn Asn
705                 710
```

<210> 49
<211> 1997
<212> DNA
<213> 現代人

<220>
<223> 凝血酶前驅體

<400> 49
aattcctcag tgacccagga gctgacacac tatggcgcac gtccgaggct tgcagctgcc 60
tggctgcctg gccctggctg ccctgtgtag ccttgtgcac agccagcatg tgttcctggc 120
tcctcagcaa gcacggtcgc tgctccagcg ggtccggcga gccaacacct tcttggagga 180
ggtgcgcaag ggcaacctag agcgagagtg cgtggaggag acgtgcagct acgaggaggc 240
cttcgaggct ctggagtcct ccacggctac ggatgtgttc tgggccaagt acacagcttg 300
tgagacagcg aggacgcctc gagataagct tgctgcatgt ctggaaggta actgtgctga 360
gggtctgggt acgaactacc gagggcatgt gaacatcacc cggtcaggca ttgagtgcca 420

gctatggagg agtcgctacc cacataagcc tgaaatcaac tccactaccc atcctggggc 480
cgacctacag gagaatttct gccgcaaccc cgacagcagc accacgggac cctggtgcta 540
cactacagac cccaccgtga ggaggcagga atgcagcatc cctgtctgtg gccaggatca 600
agtcactgta gcgatgactc cacgctccga aggctccagt gtgaatctgt cacctccatt 660
ggagcagtgt gtccctgatc gggggcagca gtaccagggg cgcctggcgg tgaccacaca 720
tgggctcccc tgcctggcct gggccagcgc acaggccaag gccctgagca agcaccagga 780
cttcaactca gctgtgcagc tggtggagaa cttctgccgc aacccagacg gggatgagga 840
gggcgtgtgg tgctatgtgg ccgggaagcc tggcgacttt gggtactgcg acctcaacta 900
ttgtgaggag gccgtggagg aggagacagg agatgggctg gatgaggact cagacagggc 960
catcgaaggg cgtaccgcca ccagtgagta ccagactttc ttcaatccga ggacctttgg 1020
ctcgggagag gcagactgtg ggctgcgacc tctgttcgag aagaagtcgc tggaggacaa 1080
aaccgaaaga gagctcctgg aatcctacat cgacgggcgc attgtggagg gctcggatgc 1140
agagatcggc atgtcacctt ggcaggtgat gcttttccgg aagagtcccc aggagctgct 1200
gtgtggggcc agcctcatca gtgaccgctg ggtcctcacc gccgcccact gcctcctgta 1260
cccgccctgg gacaagaact tcaccgagaa tgaccttctg gtgcgcattg gcaagcactc 1320
ccgcacaagg tacgagcgaa acattgaaaa gatatccatg ttggaaaaga tctacatcca 1380
ccccaggtac aactggcggg agaacctgga ccgggacatt gccctgatga agctgaagaa 1440
gcctgttgcc ttcagtgact acattcaccc tgtgtgtctg cccgacaggg agacggcagc 1500
cagcttgctc caggctggat acaaggggcg ggtgacaggc tggggcaacc tgaaggagac 1560
gtggacagcc aacgttggta aggggcagcc cagtgtcctg caggtggtga acctgcccat 1620
tgtggagcgg ccggtctgca aggactccac ccggatccgc atcactgaca acatgttctg 1680
tgctggttac aagcctgatg aagggaaacg aggggatgcc tgtgaaggtg acagtggggg 1740
acccttttgtc atgaagagcc cctttaacaa ccgctggtat caaatgggca tcgtctcatg 1800
gggtgaaggc tgtgaccggg atgggaaata tggcttctac acacatgtgt tccgcctgaa 1860
gaagtggata cagaaggtca ttgatcagtt tggagagtag gggccactca tattctgggc 1920
tcctggaacc aatcccgtga aagaattatt tttgtgtttc taaaactatg gttcccaata 1980
aaagtgactc tcagcgg 1997

<210> 50
<211> 622
<212> PRT
<213> 現代人

<220>
<223> 凝血酶前驅體

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

```
Thr Thr His Pro Gly Ala Asp Leu Gln Glu Asn Phe Cys Arg Asn Pro
145                 150                 155                 160
Asp Ser Ser Thr Thr Gly Pro Trp Cys Tyr Thr Thr Asp Pro Thr Val
                165                 170                 175
Arg Arg Gln Glu Cys Ser Ile Pro Val Cys Gly Gln Asp Gln Val Thr
            180                 185                 190
Val Ala Met Thr Pro Arg Ser Glu Gly Ser Ser Val Asn Leu Ser Pro
        195                 200                 205
Pro Leu Glu Gln Cys Val Pro Asp Arg Gly Gln Gln Tyr Gln Gly Arg
    210                 215                 220
Leu Ala Val Thr Thr His Gly Leu Pro Cys Leu Ala Trp Ala Ser Ala
225                 230                 235                 240
Gln Ala Lys Ala Leu Ser Lys His Gln Asp Phe Asn Ser Ala Val Gln
                245                 250                 255
Leu Val Glu Asn Phe Cys Arg Asn Pro Asp Gly Asp Glu Glu Gly Val
            260                 265                 270
Trp Cys Tyr Val Ala Gly Lys Pro Gly Asp Phe Gly Tyr Cys Asp Leu
        275                 280                 285
Asn Tyr Cys Glu Glu Ala Val Glu Glu Glu Thr Gly Asp Gly Leu Asp
    290                 295                 300
Glu Asp Ser Asp Arg Ala Ile Glu Gly Arg Thr Ala Thr Ser Glu Tyr
305                 310                 315                 320
Gln Thr Phe Phe Asn Pro Arg Thr Phe Gly Ser Gly Glu Ala Asp Cys
                325                 330                 335
Gly Leu Arg Pro Leu Phe Glu Lys Lys Ser Leu Glu Asp Lys Thr Glu
            340                 345                 350
Arg Glu Leu Leu Glu Ser Tyr Ile Asp Gly Arg Ile Val Glu Gly Ser
        355                 360                 365
Asp Ala Glu Ile Gly Met Ser Pro Trp Gln Val Met Leu Phe Arg Lys
    370                 375                 380
Ser Pro Gln Glu Leu Leu Cys Gly Ala Ser Leu Ile Ser Asp Arg Trp
385                 390                 395                 400
Val Leu Thr Ala Ala His Cys Leu Leu Tyr Pro Pro Trp Asp Lys Asn
                405                 410                 415
Phe Thr Glu Asn Asp Leu Leu Val Arg Ile Gly Lys His Ser Arg Thr
            420                 425                 430
Arg Tyr Glu Arg Asn Ile Glu Lys Ile Ser Met Leu Glu Lys Ile Tyr
        435                 440                 445
Ile His Pro Arg Tyr Asn Trp Arg Glu Asn Leu Asp Arg Asp Ile Ala
    450                 455                 460
Leu Met Lys Leu Lys Lys Pro Val Ala Phe Ser Asp Tyr Ile His Pro
465                 470                 475                 480
Val Cys Leu Pro Asp Arg Glu Thr Ala Ala Ser Leu Leu Gln Ala Gly
                485                 490                 495
Tyr Lys Gly Arg Val Thr Gly Trp Gly Asn Leu Lys Glu Thr Trp Thr
            500                 505                 510
Ala Asn Val Gly Lys Gly Gln Pro Ser Val Leu Gln Val Val Asn Leu
        515                 520                 525
Pro Ile Val Glu Arg Pro Val Cys Lys Asp Ser Thr Arg Ile Arg Ile
    530                 535                 540
Thr Asp Asn Met Phe Cys Ala Gly Tyr Lys Pro Asp Glu Gly Lys Arg
545                 550                 555                 560
Gly Asp Ala Cys Glu Gly Asp Ser Gly Gly Pro Phe Val Met Lys Ser
                565                 570                 575
Pro Phe Asn Asn Arg Trp Tyr Gln Met Gly Ile Val Ser Trp Gly Glu
            580                 585                 590
Gly Cys Asp Arg Asp Gly Lys Tyr Gly Phe Tyr Thr His Val Phe Arg
        595                 600                 605
Leu Lys Lys Trp Ile Gln Lys Val Ile Asp Gln Phe Gly Glu
    610                 615                 620
```

<210> 51
<211> 579
<212> PRT

<213> 現代人

<220>
<223> 成熟凝血酶

<400> 51

```
Ala Asn Thr Phe Leu Glu Glu Val Arg Lys Gly Asn Leu Glu Arg Glu
 1               5                  10                  15
Cys Val Glu Glu Thr Cys Ser Tyr Glu Glu Ala Phe Glu Ala Leu Glu
            20                  25                  30
Ser Ser Thr Ala Thr Asp Val Phe Trp Ala Lys Tyr Thr Ala Cys Glu
        35                  40                  45
Thr Ala Arg Thr Pro Arg Asp Lys Leu Ala Ala Cys Leu Glu Gly Asn
    50                  55                  60
Cys Ala Glu Gly Leu Gly Thr Asn Tyr Arg Gly His Val Asn Ile Thr
65                  70                  75                  80
Arg Ser Gly Ile Glu Cys Gln Leu Trp Arg Ser Arg Tyr Pro His Lys
                85                  90                  95
Pro Glu Ile Asn Ser Thr Thr His Pro Gly Ala Asp Leu Gln Glu Asn
            100                 105                 110
Phe Cys Arg Asn Pro Asp Ser Ser Thr Thr Gly Pro Trp Cys Tyr Thr
        115                 120                 125
Thr Asp Pro Thr Val Arg Arg Gln Glu Cys Ser Ile Pro Val Cys Gly
    130                 135                 140
Gln Asp Gln Val Thr Val Ala Met Thr Pro Arg Ser Glu Gly Ser Ser
145                 150                 155                 160
Val Asn Leu Ser Pro Pro Leu Glu Gln Cys Val Pro Asp Arg Gly Gln
                165                 170                 175
Gln Tyr Gln Gly Arg Leu Ala Val Thr Thr His Gly Leu Pro Cys Leu
            180                 185                 190
Ala Trp Ala Ser Ala Gln Ala Lys Ala Leu Ser Lys His Gln Asp Phe
        195                 200                 205
Asn Ser Ala Val Gln Leu Val Glu Asn Phe Cys Arg Asn Pro Asp Gly
    210                 215                 220
Asp Glu Glu Gly Val Trp Cys Tyr Val Ala Gly Lys Pro Gly Asp Phe
225                 230                 235                 240
Gly Tyr Cys Asp Leu Asn Tyr Cys Glu Glu Ala Val Glu Glu Glu Thr
                245                 250                 255
Gly Asp Gly Leu Asp Glu Asp Ser Asp Arg Ala Ile Glu Gly Arg Thr
            260                 265                 270
Ala Thr Ser Glu Tyr Gln Thr Phe Phe Asn Pro Arg Thr Phe Gly Ser
        275                 280                 285
Gly Glu Ala Asp Cys Gly Leu Arg Pro Leu Phe Glu Lys Lys Ser Leu
    290                 295                 300
Glu Asp Lys Thr Glu Arg Glu Leu Leu Glu Ser Tyr Ile Asp Gly Arg
305                 310                 315                 320
Ile Val Glu Gly Ser Asp Ala Glu Ile Gly Met Ser Pro Trp Gln Val
                325                 330                 335
Met Leu Phe Arg Lys Ser Pro Gln Glu Leu Leu Cys Gly Ala Ser Leu
            340                 345                 350
Ile Ser Asp Arg Trp Val Leu Thr Ala Ala His Cys Leu Leu Tyr Pro
        355                 360                 365
Pro Trp Asp Lys Asn Phe Thr Glu Asn Asp Leu Leu Val Arg Ile Gly
    370                 375                 380
Lys His Ser Arg Thr Arg Tyr Glu Arg Asn Ile Glu Lys Ile Ser Met
385                 390                 395                 400
Leu Glu Lys Ile Tyr Ile His Pro Arg Tyr Asn Trp Arg Glu Asn Leu
                405                 410                 415
Asp Arg Asp Ile Ala Leu Met Lys Leu Lys Lys Pro Val Ala Phe Ser
            420                 425                 430
Asp Tyr Ile His Pro Val Cys Leu Pro Asp Arg Glu Thr Ala Ala Ser
        435                 440                 445
Leu Leu Gln Ala Gly Tyr Lys Gly Arg Val Thr Gly Trp Gly Asn Leu
    450                 455                 460
Lys Glu Thr Trp Thr Ala Asn Val Gly Lys Gly Gln Pro Ser Val Leu
```

```
465                 470                 475                 480
Gln Val Val Asn Leu Pro Ile Val Glu Arg Pro Val Cys Lys Asp Ser
                485                 490                 495
Thr Arg Ile Arg Ile Thr Asp Asn Met Phe Cys Ala Gly Tyr Lys Pro
            500                 505                 510
Asp Glu Gly Lys Arg Gly Asp Ala Cys Glu Gly Asp Ser Gly Gly Pro
        515                 520                 525
Phe Val Met Lys Ser Pro Phe Asn Asn Arg Trp Tyr Gln Met Gly Ile
    530                 535                 540
Val Ser Trp Gly Glu Gly Cys Asp Arg Asp Gly Lys Tyr Gly Phe Tyr
545                 550                 555                 560
Thr His Val Phe Arg Leu Lys Lys Trp Ile Gln Lys Val Ile Asp Gln
                565                 570                 575
Phe Gly Glu
```

<210> 52
<211> 955
<212> DNA
<213> 現代人

<220>
<223> 顆粒酶B前驅體

<400> 52
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ccaagagcta aaagagagta agggggaaac aacagcagct ccaaccaggg cagccttcct 60
gagaagatgc aaccaatcct gcttctgctg gccttcctcc tgctgcccag ggcagatgca 120
ggggagatca tcgggggaca tgaggccaag ccccactccc gcccctacat ggcttatctt 180
atgatctggg atcagaagtc tctgaagagg tgcggtggct tcctgataca agacgacttc 240
gtgctgacag ctgctcactg ttggggaagc tccataaatg tcaccttggg ggcccacaat 300
atcaaagaac aggagccgac ccagcagttt atccctgtga aaagacccat cccccatcca 360
gcctataatc ctaagaactt ctccaacgac atcatgctac tgcagctgga gagaaaggcc 420
aagcggacca gagctgtgca gcccctcagg ctacctagca acaaggccca ggtgaagcca 480
gggcagacat gcagtgtggc cggctggggg cagacggccc ccctgggaaa acactcacac 540
acactacaag aggtgaagat gacagtgcag gaagatcgaa agtgcgaatc tgacttacgc 600
cattattacg acagtaccat tgagttgtgc gtgggggacc cagagattaa aaagacttcc 660
tttaaggggg actctggagg ccctcttgtg tgtaacaagg tggcccaggg cattgtctcc 720
tatggacgaa acaatggcat gcctccacga gcctgcacca aagtctcaag ctttgtacac 780
tggataaaga aaaccatgaa acgctactaa ctacaggaag caaactaagc ccccgctgta 840
atgaaacacc ttctctggag ccaagtccag atttacactg ggagaggtgc cagcaactga 900
ataaatacct cttagctgag tggaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa      955
```

<210> 53
<211> 247
<212> PRT
<213> 現代人

<220>
<223> 顆粒酶B前驅體

<400> 53
```
Met Gln Pro Ile Leu Leu Leu Leu Ala Phe Leu Leu Leu Pro Arg Ala
 1               5                  10                  15
Asp Ala Gly Glu Ile Ile Gly Gly His Glu Ala Lys Pro His Ser Arg
            20                  25                  30
Pro Tyr Met Ala Tyr Leu Met Ile Trp Asp Gln Lys Ser Leu Lys Arg
        35                  40                  45
Cys Gly Gly Phe Leu Ile Gln Asp Asp Phe Val Leu Thr Ala Ala His
    50                  55                  60
Cys Trp Gly Ser Ser Ile Asn Val Thr Leu Gly Ala His Asn Ile Lys
65                  70                  75                  80
Glu Gln Glu Pro Thr Gln Gln Phe Ile Pro Val Lys Arg Pro Ile Pro
                85                  90                  95
His Pro Ala Tyr Asn Pro Lys Asn Phe Ser Asn Asp Ile Met Leu Leu
```

```
                100                 105                 110
Gln Leu Glu Arg Lys Ala Lys Arg Thr Arg Ala Val Gln Pro Leu Arg
        115                 120                 125
Leu Pro Ser Asn Lys Ala Gln Val Lys Pro Gly Gln Thr Cys Ser Val
    130                 135                 140
Ala Gly Trp Gly Gln Thr Ala Pro Leu Gly Lys His Ser His Thr Leu
145                 150                 155                 160
Gln Glu Val Lys Met Thr Val Gln Glu Asp Arg Lys Cys Glu Ser Asp
                165                 170                 175
Leu Arg His Tyr Tyr Asp Ser Thr Ile Glu Leu Cys Val Gly Asp Pro
            180                 185                 190
Glu Ile Lys Lys Thr Ser Phe Lys Gly Asp Ser Gly Gly Pro Leu Val
        195                 200                 205
Cys Asn Lys Val Ala Gln Gly Ile Val Ser Tyr Gly Arg Asn Asn Gly
    210                 215                 220
Met Pro Pro Arg Ala Cys Thr Lys Val Ser Ser Phe Val His Trp Ile
225                 230                 235                 240
Lys Lys Thr Met Lys Arg Tyr
                245
```

<210> 54
<211> 227
<212> PRT
<213> 現代人

<220>
<223> 成熟顆粒酶B

<400> 54

```
Ile Ile Gly Gly His Glu Ala Lys Pro His Ser Arg Pro Tyr Met Ala
 1                5                  10                  15
Tyr Leu Met Ile Trp Asp Gln Lys Ser Leu Lys Arg Cys Gly Gly Phe
            20                  25                  30
Leu Ile Gln Asp Asp Phe Val Leu Thr Ala Ala His Cys Trp Gly Ser
        35                  40                  45
Ser Ile Asn Val Thr Leu Gly Ala His Asn Ile Lys Glu Gln Glu Pro
    50                  55                  60
Thr Gln Gln Phe Ile Pro Val Lys Arg Pro Ile Pro His Pro Ala Tyr
65                  70                  75                  80
Asn Pro Lys Asn Phe Ser Asn Asp Ile Met Leu Leu Gln Leu Glu Arg
                85                  90                  95
Lys Ala Lys Arg Thr Arg Ala Val Gln Pro Leu Arg Leu Pro Ser Asn
            100                 105                 110
Lys Ala Gln Val Lys Pro Gly Gln Thr Cys Ser Val Ala Gly Trp Gly
        115                 120                 125
Gln Thr Ala Pro Leu Gly Lys His Ser His Thr Leu Gln Glu Val Lys
    130                 135                 140
Met Thr Val Gln Glu Asp Arg Lys Cys Glu Ser Asp Leu Arg His Tyr
145                 150                 155                 160
Tyr Asp Ser Thr Ile Glu Leu Cys Val Gly Asp Pro Glu Ile Lys Lys
                165                 170                 175
Thr Ser Phe Lys Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Lys Val
            180                 185                 190
Ala Gln Gly Ile Val Ser Tyr Gly Arg Asn Asn Gly Met Pro Pro Arg
        195                 200                 205
Ala Cys Thr Lys Val Ser Ser Phe Val His Trp Ile Lys Lys Thr Met
    210                 215                 220
Lys Arg Tyr
225
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<210> 55
<211> 4100
<212> DNA

<213> 現代人

<220>
<223> 組織蛋白酶S前驅體

<400> 55
gtacctcatg tgacaagttc caatttcttt tcaagtcaat tgaactgaaa tctccttgtt 60
gctttgaaat cttagaagag agcccactaa ttcaaggact cttactgtgg gagcaactgc 120
tggttctatc acaatgaaac ggctggtttg tgtgctcttg gtgtgctcct ctgcagtggc 180
acagttgcat aaagatccta ccctggatca ccactggcat ctctggaaga aaacctatgg 240
caaacaatac aaggaaaaga atgaagaagc agtacgacgt ctcatctggg aaaagaatct 300
aaagtttgtg atgcttcaca acctggagca ttcaatggga atgcactcat acgatctggg 360
catgaaccac ctgggagaca tgaccagtga agaagtgatg tctttgatga gttccctgag 420
agttcccagc cagtggcaga gaaatatcac atataagtca aaccctaatc ggatattgcc 480
tgattctgtg gactggagag agaaagggtg tgttactgaa gtgaaatatc aaggttcttg 540
tggtgcttgc tgggctttca gtgctgtggg ggccctggaa gcacagctga agctgaaaac 600
aggaaagctg gtgtctctca gtgcccagaa cctggtggat tgctcaactg aaaaatatgg 660
aaacaaaggc tgcaatggtg gcttcatgac aacggctttc cagtacatca ttgataacaa 720
gggcatcgac tcagacgctt cctatcccta caaagccatg gatcagaaat gtcaatatga 780
ctcaaaatat cgtgctgcca catgttcaaa gtacactgaa cttccttatg gcagagaaga 840
tgtcctgaaa gaagctgtgg ccaataaagg cccagtgtct gttggtgtag atgcgcgtca 900
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gaatcatggt gtacttgtgg ttggctatgg tgatcttaat gggaaagaat actggcttgt 1020
gaaaaacagc tggggccaca actttggtga agaaggatat attcggatgg caagaaataa 1080
aggaaatcat tgtgggattg ctagctttcc ctcttaccca gaaatctaga ggatctctcc 1140
tttttataac aaatcaagaa atatgaagca ctttctctta acttaatttt tcctgctgta 1200
tccagaagaa ataattgtgt catgattaat gtgtatttac tgtactaatt agaaaatata 1260
gtttgaggcc gggcacggtg gctcacgcct gtaatcccag tacttgggag gccaaggcag 1320
gcatatcaac ttgaggccag gagttaaaga gcagcctggc taacatggtg aaaccccatc 1380
tctactaaaa atacaaaaaa ttagccgagc acggtggtgc atgcctgtaa tcccagctac 1440
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gccacatacc attcttattc ctaggcaact attaataatc tatcctgaga atattaattg 1860
tggtattctg gtgatggggt ttagcaactt tgatggaaga aaatattagg ctataaatgt 1920
cctaaggact cagattgtat ctttgtacag aagaggattc aaaacgccac gtgtagtggc 1980
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gatcacaaga gcccaggagg ttgagaatgc agtgagcttg taattgcacc actgcactcc 2220
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gcctttattt ggcaaataac tgagccaacc agaataaaat aaccaatact ccactgctca 2460
tatttttatc taattcagat ggatcttcct tacaactgct ctagattagt agatgcatct 2520
aagcaggcag caggaacttt aaatttttta agttcatgtc tatgacatga acaatgtgtg 2580
ggataatgtc attaatatat cctaaattaa cctaaacgta tttcactaac tctggctcct 2640
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tgcctcagcc tcccgagtag ctggaattat aggcgtgcac caccacgccc agctaatttt 2940
tgtattttta gtaaagacag ggttttgcca cattagccag gctggtctca aactcctgac 3000
ctcaggtgat ccacccaccc cagcctccca aagtgctaag attacaggcg tgagccactg 3060
agcccagcct acttttcagt ttttaacata atttttgttt tatccacaac ttttcaagta 3120
ttgaaagtag aataaaaaca tgggttctta gtctttagct atctgttaaa gcctatgaat 3180
gccttcttaa aatcatgttt ttaaatgcat aaaatatata ggattacaaa ggaatctaat 3240
tatatcgaaa tacagttatt aaaatgttaa aagataagtt tgttatatat taatatgcat 3300
gcttctttat aaatgcatta aataagagtt aatagctatc ctaaatttga aatagtgata 3360
agcataatga aaatagatgc aaaaaactaa tgtgatatga aaatatctgg gtttttcttt 3420
tgatgatgaa gtattgctaa tattaccgtg gtttatgaac tatgttcaga attgaagaaa 3480
atcctaactt tcagttagag gttagtgacg gggttcagga caccctacac aaaatacagc 3540

actttgacat attgaatatt ttaagctgaa ggcatttgag gaaattgcag aagcaggaag 3600
gtgactctga ccttctgcct gctgttctcc ccagaagcag ccataaaacc tgggaaggat 3660
tttctgacct tcccctgaag tagatcataa gactgtcatg taagaggtgc tctcctggca 3720
cccagagaaa aggagcatcc ttacctccaa aagcacaggg acacaaagag gaatctaaac 3780
aaacaggcct ctcagtttcc cccagtttat tacatttagc ttgttcacac tttgccctat 3840
gacatttcta catcactggc tgctcttcat caaacctact ataaaaaaca ttcaagttca 3900
actgtttctt tgggccttta tttccttatg gagcccctcg tgtcgtgtaa aacttatatt 3960
aaataaatgt gcatgctttt ctcttgctaa tctctctttt gttatagaga tctcagccct 4020
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gaatttttta cccatacaaa 4100

<210> 56
<211> 331
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶S前驅體

<400> 56

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

<210> 57

<211> 217
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶S

<400> 57
Leu Pro Asp Ser Val Asp Trp Arg Glu Lys Gly Cys Val Thr Glu Val
 1   5   10   15
Lys Tyr Gln Gly Ser Cys Gly Ala Cys Trp Ala Phe Ser Ala Val Gly
            20   25   30
Ala Leu Glu Ala Gln Leu Lys Leu Lys Thr Gly Lys Leu Val Ser Leu
        35   40   45
Ser Ala Gln Asn Leu Val Asp Cys Ser Thr Glu Lys Tyr Gly Asn Lys
    50   55   60
Gly Cys Asn Gly Gly Phe Met Thr Thr Ala Phe Gln Tyr Ile Ile Asp
65   70   75   80
Asn Lys Gly Ile Asp Ser Asp Ala Ser Tyr Pro Tyr Lys Ala Met Asp
                85   90   95
Gln Lys Cys Gln Tyr Asp Ser Lys Tyr Arg Ala Ala Thr Cys Ser Lys
            100   105   110
Tyr Thr Glu Leu Pro Tyr Gly Arg Glu Asp Val Leu Lys Glu Ala Val
        115   120   125
Ala Asn Lys Gly Pro Val Ser Val Gly Val Asp Ala Arg His Pro Ser
    130   135   140
Phe Phe Leu Tyr Arg Ser Gly Val Tyr Tyr Glu Pro Ser Cys Thr Gln
145   150   155   160
Asn Val Asn His Gly Val Leu Val Val Gly Tyr Gly Asp Leu Asn Gly
                165   170   175
Lys Glu Tyr Trp Leu Val Lys Asn Ser Trp Gly His Asn Phe Gly Glu
            180   185   190
Glu Gly Tyr Ile Arg Met Ala Arg Asn Lys Gly Asn His Cys Gly Ile
        195   200   205
Ala Ser Phe Pro Ser Tyr Pro Glu Ile
    210   215

<210> 58
<211> 1702
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶K前驅體

<400> 58
aaattttcca gccgatcact ggagctgact tccgcaatcc cgatggaata aatctagcac 60
ccctgatggt gtgcccacac tttgctgccg aaacgaagcc agacaacaga tttccatcag 120
caggatgtgg gggctcaagg ttctgctgct acctgtggtg agctttgctc tgtaccctga 180

ggagatactg gacacccact gggagctatg gaagaagacc cacaggaagc aatataacaa 240
caaggtggat gaaatctctc ggcgtttaat ttgggaaaaa aacctgaagt atatttccat 300
ccataacctt gaggcttctc ttggtgtcca tacatatgaa ctggctatga accacctggg 360
ggacatgacc agtgaagagg tggttcagaa gatgactgga ctcaaagtac ccctgtctca 420
ttcccgcagt aatgacaccc tttatatccc agaatgggaa ggtagagccc cagactctgt 480
cgactatcga aagaaaggat atgttactcc tgtcaaaaat cagggtcagt gtggttcctg 540
ttgggctttt agctctgtgg gtgccctgga gggccaactc aagaagaaaa ctggcaaact 600
cttaaatctg agtccccaga acctagtgga ttgtgtgtct gagaatgatg gctgtggagg 660
gggctacatg accaatgcct tccaatatgt gcagaagaac cggggtattg actctgaaga 720
tgcctaccca tatgtgggac aggaagagag ttgtatgtac aacccaacag gcaaggcagc 780
taaatgcaga gggtacagag agatccccga ggggaatgag aaagccctga agagggcagt 840
ggcccgagtg ggacctgtct ctgtggccat tgatgcaagc ctgacctcct tccagtttta 900
cagcaaaggt gtgtattatg atgaaagctg caatagcgat aatctgaacc atgcggtttt 960
ggcagtggga tatggaatcc agaagggaaa caagcactgg ataattaaaa acagctgggg 1020

agaaaactgg ggaaacaaag gatatatcct catggctcga aataagaaca acgcctgtgg 1080
cattgccaac ctggccagct tccccaagat gtgactccag ccagccaaat ccatcctgct 1140
cttccatttc ttccacgatg gtgcagtgta acgatgcact ttggaaggga gttggtgtgc 1200
tatttttgaa gcagatgtgg tgatactgag attgtctgtt cagtttcccc atttgtttgt 1260
gcttcaaatg atccttccta ctttgcttct ctccacccat gacctttttc actgtggcca 1320
tcaggacttt ccctgacagc tgtgtactct taggctaaga gatgtgacta cagcctgccc 1380
ctgactgtgt tgtcccaggg ctgatgctgt acaggtacag gctggagatt ttcacatagg 1440
ttagattctc attcacggga ctagttagct ttaagcaccc tagaggacta gggtaatctg 1500
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tccaattcat aaatctattc ataagtcttt ggtacaagtt tacatgataa aaagaaatgt 1620
gatttgtctt cccttctttg cacttttgaa ataaagtatt tatctcctgt ctacagttta 1680
ataaatagca tctagtacac at 1702

<210> 59
<211> 329
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶K前驅體

<400> 59

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Met Trp Gly Leu Lys Val Leu Leu Leu Pro Val Val Ser Phe Ala Leu
 1               5                  10                  15
Tyr Pro Glu Glu Ile Leu Asp Thr His Trp Glu Leu Trp Lys Lys Thr
            20                  25                  30
His Arg Lys Gln Tyr Asn Asn Lys Val Asp Glu Ile Ser Arg Arg Leu
        35                  40                  45
Ile Trp Glu Lys Asn Leu Lys Tyr Ile Ser Ile His Asn Leu Glu Ala
    50                  55                  60
Ser Leu Gly Val His Thr Tyr Glu Leu Ala Met Asn His Leu Gly Asp
65                  70                  75                  80
Met Thr Ser Glu Glu Val Val Gln Lys Met Thr Gly Leu Lys Val Pro
                85                  90                  95
Leu Ser His Ser Arg Ser Asn Asp Thr Leu Tyr Ile Pro Glu Trp Glu
            100                 105                 110
Gly Arg Ala Pro Asp Ser Val Asp Tyr Arg Lys Lys Gly Tyr Val Thr
        115                 120                 125
Pro Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ser
    130                 135                 140
Val Gly Ala Leu Glu Gly Gln Leu Lys Lys Lys Thr Gly Lys Leu Leu
145                 150                 155                 160
Asn Leu Ser Pro Gln Asn Leu Val Asp Cys Val Ser Glu Asn Asp Gly
                165                 170                 175
Cys Gly Gly Gly Tyr Met Thr Asn Ala Phe Gln Tyr Val Gln Lys Asn
            180                 185                 190
Arg Gly Ile Asp Ser Glu Asp Ala Tyr Pro Tyr Val Gly Gln Glu Glu
        195                 200                 205
Ser Cys Met Tyr Asn Pro Thr Gly Lys Ala Ala Lys Cys Arg Gly Tyr
    210                 215                 220
Arg Glu Ile Pro Glu Gly Asn Glu Lys Ala Leu Lys Arg Ala Val Ala
225                 230                 235                 240
Arg Val Gly Pro Val Ser Val Ala Ile Asp Ala Ser Leu Thr Ser Phe
                245                 250                 255
Gln Phe Tyr Ser Lys Gly Val Tyr Tyr Asp Glu Ser Cys Asn Ser Asp

            260                 265                 270
Asn Leu Asn His Ala Val Leu Ala Val Gly Tyr Gly Ile Gln Lys Gly
        275                 280                 285
Asn Lys His Trp Ile Ile Lys Asn Ser Trp Gly Glu Asn Trp Gly Asn
    290                 295                 300
Lys Gly Tyr Ile Leu Met Ala Arg Asn Lys Asn Asn Ala Cys Gly Ile
305                 310                 315                 320
Ala Asn Leu Ala Ser Phe Pro Lys Met
                325
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<210> 60
<211> 215
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶K

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

<210> 61
<211> 1731
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶L前驅體

<400> 61
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agaaccgcga cctccgcaac cttgagcggc atccgtggag tgcgcctgcg cagctacgac 120
cgcagcagga aagcgccgcc ggccaggccc agctgtggcc ggacagggac tggaagagag 180
gacgcggtcg agtaggtgtg caccagccct ggcaacgaga gcgtctaccc cgaactctgc 240
tggccttgag gtggggaagc cggggagggc agttgaggac cccgcggagg cgcgtgactg 300
gttgagcggg caggccagcc tccgagccgg gtggacacag ttttaaaaca tgaatcctac 360
actcatcctt gctgcctttt gcctgggaat tgcctcagct actctaacat ttgatcacag 420
tttagaggca cagtggacca agtggaaggc gatgcacaac agattatacg gcatgaatga 480
agaaggatgg aggagagcag tgtgggagaa gaacatgaag atgattgaac tgcacaatca 540
ggaatacagg gaagggaaac acagcttcac aatggccatg aacgcctttg gagacatgac 600
cagtgaagaa ttcaggcagg tgatgaatgg ctttcaaaac cgtaagccca ggaaggggaa 660
agtgttccag gaacctctgt tttatgaggc ccccagatct gtggattgga gagagaaagg 720
ctacgtgact cctgtgaaga atcagggtca gtgtggttct tgttgggctt ttagtgctac 780
tggtgctctt gaaggacaga tgttccggaa aactgggagg cttatctcac tgagtgagca 840
gaatctggta gactgctctg ggcctcaagg caatgaaggc tgcaatggtg gcctaatgga 900

ttatgctttc cagtatgttc aggataatgg aggcctggac tctgaggaat cctatccata 960
tgaggcaaca gaagaatcct gtaagtacaa tcccaagtat tctgttgcta atgacaccgg 1020
ctttgtggac atccctaagc aggagaaggc cctgatgaag gcagttgcaa ctgtggggcc 1080
catttctgtt gctattgatg caggtcatga gtccttcctg ttctataaag aaggcattta 1140
ttttgagcca gactgtagca gtgaagacat ggatcatggt gtgctggtgg ttggctacgg 1200
atttgaaagc acagaatcag ataacaataa atattggctg gtgaagaaca gctggggtga 1260
agaatggggc atgggtggct acgtaaagat ggccaaagac cggagaaacc attgtggaat 1320
tgcctcagca gccagctacc ccactgtgtg agctggtgga cggtgatgag gaaggacttg 1380
actggggatg gcgcatgcat gggaggaatt catcttcagt ctaccagccc ccgctgtgtc 1440
ggatacacac tcgaatcatt gaagatccga gtgtgatttg aattctgtga tattttcaca 1500
ctggtaaatg ttacctctat tttaattact gctataaata ggtttatatt attgattcac 1560
ttactgactt tgcattttcg tttttaaaag gatgtataaa tttttacctg tttaaataaa 1620
atttaatttc aaatgtagtg gtggggcttc tttctatttt tgatgcactg aatttttgtg 1680
taataaagaa cataattggg ctctaagcca taaaaaaaaa aaaaaaaaaa a 1731

<210> 62
<211> 333
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶L前驅體

<400> 62

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

325 330

<210> 63
<211> 3783
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶B前驅體

<400> 63
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ctcggctgca gcgctgggtg gatctaggat ccggcttcca acatgtggca gctctgggcc 180
tccctctgct gcctgctggt gttggccaat gcccggagca ggccctcttt ccatcccctg 240
tcggatgagc tggtcaacta tgtcaacaaa cggaatacca cgtggcaggc cgggcacaac 300
ttctacaacg tggacatgag ctacttgaag aggctatgtg gtaccttcct gggtgggccc 360
aagccacccc agagagttat gtttaccgag gacctgaagc tgcctgcaag cttcgatgca 420
cgggaacaat ggccacagtg tcccaccatc aaagagatca gagaccaggg ctcctgtggc 480
tcctgctggg ccttcggggc tgtggaagcc atctctgacc ggatctgcat ccacaccaat 540
gcgcacgtca gcgtggaggt gtcggcggag gacctgctca catgctgtgg cagcatgtgt 600
ggggacggct gtaatggtgg ctatcctgct gaagcttgga acttctggac aagaaaaggc 660
ctggtttctg gtggcctcta tgaatcccat gtagggtgca gaccgtactc catccctccc 720
tgtgagcacc acgtcaacgg ctcccggccc ccatgcacgg gggagggaga taccccaag 780
tgtagcaaga tctgtgagcc tggctacagc ccgacctaca aacaggacaa gcactacgga 840
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aatggcttct ttaaaatact cagaggacag gatcactgtg gaatcgaatc agaagtggtg 1140
gctggaattc cacgcaccga tcagtactgg gaaaagatct aatctgccgt gggcctgtcg 1200
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tgacaaggtc aggagttcaa gaccagcctg gccaacatgc tgaaacctca cctctactaa 3180

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tgaggcagga gaatcgcttg aacccgggag gcggaggttg cagtgagcca agacagtgcc 3300
agtgcactcc agcctcggtg acagcgcaag gctccgtctc aataattaaa aaaaaaaaaa 3360
aaaaaaaaaa ggccgggcgc agtggctcaa gcctgtaatc ccagcacttt gggaggctga 3420
ggcgggcaga tcacctgagg tcaggagttt tgagatcagc cttggcaaca cggtgaaacc 3480
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cgagatcacg ccattgcact ccagcctggg ggacaagagt gaatctgtgt ctcaccaaaa 3660
aaaaaaagaa aaagaaagat gcttaacaaa ggttaccata agccacaaat tcataaccac 3720
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aaa                                                               3783
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<210> 64
<211> 339
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶B前驅體

<400> 64

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 1               5                  10                  15
Ala Arg Ser Arg Pro Ser Phe His Pro Leu Ser Asp Glu Leu Val Asn
            20                  25                  30
Tyr Val Asn Lys Arg Asn Thr Thr Trp Gln Ala Gly His Asn Phe Tyr
        35                  40                  45
Asn Val Asp Met Ser Tyr Leu Lys Arg Leu Cys Gly Thr Phe Leu Gly
    50                  55                  60
Gly Pro Lys Pro Pro Gln Arg Val Met Phe Thr Glu Asp Leu Lys Leu
65                  70                  75                  80
Pro Ala Ser Phe Asp Ala Arg Glu Gln Trp Pro Gln Cys Pro Thr Ile
                85                  90                  95
Lys Glu Ile Arg Asp Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Gly
            100                 105                 110
Ala Val Glu Ala Ile Ser Asp Arg Ile Cys Ile His Thr Asn Ala His
        115                 120                 125
Val Ser Val Glu Val Ser Ala Glu Asp Leu Leu Thr Cys Cys Gly Ser
    130                 135                 140
Met Cys Gly Asp Gly Cys Asn Gly Gly Tyr Pro Ala Glu Ala Trp Asn
145                 150                 155                 160
Phe Trp Thr Arg Lys Gly Leu Val Ser Gly Gly Leu Tyr Glu Ser His
                165                 170                 175
Val Gly Cys Arg Pro Tyr Ser Ile Pro Pro Cys Glu His His Val Asn
            180                 185                 190
Gly Ser Arg Pro Pro Cys Thr Gly Glu Gly Asp Thr Pro Lys Cys Ser
        195                 200                 205
Lys Ile Cys Glu Pro Gly Tyr Ser Pro Thr Tyr Lys Gln Asp Lys His
    210                 215                 220
Tyr Gly Tyr Asn Ser Tyr Ser Val Ser Asn Ser Glu Lys Asp Ile Met
225                 230                 235                 240
Ala Glu Ile Tyr Lys Asn Gly Pro Val Glu Gly Ala Phe Ser Val Tyr
                245                 250                 255
Ser Asp Phe Leu Leu Tyr Lys Ser Gly Val Tyr Gln His Val Thr Gly
            260                 265                 270
Glu Met Met Gly Gly His Ala Ile Arg Ile Leu Gly Trp Gly Val Glu
        275                 280                 285
Asn Gly Thr Pro Tyr Trp Leu Val Ala Asn Ser Trp Asn Thr Asp Trp
    290                 295                 300
Gly Asp Asn Gly Phe Phe Lys Ile Leu Arg Gly Gln Asp His Cys Gly
305                 310                 315                 320
Ile Glu Ser Glu Val Val Ala Gly Ile Pro Arg Thr Asp Gln Tyr Trp
                325                 330                 335
Glu Lys Ile
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<210> 65
<211> 260
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶B

<220>
<223> 組織蛋白酶B輕鏈1-47

<220>
<223> 組織蛋白酶B重鏈48-254

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

Tyr Ser Asp Phe Leu Leu Tyr Lys Ser Gly Val Tyr Gln His Val Thr
180 185 190
Gly Glu Met Met Gly Gly His Ala Ile Arg Ile Leu Gly Trp Gly Val
195 200 205
Glu Asn Gly Thr Pro Tyr Trp Leu Val Ala Asn Ser Trp Asn Thr Asp
210 215 220
Trp Gly Asp Asn Gly Phe Phe Lys Ile Leu Arg Gly Gln Asp His Cys
225 230 235 240
Gly Ile Glu Ser Glu Val Val Ala Gly Ile Pro Arg Thr Asp Gln Tyr
245 250 255
Trp Glu Lys Ile
260

<210> 66
<211> 1399
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶H前驅體

<400> 66
ttgccggcgc aagagccaag ccgccagcgc tgctatgtgg gccacgctgc cgctgctctg 60

cgccggggcc tggctcctgg gagtccccgt ctgcggtgcc gccgaactgt ccgtgaactc 120
cttagagaag tttcacttca agtcatggat gtctaagcac cgtaagacct acagtacgga 180
ggagtaccac cacaggctgc agacgtttgc cagcaactgg aggaagataa acgcccacaa 240
caatgggaac cacacattta aaatggcact gaaccaattt tcagacatga gctttgctga 300
aataaaacac aagtatctct ggtcagagcc tcagaattgc tcagccacca aaagtaacta 360
ccttcgaggt actggtccct acccaccttc cgtggactgg cggaaaaaag gaaatttgt 420
ctcacctgtg aaaaatcagg gtgcctgcgg cagttgctgg actttctcca ccactggggc 480
cctggagtct gcaatcgcca tcgcaaccgg aaagatgctg tccttggcgg aacagcagct 540
ggtggactgc gcccaggact tcaataatta cggctgccaa gggggtctcc ccagccaggc 600
tttcgagtat atcctgtaca acaaggggat catgggtgaa gacacctacc cctaccaggg 660
caaggatggt tattgcaagt tccaacctgg aaaggccatc ggctttgtca aggatgtagc 720
caacatcaca atctatgacg aggaagcgat ggtggaggct gtggccctct acaaccctgt 780
gagctttgcc tttgaggtga ctcaggactt catgatgtat agaacgggca tctactccag 840
tacttcctgc ataaaactc cagataaagt aaaccatgca gtactggctg ttgggtatgg 900
agaaaaaaat gggatccctt actggatcgt gaaaaactct tggggtcccc agtggggaat 960
gaacgggtac ttcctcatcg agcgcggaaa gaacatgtgt ggcctggctg cctgcgcctc 1020
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ggaacgggca gcctgggcct gggtggaaat cctgccctgg aggaagttgt ggggagatcc 1140
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gaggagttcc accatgagct cacccgtgtc tatgacgcaa agatcaccag ccatgtgcct 1260
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cattgagtga gcacctcca 1399

<210> 67
<211> 335
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶H前驅體

<400> 67

Met	Trp	Ala	Thr	Leu	Pro	Leu	Leu	Cys	Ala	Gly	Ala	Trp	Leu	Leu	Gly
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Val	Pro	Val	Cys	Gly	Ala	Ala	Glu	Leu	Ser	Val	Asn	Ser	Leu	Glu	Lys
			20					25					30		
Phe	His	Phe	Lys	Ser	Trp	Met	Ser	Lys	His	Arg	Lys	Thr	Tyr	Ser	Thr
		35					40					45			
Glu	Glu	Tyr	His	His	Arg	Leu	Gln	Thr	Phe	Ala	Ser	Asn	Trp	Arg	Lys
	50					55					60				
Ile	Asn	Ala	His	Asn	Asn	Gly	Asn	His	Thr	Phe	Lys	Met	Ala	Leu	Asn
65					70					75					80
Gln	Phe	Ser	Asp	Met	Ser	Phe	Ala	Glu	Ile	Lys	His	Lys	Tyr	Leu	Trp
				85					90					95	
Ser	Glu	Pro	Gln	Asn	Cys	Ser	Ala	Thr	Lys	Ser	Asn	Tyr	Leu	Arg	Gly
			100					105					110		
Thr	Gly	Pro	Tyr	Pro	Pro	Ser	Val	Asp	Trp	Arg	Lys	Lys	Gly	Asn	Phe
		115					120					125			
Val	Ser	Pro	Val	Lys	Asn	Gln	Gly	Ala	Cys	Gly	Ser	Cys	Trp	Thr	Phe
	130					135					140				
Ser	Thr	Thr	Gly	Ala	Leu	Glu	Ser	Ala	Ile	Ala	Ile	Ala	Thr	Gly	Lys
145					150					155					160
Met	Leu	Ser	Leu	Ala	Glu	Gln	Gln	Leu	Val	Asp	Cys	Ala	Gln	Asp	Phe
				165					170					175	
Asn	Asn	His	Gly	Cys	Gln	Gly	Gly	Leu	Pro	Ser	Gln	Ala	Phe	Glu	Tyr
			180					185					190		
Ile	Leu	Tyr	Asn	Lys	Gly	Ile	Met	Gly	Glu	Asp	Thr	Tyr	Pro	Tyr	Gln
		195					200					205			
Gly	Lys	Asp	Gly	Tyr	Cys	Lys	Phe	Gln	Pro	Gly	Lys	Ala	Ile	Gly	Phe
	210					215					220				
Val	Lys	Asp	Val	Ala	Asn	Ile	Thr	Ile	Tyr	Asp	Glu	Glu	Ala	Met	Val
225					230					235					240
Glu	Ala	Val	Ala	Leu	Tyr	Asn	Pro	Val	Ser	Phe	Ala	Phe	Glu	Val	Thr

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                245                 250                 255
Gln Asp Phe Met Met Tyr Arg Thr Gly Ile Tyr Ser Ser Thr Ser Cys
            260                 265                 270
His Lys Thr Pro Asp Lys Val Asn His Ala Val Leu Ala Val Gly Tyr
        275                 280                 285
Gly Glu Lys Asn Gly Ile Pro Tyr Trp Ile Val Lys Asn Ser Trp Gly
    290                 295                 300
Pro Gln Trp Gly Met Asn Gly Tyr Phe Leu Ile Glu Arg Gly Lys Asn
305                 310                 315                 320
Met Cys Gly Leu Ala Ala Cys Ala Ser Tyr Pro Ile Pro Leu Val
                325                 330                 335
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<210> 68
<211> 238
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶H

<400> 68

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Gly Pro Tyr Pro Pro Ser Val Asp Trp Arg Lys Lys Gly Asn Phe Val
            20                  25                  30
Ser Pro Val Lys Asn Gln Gly Ala Cys Gly Ser Cys Trp Thr Phe Ser
        35                  40                  45
Thr Thr Gly Ala Leu Glu Ser Ala Ile Ala Ile Ala Thr Gly Lys Met
    50                  55                  60
Leu Ser Leu Ala Glu Gln Gln Leu Val Asp Cys Ala Gln Asp Phe Asn
65                  70                  75                  80
Asn His Gly Cys Gln Gly Gly Leu Pro Ser Gln Ala Phe Glu Tyr Ile
                85                  90                  95
Leu Tyr Asn Lys Gly Ile Met Gly Glu Asp Thr Tyr Pro Tyr Gln Gly
            100                 105                 110
Lys Asp Gly Tyr Cys Lys Phe Gln Pro Gly Lys Ala Ile Gly Phe Val
        115                 120                 125
Lys Asp Val Ala Asn Ile Thr Ile Tyr Asp Glu Glu Ala Met Val Glu
    130                 135                 140
Ala Val Ala Leu Tyr Asn Pro Val Ser Phe Ala Phe Glu Val Thr Gln
145                 150                 155                 160
Asp Phe Met Met Tyr Arg Thr Gly Ile Tyr Ser Ser Thr Ser Cys His
                165                 170                 175
Lys Thr Pro Asp Lys Val Asn His Ala Val Leu Ala Val Gly Tyr Gly
            180                 185                 190
Glu Lys Asn Gly Ile Pro Tyr Trp Ile Val Lys Asn Ser Trp Gly Pro
        195                 200                 205
Gln Trp Gly Met Asn Gly Tyr Phe Leu Ile Glu Arg Gly Lys Asn Met
    210                 215                 220
Cys Gly Leu Ala Ala Cys Ala Ser Tyr Pro Ile Pro Leu Val
225                 230                 235
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<210> 69
<211> 1975
<212> DNA
<213> 小家鼠

<220>
<223> 組織蛋白酶F前驅體

<400> 69

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gacagcaggc tccgcctcgg gtctcttgat ccgtgtgttt gtgggtcagt gaatccgggc 120
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gagcagcttc gacctcgcta tggcgcccct actgcagctt ctgtggctgc tgacactgct 180
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gaacttgtcg tcccaggagc tgctggcccc cgcccgcttc gcgctggaca tgtacaatta 300
cggccgtgct gcggggacaa gggccgtgct aggagcggtg cgcggacgcg tccgccgggc 360
cggccagggc tctctgttct ccctggaagc cacactagag gagccacctt gcaatgatcc 420
cctggtgtgc ccactgcctg agacgaagaa aacagtgctc tgcagttttg aagtcctgga 480
agagctaaaa gaacacttgc tgctgaggag ggactgtagc ccagtgaatg ccaaggtcac 540
agagtttaga aatgcgactt tcagctcatt ccttccattg ttggacaagg atcccctgcc 600
ccaggacttc tctgtgaaga tggctccact cttcaaggac ttcatgacca cctataaccg 660
gacttatgaa tcaagggaag aagcccagtg gcgattgact gtctttgcaa gaaatatgat 720
acgagcacag aagattcagg ccctggaccg cggcacagct cagtatggga tcaccaagtt 780
cagtgacctc acagaggagg aattccacac catctacctg aatcccctct tacagaagga 840
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ctgtcttttt gctttggtgc tcctcggtct gatgctgtca gttttctggt ccctttccac 1920
atccaggaaa gttgtgaccg gccttctcta agggcaataa agaggtagcc tgctc 1975

<210> 70
<211> 462
<212> PRT
<213> 小家鼠

<220>
<223> 組織蛋白酶F前驅體

<400> 70

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

```
Met Ile Arg Ala Gln Lys Ile Gln Ala Leu Asp Arg Gly Thr Ala Gln
        195                 200                 205
Tyr Gly Ile Thr Lys Phe Ser Asp Leu Thr Glu Glu Glu Phe His Thr
    210                 215                 220
Ile Tyr Leu Asn Pro Leu Leu Gln Lys Glu Ser Gly Arg Lys Met Ser
225                 230                 235                 240
Pro Ala Lys Ser Ile Asn Asp Leu Ala Pro Pro Glu Trp Asp Trp Arg
                245                 250                 255
Lys Lys Gly Ala Val Thr Glu Val Lys Asn Gln Gly Met Cys Gly Ser
            260                 265                 270
Cys Trp Ala Phe Ser Val Thr Gly Asn Val Glu Gly Gln Trp Phe Leu
        275                 280                 285
Asn Arg Gly Thr Leu Leu Ser Leu Ser Glu Gln Glu Leu Leu Asp Cys
    290                 295                 300
Asp Lys Val Asp Lys Ala Cys Leu Gly Gly Leu Pro Ser Asn Ala Tyr
305                 310                 315                 320
Ala Ala Ile Lys Asn Leu Gly Gly Leu Glu Thr Glu Asp Asp Tyr Gly
                325                 330                 335
Tyr Gln Gly His Val Gln Thr Cys Asn Phe Ser Ala Gln Met Ala Lys
            340                 345                 350
Val Tyr Ile Asn Asp Ser Val Glu Leu Ser Arg Asn Glu Asn Lys Ile
        355                 360                 365
Ala Ala Trp Leu Ala Gln Lys Gly Pro Ile Ser Val Ala Ile Asn Ala
    370                 375                 380
Phe Gly Met Gln Phe Tyr Arg His Gly Ile Ala His Pro Phe Arg Pro
385                 390                 395                 400
Leu Cys Ser Pro Trp Phe Ile Asp His Ala Val Leu Leu Val Gly Tyr
                405                 410                 415
Gly Asn Arg Ser Asn Ile Pro Tyr Trp Ala Ile Lys Asn Ser Trp Gly
            420                 425                 430
Ser Asp Trp Gly Glu Glu Gly Tyr Tyr Tyr Leu Tyr Arg Gly Ser Gly
        435                 440                 445
Ala Cys Gly Val Asn Thr Met Ala Ser Ser Ala Val Val Asn
    450                 455                 460
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<210> 71
<211> 214
<212> PRT
<213> 小家鼠

<220>
<223> 成熟組織蛋白酶F

<400> 71

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

```
His Ala Val Leu Leu Val Gly Tyr Gly Asn Arg Ser Asn Ile Pro Tyr
                165                 170                 175
Trp Ala Ile Lys Asn Ser Trp Gly Ser Asp Trp Gly Glu Glu Gly Tyr
            180                 185                 190
Tyr Tyr Leu Tyr Arg Gly Ser Gly Ala Cys Gly Val Asn Thr Met Ala
        195                 200                 205
Ser Ser Ala Val Val Asn
    210
```

<210> 72
<211> 3453
<212> DNA
<213> 小家鼠

<220>
<223> 組織蛋白酶O前驅體

<400> 72

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gaaaccgaaa gagaaagcgg gccgggcaca gtggacctcg ggcaccggga tgaagccgca 60
gttggtgaac ctcttgctac tgtgttgctg ctgtctcggc cgccacgggg tcgccgggac 120
ctggtcttgg agccaccagc gggaggccgc cgccttgcgg gaaagccttc atagacaccg 180
atacttgaac tcttttcctc atgaaaactc cactgccttc tatggagtaa atcagttttc 240
ttatttgttt cctgaagagt ttaaagcttt gtatttaggc agcaaatatg cctgggctcc 300
cagataccca gcagaaggac agagacctat ccccaatgtg tctttgccat tgagatttga 360
ctggagggac aagcatgttg tgaatcctgt aaggaaccag gagatgtgtg gaggatgctg 420
ggccttcagc gtggtgagtg ccatagagtc agctcgtgca atccaaggga aatctctgga 480
ttacctgagc gtgcagcagg tcatcgactg ctcctttaat aattctggct gcctcggtgg 540
ctctcctctc tgtgccttgc gctggctaaa tgagacacag ttgaagttgg tggcagattc 600
acagtaccca ttcaaggcag taaatggcca gtgtcgccac tttcctcaat cacaagctgg 660
agtttcagtc aaggattttt ctgcatataa cttcaggggc caagaggatg aaatggccag 720
agcacttctg tccttcggcc ctttggttgt gatagttgat gcgatgagct ggcaggatta 780
tctgggggggc ataatccaac atcactgctc cagtggggag gccaaccatg ccgttctcat 840
cacaggcttt gataggacag gaaatacacc atattggatg gtgcgaaact cctggggatc 900
ctcctgggga gtagaaggct atgcccacgt gaaaatggga ggtaatgttt gtggcattgc 960
agactctgta gctgctgtct ttgtgtgatc atgaattgtt ttggattcac catgagacaa 1020
ctacgaaaat gatgcacttc atagtgtgat ccaacatcat actcaactct aagcattatg 1080
caccttcaag ttccaacaat ttgtctacag agaggttcta agagcaaact ggcattttgt 1140
aaagcaacct aggacattct atttttgca aagacatgga cagccaaact tcataggaaa 1200
tccccaggac gttgactgat caacggactc tgtgggatag tgtgcacctc tgagagtttg 1260
gtgggatcag aagtcacata gtattctcct cctggaagca gttgggactt ttgcttgctt 1320
gttgtctttc tggctgtcta cattaaggaa gtattttggt cagggtgaat tgaagatatg 1380
atgagccttt gtttttccct tgtgacttat aatcaccagt cttagattac ctcatctaca 1440
agaactctca acctgatgca atgtgtgcct cataattaga atggccttct gttccatgtg 1500
aacagatttg gaatatcagt tgttttattt cagcaaatgg aacttactct agacagtaga 1560
acaaatgtgc accaagatga aacaacgatg cacaaagaga atcccatctt cagagagaca 1620
atccaactgg agttaaataa acacgtgaca acagtgtgat aaggagtaca ctatgccact 1680
tccagggagt catgatgtct ataaagcttc acttttaaac acccaaaatg tttagcttct 1740
tgccttcttc cctctgaggt agagaatgaa gtattgtcca catttattcc ctctcttgtc 1800
ctttatggta caagtcctat ggtttcctgg tggtttacct tccagtccaa agtaactcag 1860
taccgttggt tgtattccat ttctgttacc caatctctta cttaaaaaca aaatctctga 1920
cacaggctca cattgctcct tgtttatgtc cttcattaga ataccagcat caataacaaa 1980
gctccttact cttttgtctg taccagtgag aagcaatctt gaatgtgcag atcatggagg 2040
gtaaagaaac ggcagaagac atttcttaag gttttgaata aagtagccta attatcgaag 2100
gaatccagga aggaatgtag ttcagctata gtgtttctta atgactttca ttatgttatc 2160
agcaatgttt ctaataccca gtttcaaatg cagataaact tgaaattttc aaaatcactg 2220
ttactcttta agtattctgg attgataaca tttataataa tacaacctac atttgacttt 2280
gaattaaaag taacttattc ttaaatatgt agtctatgat ttattattat ttatgagcac 2340
taatagatat ttattagtat cgataagctt tatatttaca ttttcttgga tttgaaccct 2400
tatatccaat gtgcttttct ccatagatga ttttaattcc accatgtcca agattcctct 2460
catcatcttc ccatatctgt tgtcaatgct cagtggtcct cttctcctta ccttttcttt 2520
ctgtcagcag cattgctatt gtataagcag gccatagagt caaaaggaat tctagacaat 2580
caagttgtct cctccttaga acccattcct acatctgtct ccatcctctc tttcacgcat 2640
cctttctggg aggtacactt tttattatct cctatctaca ctcttcagtt gtttccagcc 2700
aacctaaaat aaaaagggag atatcttcat aaaagtttag gtttttttt tgtttgtttg 2760
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tttgtttggt tggcttttgt cttttatttt tgtatagagt tatgatgagt tttgatgtga 2820
tgcacttcaa acacttttttg tgatagtttt tgttatgtat caattatatg taacactccc 2880
tttcagtgac ttgttagctt tattcctttc gttttcttgt tagtgcctgg tgtaagtaac 2940
tccctatggt tctgacaacc tttattagta actaaactat gtgaccttta acacagtagg 3000
tcctgaacag taatctccag agcagaacag atggctttga aagatgctac tataatgtgt 3060
cctatatttc cccagattta tatttctaaa atgatgttat cattttactc acaagtttta 3120
cagcactgga aatcagtaag ataacatgca aatttttttca aataagcatt atggagaggt 3180
ctctctctac ctttgtatcc cctgtaaata agtgatgacg catatacacc agctcatggg 3240
tgctcctgcc ccagaaaacc agagacagag cagccgaatg tgttccttac tacacagcat 3300
tcatactgaa gatcaccaac aggtcctgaa agtgatttga caaggtcccc attgcaactg 3360
ttaaatgggt caactttgca gtgcctttga aatatcccat cacttgggag gcagaggcag 3420
gtgaatttct gaggtcaagg ccagcccccc cac                              3453
```

<210> 73
<211> 312
<212> PRT
<213> 小家鼠

<220>
<223> 組織蛋白酶O前驅體

<400> 73

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

<210> 74

<211> 214
<212> PRT
<213> 小家鼠

<220>
<223> 成熟組織蛋白酶O

<400> 74
Leu Pro Leu Arg Phe Asp Trp Arg Asp Lys His Val Val Asn Pro Val
 1   5   10   15
Arg Asn Gln Glu Met Cys Gly Gly Cys Trp Ala Phe Ser Val Val Ser
            20   25   30
Ala Ile Glu Ser Ala Arg Ala Ile Gln Gly Lys Ser Leu Asp Tyr Leu
        35   40   45
Ser Val Gln Gln Val Ile Asp Cys Ser Phe Asn Asn Ser Gly Cys Leu
    50   55   60
Gly Gly Ser Pro Leu Cys Ala Leu Arg Trp Leu Asn Glu Thr Gln Leu
65   70   75   80
Lys Leu Val Ala Asp Ser Gln Tyr Pro Phe Lys Ala Val Asn Gly Gln
                85   90   95
Cys Arg His Phe Pro Gln Ser Gln Ala Gly Val Ser Val Lys Asp Phe
            100   105   110
Ser Ala Tyr Asn Phe Arg Gly Gln Glu Asp Glu Met Ala Arg Ala Leu
        115   120   125
Leu Ser Phe Gly Pro Leu Val Val Ile Val Asp Ala Met Ser Trp Gln
    130   135   140
Asp Tyr Leu Gly Gly Ile Ile Gln His His Cys Ser Ser Gly Glu Ala
145   150   155   160
Asn His Ala Val Leu Ile Thr Gly Phe Asp Arg Thr Gly Asn Thr Pro
                165   170   175
Tyr Trp Met Val Arg Asn Ser Trp Gly Ser Ser Trp Gly Val Glu Gly
            180   185   190
Tyr Ala His Val Lys Met Gly Gly Asn Val Cys Gly Ile Ala Asp Ser
        195   200   205
Val Ala Ala Val Phe Val
    210

<210> 75
<211> 1335
<212> DNA
<213> 小家鼠

<220>
<223> 組織蛋白酶R前驅體

<400> 75
agcaactttt gaagagttga gtctgtggag tggattgagg cagaggcagt cacctcaggt 60
acttgagaca tggctgctgt tgtcttcata gccttcctgt atttgggagt ggcctcaggt 120
gttccagtac ttgattcaag tttggatgct gaatggcaag actggaagat aaagtataac 180
aaatcatata gcctgaagga agaaaaactg aagagagtgg tttgggaaga aaaattgaaa 240
atgatcaaac tacacaacag ggagaacagc ctgggtaaga atggcttcac catgaaaatg 300
aatgaatttg gtgaccagac tgatgaagaa ttcaggaaaa tgatgattga aatttcagtt 360
tggactcaca gagaggggaa aagtatcatg aaacgggaag ctggcagtat tctccccaaa 420
tttgtcgatt ggcgaaagaa aggatatgtg actcctgtac ggagacaggg agattgtgat 480
gcttgttggg catttgctgt gactggtgcc atagaagcac aggcaatctg gcaaacgggc 540
aaactcaccc ctctgagtgt gcagaacctg gtggactgtt ctaaacctca aggcaacaat 600
ggttgtcttg gtggtgatac atacaatgcc ttccagtatg ttttgcacaa tggtggtctg 660

gagtctgagg caacatatcc atatgaaggg aaagatggac catgcaggta taatccaaag 720
aattctaagg ctgaaatcac aggatttgtg tccctccccc aaagtgagga tatcctaatg 780
gctgctgtag caactattgg gcccatcact gctggaattg atgcttcaca tgagtctttc 840
aagaactata agggaggtat ttaccatgag ccaaattgta gcagtgatac tgtgactcat 900
ggagtcctcg tggttggtta cggatttaag ggaattgaga ccgatggtaa tcactactgg 960
ctgatcaaga atagctgggg taaacgatgg ggcattagag gctacatgaa gctcgccaaa 1020

gacaagaaca accactgtgg aattgcttca tatgctcact accctactat ttgagcaacc 1080
tggtggccac aaggaaggtt ttggcacaag acagcatttc taggggaggg ctatctgcta 1140
gtcagcgacc agcctttgct tggtatattc aagacttgtg tccctgaaga gcaaccttgt 1200
aatgtgattc tgggaccctt caactatttt gacatcatga acactattgc tctaactaac 1260
gtatgtttat tattccttca aaaaaatcag ctttaccgat tgtgcaaata aaatccttta 1320
aaaaataaaa tgcaa 1335

<210> 76
<211> 334
<212> PRT
<213> 小家鼠

<220>
<223> 組織蛋白酶R前驅體

<400> 76

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

<210> 77
<211> 220
<212> PRT
<213> 小家鼠

<220>
<223> 成熟組織蛋白酶R

<400> 77
Leu Pro Lys Phe Val Asp Trp Arg Lys Lys Gly Tyr Val Thr Pro Val
1 5 10 15
Arg Arg Gln Gly Asp Cys Asp Ala Cys Trp Ala Phe Ala Val Thr Gly
20 25 30
Ala Ile Glu Ala Gln Ala Ile Trp Gln Thr Gly Lys Leu Thr Pro Leu
35 40 45
Ser Val Gln Asn Leu Val Asp Cys Ser Lys Pro Gln Gly Asn Asn Gly
50 55 60
Cys Leu Gly Gly Asp Thr Tyr Asn Ala Phe Gln Tyr Val Leu His Asn
65 70 75 80
Gly Gly Leu Glu Ser Glu Ala Thr Tyr Pro Tyr Glu Gly Lys Asp Gly
85 90 95
Pro Cys Arg Tyr Asn Pro Lys Asn Ser Lys Ala Glu Ile Thr Gly Phe
100 105 110
Val Ser Leu Pro Gln Ser Glu Asp Ile Leu Met Ala Ala Val Ala Thr
115 120 125
Ile Gly Pro Ile Thr Ala Gly Ile Asp Ala Ser His Glu Ser Phe Lys
130 135 140
Asn Tyr Lys Gly Gly Ile Tyr His Glu Pro Asn Cys Ser Ser Asp Thr
145 150 155 160
Val Thr His Gly Val Leu Val Val Gly Tyr Gly Phe Lys Gly Ile Glu
165 170 175
Thr Asp Gly Asn His Tyr Trp Leu Ile Lys Asn Ser Trp Gly Lys Arg
180 185 190
Trp Gly Ile Arg Gly Tyr Met Lys Leu Ala Lys Asp Lys Asn Asn His
195 200 205
Cys Gly Ile Ala Ser Tyr Ala His Tyr Pro Thr Ile
210 215 220

<210> 78
<211> 1327
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶W前驅體

<400> 78
tgcgcggctt cctgcctcca tgccactcca gactgcaccg gcatggcact gactgcccac 60
ccctcctgcc tcctggccct gttggtggca ggcctagccc aaggcatcag aggccccctt 120
agggcccagg acctaggtcc ccagccgcta gagctgaaag aggccttcaa gttgttccag 180
atccagttca accggagtta cctgagccca gaagagcatg ctcaccgcct ggacatcttt 240
gcccacaacc tggcccaggc tcagaggctg caggaggagg acttgggcac agctgagttt 300
ggggtgactc cattcagtga cctcacagag gaggagtttg gccagctcta tggctatcgg 360
agggcagctg gaggggtccc cagcatgggc agagaaataa ggtctgaaga gccagaggag 420
tcagtacctt tcagctgtga ctggcggaag gtggccggcg ccatctcacc catcaaggac 480
cagaaaaact gcaactgctg ctgggccatg gcagcggcag gcaacataga gaccctgtgg 540
cgcatcagtt tctgggattt tgtggacgtc tccgtgcagg aactgctgga ctgtggccgc 600
tgtggggatg gctgccacgg tggcttcgtc tgggacgcgt tcataactgt cctcaacaac 660
agcggcctgg ccagtgaaaa ggactacccg ttccagggca aagtcagagc ccacaggtgc 720
caccccaaga agtaccagaa ggtggcctgg atccaggact tcatcatgct gcagaacaac 780
gagcacagaa ttgcgcagta cctggccact tatggcccca tcaccgtgac catcaacatg 840
aagccccttc agctataccg gaaaggtgtg atcaaggcca cacccaccac ctgtgacccc 900
cagcttgtgg accactctgt cctgctggtg ggttttggca gcgtcaagtc agaggagggg 960
atatgggcag agacagtctc atcgcagtct cagcctcagc ctccacaccc caccccatac 1020
tggatcctga agaactcctg gggggcccaa tggggagaga agggctattt ccggctgcac 1080
cgagggagca atacctgtgg catcaccaag ttcccgctca ctgcccgtgt gcagaaaccg 1140
gatatgaagc cccgagtctc ctgccctccc tgaacccacc tggccccctc agctctgtcc 1200
tgttaggcca actgcctcct tgccagcccc acccccaggt ttttgcccat cctcccaatc 1260

tcaatacagc ctgaataaac caagacaaga cctctgaaaa aaaaaaaaaa aaaaaaaaaa 1320
aaaaaaa 1327

<210> 79
<211> 376
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶w前驅體

<400> 79
Met Ala Leu Thr Ala His Pro Ser Cys Leu Leu Ala Leu Leu Val Ala
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Gly Leu Ala Gln Gly Ile Arg Gly Pro Leu Arg Ala Gln Asp Leu Gly
            20   25   30

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

<210> 80
<211> 249

<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶W

<400> 80
Val Pro Phe Ser Cys Asp Trp Arg Lys Val Ala Gly Ala Ile Ser Pro
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Ile Lys Asp Gln Lys Asn Cys Asn Cys Cys Trp Ala Met Ala Ala Ala
20 25 30
Gly Asn Ile Glu Thr Leu Trp Arg Ile Ser Phe Trp Asp Phe Val Asp
35 40 45
Val Ser Val His Glu Leu Leu Asp Cys Gly Arg Cys Gly Asp Gly Cys
50 55 60
His Gly Gly Phe Val Trp Asp Ala Phe Ile Thr Val Leu Asn Asn Ser
65 70 75 80
Gly Leu Ala Ser Glu Lys Asp Tyr Pro Phe Gln Gly Lys Val Arg Ala
85 90 95
His Arg Cys His Pro Lys Lys Tyr Gln Lys Val Ala Trp Ile Gln Asp
100 105 110
Phe Ile Met Leu Gln Asn Asn Glu His Arg Ile Ala Gln Tyr Leu Ala
115 120 125
Thr Tyr Gly Pro Ile Thr Val Thr Ile Asn Met Lys Pro Leu Gln Leu
130 135 140
Tyr Arg Lys Gly Val Ile Lys Ala Thr Pro Thr Thr Cys Asp Pro Gln
145 150 155 160
Leu Val Asp His Ser Val Leu Leu Val Gly Phe Gly Ser Val Lys Ser
165 170 175
Glu Glu Gly Ile Trp Ala Glu Thr Val Ser Ser Gln Ser Gln Pro Gln
180 185 190
Pro Pro His Pro Thr Pro Tyr Trp Ile Leu Lys Asn Ser Trp Gly Ala
195 200 205
Gln Trp Gly Glu Lys Gly Tyr Phe Arg Leu His Arg Gly Ser Asn Thr
210 215 220
Cys Gly Ile Thr Lys Phe Pro Leu Thr Ala Arg Val Gln Lys Pro Asp
225 230 235 240
Met Lys Pro Arg Val Ser Cys Pro Pro
245

<210> 81
<211> 3007
<212> DNA
<213> 現代人

<220>
<223> 鈣蛋白酶1大亞單位前驅體

<400> 81
aaggagagag ggagggcgga gggcggaggg gcggcgggag gagggcgggg aggagcgctc 60
ttcctggttg ggccctgccc tgagctgcca ccgggaagcc agcctcaggg actgcagcga 120
cccccaaaca cccctccccc aggatgtcgg aggagatcat cacgccggtg tactgcactg 180
gggtgtcagc ccaagtgcag aagcagcggg ccagggagct gggcctgggc cgccatgaga 240
atgccatcaa gtacctgggc caggattatg agcagctgcg ggtgcgatgc ctgcagagtg 300
ggaccctctt ccgtgatgag gccttccccc cggtacccca gagcctgggt tacaaggacc 360
tgggtcccaa ttcctccaag acctatggca tcaagtggaa gcgtcccacg gaactgctgt 420
caaaccccca gttcattgtg gatggagcta cccgcacaga catctgccag ggagcactgg 480
gggactgctg gctcttggcg gccattgcct ccctcactct caacgacacc ctcctgcacc 540
gagtggttcc gcacggccag agcttccaga atggctatgc cggcatcttc catttccagc 600
tgtggcaatt tggggagtgg gtggacgtgg tcgtggatga cctgctgccc atcaaggacg 660
ggaagctagt gttcgtgcac tctgccgaag gcaacgagtt ctggagcgcc ctgcttgaga 720
aggcctatgc caaggtaaat ggcagctacg aggccctgtc aggggggcagc acctcagagg 780
gctttgagga cttcacaggc ggggttaccg agtggtacga gttgcgcaag gctcccagtg 840
acctctacca gatcatcctc aaggcgctgg agcggggctc cctgctgggc tgctccatag 900

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cctactctgt gaccggggcc aagcaggtga actaccgagg ccaggtggtg agcctgatcc 1020
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tcacacccga cgccctcaag agccggacca tccgcaaatg gaacaccaca ctctacgaag 1260
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gcgagtcagg ctgcagcttc gtgctcgccc ttatgcagaa gcaccgtcgc cgcgagcgcc 1440
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gcagcatgag tgcctacgag atgcggatgg ccattgagtc ggcaggcttc aagctcaaca 2100
agaagctgta cgagctcatc atcacccgct actcggagcc cgacctggcg gtcgactttg 2160
acaatttcgt ttgctgcctg gtgcggctag agaccatgtt ccgatttttc aaaactctgg 2220
acacagatct ggatggagtt gtgacctttg acttgtttaa gtggttgcag ctgaccatgt 2280
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ccggcctggc cttgcctgca gactataaac tataaccact agctcgacac agtctgcagt 2700
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gtctgtg 3007

<210> 82
<211> 714
<212> PRT
<213> 現代人

<220>
<223> 鈣蛋白酶1大亞單位

<400> 82
Met Ser Glu Glu Ile Ile Thr Pro Val Tyr Cys Thr Gly Val Ser Ala
 1   5   10   15
Gln Val Gln Lys Gln Arg Ala Arg Glu Leu Gly Leu Gly Arg His Glu
            20   25   30
Asn Ala Ile Lys Tyr Leu Gly Gln Asp Tyr Glu Gln Leu Arg Val Arg
        35   40   45
Cys Leu Gln Ser Gly Thr Leu Phe Arg Asp Glu Ala Phe Pro Pro Val
    50   55   60
Pro Gln Ser Leu Gly Tyr Lys Asp Leu Gly Pro Asn Ser Ser Lys Thr
65   70   75   80
Tyr Gly Ile Lys Trp Lys Arg Pro Thr Glu Leu Leu Ser Asn Pro Gln
                85   90   95
Phe Ile Val Asp Gly Ala Thr Arg Thr Asp Ile Cys Gln Gly Ala Leu
            100   105   110
Gly Asp Cys Trp Leu Leu Ala Ala Ile Ala Ser Leu Thr Leu Asn Asp
        115   120   125
Thr Leu Leu His Arg Val Val Pro His Gly Gln Ser Phe Gln Asn Gly
    130   135   140
Tyr Ala Gly Ile Phe His Phe Gln Leu Trp Gln Phe Gly Glu Trp Val

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145                 150                 155                 160
Asp Val Val Val Asp Asp Leu Leu Pro Ile Lys Asp Gly Lys Leu Val
                165                 170                 175
Phe Val His Ser Ala Glu Gly Asn Glu Phe Trp Ser Ala Leu Leu Glu
            180                 185                 190
Lys Ala Tyr Ala Lys Val Asn Gly Ser Tyr Glu Ala Leu Ser Gly Gly
        195                 200                 205
Ser Thr Ser Glu Gly Phe Glu Asp Phe Thr Gly Gly Val Thr Glu Trp
    210                 215                 220
Tyr Glu Leu Arg Lys Ala Pro Ser Asp Leu Tyr Gln Ile Ile Leu Lys
225                 230                 235                 240
Ala Leu Glu Arg Gly Ser Leu Leu Gly Cys Ser Ile Asp Ile Ser Ser
                245                 250                 255
Val Leu Asp Met Glu Ala Ile Thr Phe Lys Lys Leu Val Lys Gly His
            260                 265                 270
Ala Tyr Ser Val Thr Gly Ala Lys Gln Val Asn Tyr Arg Gly Gln Val
        275                 280                 285
Val Ser Leu Ile Arg Met Arg Asn Pro Trp Gly Glu Val Glu Trp Thr
    290                 295                 300
Gly Ala Trp Ser Asp Ser Ser Ser Glu Trp Asn Asn Val Asp Pro Tyr
305                 310                 315                 320
Glu Arg Asp Gln Leu Arg Val Lys Met Glu Asp Gly Glu Phe Trp Met
                325                 330                 335
Ser Phe Arg Asp Phe Met Arg Glu Phe Thr Arg Leu Glu Ile Cys Asn
            340                 345                 350
Leu Thr Pro Asp Ala Leu Lys Ser Arg Thr Ile Arg Lys Trp Asn Thr
        355                 360                 365
Thr Leu Tyr Glu Gly Thr Trp Arg Arg Gly Ser Thr Ala Gly Gly Cys
    370                 375                 380
Arg Asn Tyr Pro Ala Thr Phe Trp Val Asn Pro Gln Phe Lys Ile Arg
385                 390                 395                 400
Leu Asp Glu Thr Asp Asp Pro Asp Asp Tyr Gly Asp Arg Glu Ser Gly
                405                 410                 415
Cys Ser Phe Val Leu Ala Leu Met Gln Lys His Arg Arg Arg Glu Arg
            420                 425                 430
Arg Phe Gly Arg Asp Met Glu Thr Ile Gly Phe Ala Val Tyr Glu Val
        435                 440                 445
Pro Pro Glu Leu Val Gly Gln Pro Ala Val His Leu Lys Arg Asp Phe
    450                 455                 460
Phe Leu Ala Asn Ala Ser Arg Ala Arg Ser Glu Gln Phe Ile Asn Leu
465                 470                 475                 480
Arg Glu Val Ser Thr Arg Phe Arg Leu Pro Pro Gly Glu Tyr Val Val
                485                 490                 495
Val Pro Ser Thr Phe Glu Pro Asn Lys Glu Gly Asp Phe Val Leu Arg
            500                 505                 510
Phe Phe Ser Glu Lys Ser Ala Gly Thr Val Glu Leu Asp Asp Gln Ile
        515                 520                 525
Gln Ala Asn Leu Pro Asp Glu Gln Val Leu Ser Glu Glu Glu Ile Asp
    530                 535                 540
Glu Asn Phe Lys Ala Leu Phe Arg Gln Leu Ala Gly Glu Asp Met Glu
545                 550                 555                 560
Ile Ser Val Lys Glu Leu Arg Thr Ile Leu Asn Arg Ile Ile Ser Lys
                565                 570                 575
His Lys Asp Leu Arg Thr Lys Gly Phe Ser Leu Glu Ser Cys Arg Ser
            580                 585                 590
Met Val Asn Leu Met Asp Arg Asp Gly Asn Gly Lys Leu Gly Leu Val
        595                 600                 605
Glu Phe Asn Ile Leu Trp Asn Arg Ile Arg Asn Tyr Leu Ser Ile Phe
    610                 615                 620
Arg Lys Phe Asp Leu Asp Lys Ser Gly Ser Met Ser Ala Tyr Glu Met
625                 630                 635                 640
Arg Met Ala Ile Glu Ser Ala Gly Phe Lys Leu Asn Lys Lys Leu Tyr
                645                 650                 655
Glu Leu Ile Ile Thr Arg Tyr Ser Glu Pro Asp Leu Ala Val Asp Phe
            660                 665                 670
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Asp Asn Phe Val Cys Cys Leu Val Arg Leu Glu Thr Met Phe Arg Phe
        675                 680                 685
Phe Lys Thr Leu Asp Thr Asp Leu Asp Gly Val Val Thr Phe Asp Leu
    690                 695                 700
Phe Lys Trp Leu Gln Leu Thr Met Phe Ala
705                 710
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<210> 83
<211> 3492
<212> DNA
<213> 現代人

<220>
<223> 鈣蛋白酶2大亞單位前驅體

<400> 83

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cacaccccgc gggccgggcc gcttcctctc ggtgaatcat cgctcgcagc ggcggcgccc 120
gcagtggccg cagcagcgcg ccgggccctg gccgcgcccc agccgagcgc agcgcggagt 180
cgccccgacc tttctctgcg cagtacggcc gccgggaccg cagcatggcg ggcatcgcgg 240
ccaagctggc gaaggaccgg gaggcggccg aggggctggg ctcccacgag agggccatca 300
agtacctcaa ccaggactac gaggcgctgc ggaacgagtg cctggaggcc gggacgctct 360
tccaggaccc gtccttcccg gccatcccct cggccctggg cttcaaggag ttggggccct 420
actccagcaa aacccggggc atcgagtgga agcgccccac ggagatctgc gctgaccccc 480
agtttatcat tggaggagcc acccgcacag acatctgcca aggagccctg ggtgactgct 540
ggctgctggc agccattgcc tccctcacct tgaatgaaga aatcctggct cgagtcgtcc 600
ccctaaacca gagcttccag gaaaactatg cagggatctt tcacttccag ttctggcaat 660
acggcgagtg ggtggaggtg gtggtggatg acaggctgcc caccaaggac ggggagctgc 720
tctttgtgca ttcagccgaa gggagcgagt tctggagcgc cctgctggag aaggcatacg 780
ccaagatcaa cggatgctat gaagcgctat caggggtgc caccactgag ggcttcgaag 840
acttcaccgg aggcattgct gagtggtatg agttgaagaa gccccctccc aacctgttca 900
agatcatcca gaaagctctg caaaaaggct ctctccttgg ctgctccatc gacatcacca 960
gcgccgcgga ctcggaggcc atcacgtttc agaagctggt gaaggggcac gcgtactcgg 1020
tcaccggagc cgaggaggtt gaaagtaacg gaagcctaca gaaactgatc cgcatccgaa 1080
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tgtctttcag tgacttcctg aggcactatt cccgcctgga gatctgtaac ctgaccccag 1260
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aaatgcggaa ggcattagaa gaagcaggtt tcaagatgcc ctgtcaactc caccaagtca 2160
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tggttcggct ggaaacgcta ttcaagatat ttaagcagct ggatcccgag aatactggaa 2280
caatagagct cgaccttatc tcttggctct gtttctcagt actttgaagt tataactaat 2340
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ctttgtatct ggacctcaaa attatgggaa catttactta aacggatgat catagctgaa 2460
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atatcattat actaaatgca aatgagtcgc ttaacccttg acaaggtcaa agaaagcttt 2580
aaatctgtaa atagtataca ctttttactt ttacacactt tcctgttcat agcaatatta 2640
aatcaggaaa aaaaaatgca gggaggtatt taacagctga gcaaaaacat tgagtcgctc 2700
tcaaaggaca cgaggccctt ggcagggaat atttaaagca acttcaagtt taaaatgcag 2760
ctgttgattc taccaaacaa cagtccaaga ttaccatttc ccatgagcca actgggaaac 2820
atggtatatc atgaagtaat cttgtcaagg catctggaga gtccaggaga gaagactcac 2880
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ctctgtcgct tgggttaaac aagagacagg ttttgtagaa tattgattgg taatagtaaa 2940
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gaccaaaggg atcctgcgct tgatcaactg aaccagtatg ccaaaaccag gcatccaatt 3060
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<210> 84
<211> 700
<212> PRT
<213> 現代人

<220>
<223> 鈣蛋白酶2大亞單位前驅體

<400> 84

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Met Ala Gly Ile Ala Ala Lys Leu Ala Lys Asp Arg Glu Ala Ala Glu
 1               5                  10                  15
Gly Leu Gly Ser His Glu Arg Ala Ile Lys Tyr Leu Asn Gln Asp Tyr
            20                  25                  30
Glu Ala Leu Arg Asn Glu Cys Leu Glu Ala Gly Thr Leu Phe Gln Asp
        35                  40                  45
Pro Ser Phe Pro Ala Ile Pro Ser Ala Leu Gly Phe Lys Glu Leu Gly
    50                  55                  60
Pro Tyr Ser Ser Lys Thr Arg Gly Ile Glu Trp Lys Arg Pro Thr Glu
65                  70                  75                  80
Ile Cys Ala Asp Pro Gln Phe Ile Ile Gly Gly Ala Thr Arg Thr Asp
                85                  90                  95
Ile Cys Gln Gly Ala Leu Gly Asp Cys Trp Leu Leu Ala Ala Ile Ala
            100                 105                 110
Ser Leu Thr Leu Asn Glu Glu Ile Leu Ala Arg Val Val Pro Leu Asn
        115                 120                 125
Gln Ser Phe Gln Glu Asn Tyr Ala Gly Ile Phe His Phe Gln Phe Trp
    130                 135                 140
Gln Tyr Gly Glu Trp Val Glu Val Val Val Asp Asp Arg Leu Pro Thr
145                 150                 155                 160
Lys Asp Gly Glu Leu Leu Phe Val His Ser Ala Glu Gly Ser Glu Phe
                165                 170                 175
Trp Ser Ala Leu Leu Glu Lys Ala Tyr Ala Lys Ile Asn Gly Cys Tyr
            180                 185                 190
Glu Ala Leu Ser Gly Gly Ala Thr Thr Glu Gly Phe Glu Asp Phe Thr
        195                 200                 205
Gly Gly Ile Ala Glu Trp Tyr Glu Leu Lys Lys Pro Pro Pro Asn Leu
    210                 215                 220
Phe Lys Ile Ile Gln Lys Ala Leu Gln Lys Gly Ser Leu Leu Gly Cys
225                 230                 235                 240
Ser Ile Asp Ile Thr Ser Ala Ala Asp Ser Glu Ala Ile Thr Phe Gln
                245                 250                 255
Lys Leu Val Lys Gly His Ala Tyr Ser Val Thr Gly Ala Glu Glu Val
            260                 265                 270
Glu Ser Asn Gly Ser Leu Gln Lys Leu Ile Arg Ile Arg Asn Pro Trp
        275                 280                 285
Gly Glu Val Glu Trp Thr Gly Arg Trp Asn Asp Asn Cys Pro Ser Trp
    290                 295                 300
Asn Thr Ile Asp Pro Glu Glu Arg Glu Arg Leu Thr Arg Arg His Glu
305                 310                 315                 320
Asp Gly Glu Phe Trp Met Ser Phe Ser Asp Phe Leu Arg His Tyr Ser
                325                 330                 335
Arg Leu Glu Ile Cys Asn Leu Thr Pro Asp Thr Leu Thr Ser Asp Thr
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            340                 345                 350
Tyr Lys Lys Trp Lys Leu Thr Lys Met Asp Gly Asn Trp Arg Arg Gly
        355                 360                 365
Ser Thr Ala Gly Gly Cys Arg Asn Tyr Pro Asn Thr Phe Trp Met Asn
    370                 375                 380
Pro Gln Tyr Leu Ile Lys Leu Glu Glu Glu Asp Glu Asp Glu Glu Asp
385                 390                 395                 400
Gly Glu Ser Gly Cys Thr Phe Leu Val Gly Leu Ile Gln Lys His Arg
                405                 410                 415
Arg Arg Gln Arg Lys Met Gly Glu Asp Met His Thr Ile Gly Phe Gly
            420                 425                 430
Ile Tyr Glu Val Pro Glu Glu Leu Ser Gly Gln Thr Asn Ile His Leu
        435                 440                 445
Ser Lys Asn Phe Phe Leu Thr Asn Arg Ala Arg Glu Arg Ser Asp Thr
    450                 455                 460
Phe Ile Asn Leu Arg Glu Val Leu Asn Arg Phe Lys Leu Pro Pro Gly
465                 470                 475                 480
Glu Tyr Ile Leu Val Pro Ser Thr Phe Glu Pro Asn Lys Asp Gly Asp
                485                 490                 495
Phe Cys Ile Arg Val Phe Ser Glu Lys Lys Ala Asp Tyr Gln Ala Val
            500                 505                 510
Asp Asp Glu Ile Glu Ala Asn Leu Glu Glu Phe Asp Ile Ser Glu Asp
        515                 520                 525
Asp Ile Asp Asp Gly Phe Arg Arg Leu Phe Ala Gln Leu Ala Gly Glu
    530                 535                 540
Asp Ala Glu Ile Ser Ala Phe Glu Leu Gln Thr Ile Leu Arg Arg Val
545                 550                 555                 560
Leu Ala Lys Arg Gln Asp Ile Lys Ser Asp Gly Phe Ser Ile Glu Thr
                565                 570                 575
Cys Lys Ile Met Val Asp Met Leu Asp Ser Asp Gly Ser Gly Lys Leu
            580                 585                 590
Gly Leu Lys Glu Phe Tyr Ile Leu Trp Thr Lys Ile Gln Lys Tyr Gln
        595                 600                 605
Lys Ile Tyr Arg Glu Ile Asp Val Asp Arg Ser Gly Thr Met Asn Ser
    610                 615                 620
Tyr Glu Met Arg Lys Ala Leu Glu Glu Ala Gly Phe Lys Met Pro Cys
625                 630                 635                 640
Gln Leu His Gln Val Ile Val Ala Arg Phe Ala Asp Asp Gln Leu Ile
                645                 650                 655
Ile Asp Phe Asp Asn Phe Val Arg Cys Leu Val Arg Leu Glu Thr Leu
            660                 665                 670
Phe Lys Ile Phe Lys Gln Leu Asp Pro Glu Asn Thr Gly Thr Ile Glu
        675                 680                 685
Leu Asp Leu Ile Ser Trp Leu Cys Phe Ser Val Leu
    690                 695                 700
```

<210> 85
<211> 699
<212> PRT
<213> 現代人

<220>
<223> 鈣蛋白酶2大亞單位

<400> 85

```
Ala Gly Ile Ala Ala Lys Leu Ala Lys Asp Arg Glu Ala Ala Glu Gly
 1                5                  10                  15
Leu Gly Ser His Glu Arg Ala Ile Lys Tyr Leu Asn Gln Asp Tyr Glu
            20                  25                  30
Ala Leu Arg Asn Glu Cys Leu Glu Ala Gly Thr Leu Phe Gln Asp Pro
        35                  40                  45
Ser Phe Pro Ala Ile Pro Ser Ala Leu Gly Phe Lys Glu Leu Gly Pro
    50                  55                  60
```

```
Tyr Ser Ser Lys Thr Arg Gly Ile Glu Trp Lys Arg Pro Thr Glu Ile
65                  70                  75                  80
Cys Ala Asp Pro Gln Phe Ile Ile Gly Gly Ala Thr Arg Thr Asp Ile
                85                  90                  95
Cys Gln Gly Ala Leu Gly Asp Cys Trp Leu Leu Ala Ala Ile Ala Ser
            100                 105                 110
Leu Thr Leu Asn Glu Glu Ile Leu Ala Arg Val Val Pro Leu Asn Gln
        115                 120                 125
Ser Phe Gln Glu Asn Tyr Ala Gly Ile Phe His Phe Gln Phe Trp Gln
    130                 135                 140
Tyr Gly Glu Trp Val Glu Val Val Val Asp Asp Arg Leu Pro Thr Lys
145                 150                 155                 160
Asp Gly Glu Leu Leu Phe Val His Ser Ala Glu Gly Ser Glu Phe Trp
                165                 170                 175
Ser Ala Leu Leu Glu Lys Ala Tyr Ala Lys Ile Asn Gly Cys Tyr Glu
            180                 185                 190
Ala Leu Ser Gly Gly Ala Thr Thr Glu Gly Phe Glu Asp Phe Thr Gly
        195                 200                 205
Gly Ile Ala Glu Trp Tyr Glu Leu Lys Lys Pro Pro Asn Leu Phe
    210                 215                 220
Lys Ile Ile Gln Lys Ala Leu Gln Lys Gly Ser Leu Leu Gly Cys Ser
225                 230                 235                 240
Ile Asp Ile Thr Ser Ala Ala Asp Ser Glu Ala Ile Thr Phe Gln Lys
                245                 250                 255
Leu Val Lys Gly His Ala Tyr Ser Val Thr Gly Ala Glu Glu Val Glu
            260                 265                 270
Ser Asn Gly Ser Leu Gln Lys Leu Ile Arg Ile Arg Asn Pro Trp Gly
        275                 280                 285
Glu Val Glu Trp Thr Gly Arg Trp Asn Asp Asn Cys Pro Ser Trp Asn
    290                 295                 300
Thr Ile Asp Pro Glu Glu Arg Glu Arg Leu Thr Arg Arg His Glu Asp
305                 310                 315                 320
Gly Glu Phe Trp Met Ser Phe Ser Asp Phe Leu Arg His Tyr Ser Arg
                325                 330                 335
Leu Glu Ile Cys Asn Leu Thr Pro Asp Thr Leu Thr Ser Asp Thr Tyr
            340                 345                 350
Lys Lys Trp Lys Leu Thr Lys Met Asp Gly Asn Trp Arg Arg Gly Ser
        355                 360                 365
Thr Ala Gly Gly Cys Arg Asn Tyr Pro Asn Thr Phe Trp Met Asn Pro
    370                 375                 380
Gln Tyr Leu Ile Lys Leu Glu Glu Glu Asp Glu Asp Glu Glu Asp Gly
385                 390                 395                 400
Glu Ser Gly Cys Thr Phe Leu Val Gly Leu Ile Gln Lys His Arg Arg
                405                 410                 415
Arg Gln Arg Lys Met Gly Glu Asp Met His Thr Ile Gly Phe Gly Ile
            420                 425                 430
Tyr Glu Val Pro Glu Glu Leu Ser Gly Gln Thr Asn Ile His Leu Ser
        435                 440                 445
Lys Asn Phe Phe Leu Thr Asn Arg Ala Arg Glu Arg Ser Asp Thr Phe
    450                 455                 460
Ile Asn Leu Arg Glu Val Leu Asn Arg Phe Lys Leu Pro Pro Gly Glu
465                 470                 475                 480
Tyr Ile Leu Val Pro Ser Thr Phe Glu Pro Asn Lys Asp Gly Asp Phe
                485                 490                 495
Cys Ile Arg Val Phe Ser Glu Lys Lys Ala Asp Tyr Gln Ala Val Asp
            500                 505                 510
Asp Glu Ile Glu Ala Asn Leu Glu Glu Phe Asp Ile Ser Glu Asp Asp
        515                 520                 525
Ile Asp Asp Gly Phe Arg Arg Leu Phe Ala Gln Leu Ala Gly Glu Asp
    530                 535                 540
Ala Glu Ile Ser Ala Phe Glu Leu Gln Thr Ile Leu Arg Arg Val Leu
545                 550                 555                 560
Ala Lys Arg Gln Asp Ile Lys Ser Asp Gly Phe Ser Ile Glu Thr Cys
                565                 570                 575
Lys Ile Met Val Asp Met Leu Asp Ser Asp Gly Ser Gly Lys Leu Gly
```

```
            580                 585                 590
Leu Lys Glu Phe Tyr Ile Leu Trp Thr Lys Ile Gln Lys Tyr Gln Lys
        595                 600                 605
Ile Tyr Arg Glu Ile Asp Val Asp Arg Ser Gly Thr Met Asn Ser Tyr
    610                 615                 620
Glu Met Arg Lys Ala Leu Glu Glu Ala Gly Phe Lys Met Pro Cys Gln
625                 630                 635                 640
Leu His Gln Val Ile Val Ala Arg Phe Ala Asp Asp Gln Leu Ile Ile
                645                 650                 655
Asp Phe Asp Asn Phe Val Arg Cys Leu Val Arg Leu Glu Thr Leu Phe
            660                 665                 670
Lys Ile Phe Lys Gln Leu Asp Pro Glu Asn Thr Gly Thr Ile Glu Leu
        675                 680                 685
Asp Leu Ile Ser Trp Leu Cys Phe Ser Val Leu
    690                 695
```

<210> 86
<211> 1492
<212> DNA
<213> 現代人

<220>
<223> 鈣蛋白酶小亞單位1

<400> 86

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cgggcgacag cagggccgcg gtgcagtgtc cgacccgaga gttgcggcct gagtcaccgg 60
ccccgccctc cggagccgga cgctgcggga ggcccgggag cggcagtgga accgactccc 120
agaactccgg acgtgtgcgg cgcagtgagt cgcagccatg ttcctggtta actcgttctt 180
gaagggcggc ggcggcggcg gcgggggagg cgggggcctg ggtgggggcc tgggaaatgt 240
gcttggaggc ctgatcagcg gggccgggag cggcggcggc ggcggcggcg gcggcggcgg 300
tggtggaggc ggcggtggcg gtggaacggc catgcgcatc ctaggcggag tcatcagcgc 360
catcagcgag gcggctgcgc agtacaaccc ggagcccccg cccccacgca cacattactc 420
caacattgag gccaacgaga gtgaggaggt ccggcagttc cggagactct ttgcccagct 480
ggctggagat gacatggagg tcagcgccac agaactcatg aacattctca ataaggttgt 540
gacacgacac cctgatctga agactgatgg ttttggcatt gacacatgtc gcagcatggt 600
ggccgtgatg gatagcgaca ccacaggcaa gctgggcttt gaggaattca agtacttgtg 660
gaacaacatc aaaaggtggc aggccatata caaacagttc gacactgacc gatcagggac 720
catttgcagt agtgaactcc caggtgcctt tgaggcagca gggttccacc tgaatgagca 780
tctctataac atgatcatcc gacgctactc agatgaaagt gggaacatgg attttgacaa 840
cttcatcagc tgcttggtca ggctggacgc catgttccgt gccttcaaat ctcttgacaa 900
agatggcact ggacaaatcc aggtgaacat ccaggagtgg ctgcagctga ctatgtattc 960
ctgaactgga gccccagacc cgccccctca ctgccttgct ataggagtca cctggagcct 1020
cggtctctcc cagggccgat cctgtctgca gtcacatctt tgtggggcct gctgacccac 1080
aagcttttgt tctctcagta cttgttaccc agcttctcaa catccagggc ccaatttgcc 1140
ctgcctggag ttccccctgg ctctaggaca ctctaacaag ctctgtccac gggtctcccc 1200
attcccacca ggccctgcac acacccactc cgtaacctct cccctgtacc tgtgccaagc 1260
ctagcacttg tgatgcctcc atgccccgag ggccctctct cagttctggg aggatgactc 1320
cagtccctgc acgccctggc acacccttca cggttgctac ccaggcggcc aagctccaga 1380
ccgtgccaga cccaggtgcc ccagtgcctt tgtctatatt ctgctcccag cctgccaggc 1440
ccaggaggaa ataaacatgc cccagttgct gatctctaaa aaaaaaaaaa aa          1492
```

<210> 87
<211> 268
<212> PRT
<213> 現代人

<220>
<223> 鈣蛋白酶小亞單位1

<400> 87

```
Met Phe Leu Val Asn Ser Phe Leu Lys Gly Gly Gly Gly Gly Gly Gly
 1               5                  10                  15
Gly Gly Gly Gly Leu Gly Gly Gly Leu Gly Asn Val Leu Gly Gly Leu
            20                  25                  30
```

```
Ile Ser Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
          35                  40                  45
Gly Gly Gly Gly Gly Gly Gly Gly Thr Ala Met Arg Ile Leu Gly Gly
      50                  55                  60
Val Ile Ser Ala Ile Ser Glu Ala Ala Ala Gln Tyr Asn Pro Glu Pro
65                  70                  75                  80
Pro Pro Pro Arg Thr His Tyr Ser Asn Ile Glu Ala Asn Glu Ser Glu
                  85                  90                  95
Glu Val Arg Gln Phe Arg Arg Leu Phe Ala Gln Leu Ala Gly Asp Asp
              100                 105                 110
Met Glu Val Ser Ala Thr Glu Leu Met Asn Ile Leu Asn Lys Val Val
          115                 120                 125
Thr Arg His Pro Asp Leu Lys Thr Asp Gly Phe Gly Ile Asp Thr Cys
      130                 135                 140
Arg Ser Met Val Ala Val Met Asp Ser Asp Thr Thr Gly Lys Leu Gly
145                 150                 155                 160
Phe Glu Glu Phe Lys Tyr Leu Trp Asn Asn Ile Lys Arg Trp Gln Ala
                  165                 170                 175
Ile Tyr Lys Gln Phe Asp Thr Asp Arg Ser Gly Thr Ile Cys Ser Ser
              180                 185                 190
Glu Leu Pro Gly Ala Phe Glu Ala Ala Gly Phe His Leu Asn Glu His
          195                 200                 205
Leu Tyr Asn Met Ile Ile Arg Arg Tyr Ser Asp Glu Ser Gly Asn Met
      210                 215                 220
Asp Phe Asp Asn Phe Ile Ser Cys Leu Val Arg Leu Asp Ala Met Phe
225                 230                 235                 240
Arg Ala Phe Lys Ser Leu Asp Lys Asp Gly Thr Gly Gln Ile Gln Val
                  245                 250                 255
Asn Ile Gln Glu Trp Leu Gln Leu Thr Met Tyr Ser
              260                 265
```

<210> 88
<211> 2205
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶D前驅體

<400> 88
gcgcacgccg gccgcgccca cgtgaccggt ccgggtgcaa acacgcgggt cagctgatcc 60
ggcccaactg cggcgtcatc ccggctataa gcgcacggcc tcggcgaccc tctccgaccc 120
ggccgccgcc gccatgcagc cctccagcct tctgccgctc gccctctgcc tgctggctgc 180
acccgcctcc gcgctcgtca ggatcccgct gcacaagttc acgtccatcc gccggaccat 240
gtcggaggtt gggggctctg tggaggacct gattgccaaa ggccccgtct caaagtactc 300
ccaggcggtg ccagccgtga ccgaggggcc cattcccgag gtgctcaaga actacatgga 360
cgcccagtac tacggggaga ttggcatcgg gacgcccccc cagtgcttca cagtcgtctt 420
cgacacgggc tcctccaacc tgtgggtccc ctccatccac tgcaaactgc tggacatcgc 480
ttgctggatc caccacaagt acaacagcga caagtccagc acctacgtga agaatggtac 540
ctcgtttgac atccactatg gctcgggcag cctctccggg tacctgagcc aggacactgt 600
gtcggtgccc tgccagtcag cgtcgtcagc ctctgccctg ggcggtgtca aagtggagag 660
gcaggtcttt ggggaggcca ccaagcagcc aggcatcacc ttcatcgcag ccaagttcga 720
tggcatcctg ggcatggcct acccccgcat ctccgtcaac aacgtgctgc ccgtcttcga 780
caacctgatg cagcagaagc tggtggacca gaacatcttc tccttctacc tgagcaggga 840
cccagatgcg cagcctgggg gtgagctgat gctgggtggc acagactcca agtattacaa 900
gggttctctg tcctacctga atgtcacccg caaggcctac tggcaggtcc acctggacca 960
ggtggaggtg gccagcgggc tgaccctgtg caaggagggc tgtgaggcca ttgtggacac 1020
aggcacttcc ctcatggtgg gcccggtgga tgaggtgcgc gagctgcaga aggccatcgg 1080
ggccgtgccg ctgattcagg gcgagtacat gatcccctgt gagaaggtgt ccaccctgcc 1140
cgcgatcaca ctgaagctgg gaggcaaagg ctacaagctg tccccagagg actacacgct 1200
caaggtgtcg caggccggga agaccctctg cctgagcggc ttcatgggca tggacatccc 1260
gccacccagc gggccactct ggatcctggg cgacgtcttc atcggccgct actacactgt 1320
gtttgaccgt gacaacaaca gggtgggctt cgccgaggct gcccgcctct agttcccaag 1380
gcgtccgcgc gccagcacag aaacagagga gagtcccaga gcaggaggcc cctggcccag 1440

cggcccctcc cacacacacc cacacactcg cccgcccact gtcctgggcg ccctggaagc 1500
cggcggccca agcccgactt gctgttttgt tctgtggttt tcccctccct gggttcagaa 1560
atgctgcctg cctgtctgtc tctccatctg tttggtgggg gtagagctga tccagagcac 1620
agatctgttt cgtgcattgg aagaccccac ccaagcttgg cagccgagct cgtgtatcct 1680
ggggctccct tcatctccag ggagtcccct ccccggccct accagcgccc gctgggctga 1740
gcccctaccc cacaccaggc cgtcctcccg ggccctccct tggaaacctg ccctgcctga 1800
gggcccctct gcccagcttg ggcccagctg ggctctgcca ccctacctgt tcagtgtccc 1860
gggcccgttg aggatgaggc cgctagaggc ctgaggatga gctggaagga gtgagagggg 1920
acaaaaccca ccttgttgga gcctgcaggg tggtgctggg actgagccag tcccaggggc 1980
atgtattggc ctggaggtgg ggttgggatt gggggctggt gccagccttc ctctgcagct 2040
gacctctgtt gtcctcccct tgggcggctg agagccccag ctgacatgga aatacagttg 2100
ttggcctccg gcctcccctc aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2160
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 2205

<210> 89
<211> 412
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶D前驅體

<400> 89
Met Gln Pro Ser Ser Leu Leu Pro Leu Ala Leu Cys Leu Leu Ala Ala
 1   5   10   15
Pro Ala Ser Ala Leu Val Arg Ile Pro Leu His Lys Phe Thr Ser Ile
            20   25   30
Arg Arg Thr Met Ser Glu Val Gly Gly Ser Val Glu Asp Leu Ile Ala
        35   40   45
Lys Gly Pro Val Ser Lys Tyr Ser Gln Ala Val Pro Ala Val Thr Glu
    50   55   60
Gly Pro Ile Pro Glu Val Leu Lys Asn Tyr Met Asp Ala Gln Tyr Tyr
65   70   75   80
Gly Glu Ile Gly Ile Gly Thr Pro Pro Gln Cys Phe Thr Val Val Phe
                85   90   95
Asp Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Ile His Cys Lys Leu
            100   105   110
Leu Asp Ile Ala Cys Trp Ile His His Lys Tyr Asn Ser Asp Lys Ser
        115   120   125
Ser Thr Tyr Val Lys Asn Gly Thr Ser Phe Asp Ile His Tyr Gly Ser
    130   135   140
Gly Ser Leu Ser Gly Tyr Leu Ser Gln Asp Thr Val Ser Val Pro Cys
145   150   155   160
Gln Ser Ala Ser Ser Ala Ser Ala Leu Gly Gly Val Lys Val Glu Arg
                165   170   175
Gln Val Phe Gly Glu Ala Thr Lys Gln Pro Gly Ile Thr Phe Ile Ala
            180   185   190
Ala Lys Phe Asp Gly Ile Leu Gly Met Ala Tyr Pro Arg Ile Ser Val
        195   200   205
Asn Asn Val Leu Pro Val Phe Asp Asn Leu Met Gln Gln Lys Leu Val
    210   215   220
Asp Gln Asn Ile Phe Ser Phe Tyr Leu Ser Arg Asp Pro Asp Ala Gln
225   230   235   240
Pro Gly Gly Glu Leu Met Leu Gly Gly Thr Asp Ser Lys Tyr Tyr Lys
                245   250   255
Gly Ser Leu Ser Tyr Leu Asn Val Thr Arg Lys Ala Tyr Trp Gln Val
            260   265   270
His Leu Asp Gln Val Glu Val Ala Ser Gly Leu Thr Leu Cys Lys Glu
        275   280   285
Gly Cys Glu Ala Ile Val Asp Thr Gly Thr Ser Leu Met Val Gly Pro
    290   295   300
Val Asp Glu Val Arg Glu Leu Gln Lys Ala Ile Gly Ala Val Pro Leu
305   310   315   320
Ile Gln Gly Glu Tyr Met Ile Pro Cys Glu Lys Val Ser Thr Leu Pro
                325   330   335

```
Ala Ile Thr Leu Lys Leu Gly Gly Lys Gly Tyr Lys Leu Ser Pro Glu
            340                 345                 350
Asp Tyr Thr Leu Lys Val Ser Gln Ala Gly Lys Thr Leu Cys Leu Ser
        355                 360                 365
Gly Phe Met Gly Met Asp Ile Pro Pro Pro Ser Gly Pro Leu Trp Ile
    370                 375                 380
Leu Gly Asp Val Phe Ile Gly Arg Tyr Tyr Thr Val Phe Asp Arg Asp
385                 390                 395                 400
Asn Asn Arg Val Gly Phe Ala Glu Ala Ala Arg Leu
                405                 410
```

<210> 90
<211> 348
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶D

<400> 90

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

<210> 91
<211> 2228
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶e轉錄變異體1

<400> 91
atcattcggc cctcagactg ggctgggcag gtctgagagt tagggaaagt ccgttcccac 60
tgccctcggg gagagaagaa aggaggggc aagggagaag ctgctggtcg gactcacaat 120
gaaaacgctc cttcttttgc tgctggtgct cctggagctg ggagaggccc aaggatccct 180
tcacagggtg cccctcagga ggcatccgtc cctcaagaag aagctgcggg cacggagcca 240
gctctctgag ttctggaaat cccataattt ggacatgatc cagttcaccg agtcctgctc 300
aatggaccag agtgccaagg aacccctcat caactacttg gatatggaat acttcggcac 360
tatctccatt ggctccccac cacagaactt cactgtcatc ttcgacactg gctcctccaa 420
cctctgggtc ccctctgtgt actgcactag cccagcctgc aagacgcaca gcaggttcca 480
gccttcccag tccagcacat acagccagcc aggtcaatct ttctccattc agtatggaac 540
cgggagcttg tccgggatca ttggagccga ccaagtctct gtggaaggac taaccgtggt 600
tggccagcag tttggagaaa gtgtcacaga gccaggccag acctttgtgg atgcagagtt 660
tgatggaatt ctgggcctgg gataccctc cttggctgtg ggaggagtga ctccagtatt 720
tgacaacatg atggctcaga acctggtgga cttgccgatg ttttctgtct acatgagcag 780
taacccagaa ggtggtgcgg ggagcgagct gatttttgga ggctacgacc actcccattt 840
ctctgggagc ctgaattggg tcccagtcac caagcaagct tactggcaga ttgcactgga 900
taacatccag gtgggaggca ctgttatgtt ctgctccgag ggctgccagg ccattgtgga 960
cacagggact tccctcatca ctggcccttc cgacaagatt aagcagctgc aaaacgccat 1020
tggggcagcc cccgtggatg gagaatatgc tgtggagtgt gccaacctta acgtcatgcc 1080
ggatgtcacc ttcaccatta acggagtccc ctataccctc agcccaactg cctacaccct 1140
actggacttc gtggatggaa tgcagttctg cagcagtggc tttcaaggac ttgacatcca 1200
ccctccagct gggcccctct ggatcctggg ggatgtcttc attcgacagt tttactcagt 1260
ctttgaccgt gggaataacc gtgtgggact ggccccagca gtcccctaag gaggggcctt 1320
gtgtctgtgc ctgcctgtct gacagacctt gaatatgtta ggctggggca ttctttacac 1380
ctacaaaaag ttattttcca gagaatgtag ctgtttccag ggttgcaact tgaattaaga 1440
ccaaacagaa catgagaata cacacacaca cacacatata cacacacaca cacttcacac 1500
atacacacca ctcccaccac cgtcatgatg gaggaattac gttatacatt catattttgt 1560
attgattttt gattatgaaa atcaaaaatt ttcacatttg attatgaaaa tctccaaaca 1620
tatgcacaag cagagatcat ggtataataa atccctttgc aactccactc agccctgaca 1680
acccatccac acacggccag gcctgtttat ctacactgct gcccactcct ctctccagct 1740
ccacatgctg tacctggatc attctgaagc aaattccgag cattacatca ttttgtccat 1800
aaatatttct aacatcctta aatatacaat cggaattcaa gcatctccca ttgtcccaca 1860
aatgtttggc tgtttttgta gttggattgt ttgtattagg attcaagcaa ggcccatata 1920
ttgcatttat ttgaaatgtc tgtaagtctc tttccatcta cagagtttag cacatttgaa 1980
cgttgctggt tgaaatcccg aggtgtcatt tgacatggtt ctctgaactt atctttccta 2040
taaaatggta gttagatctg gaggtctgat tttgtggcaa aaatacttcc taggtggtgc 2100
tgggtacttc ttgttgcatc ctgtcaggag gcagataatg ctggtgcctc tctattggta 2160
atgttaagac tgctgggtgg gtttggagtt cttggcttta atcattcatt acaaagttca 2220
gcatttta 2228

<210> 92
<211> 396
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶E同功異型物前驅體

<400> 92
Met Lys Thr Leu Leu Leu Leu Leu Leu Val Leu Leu Glu Leu Gly Glu
 1   5   10   15
Ala Gln Gly Ser Leu His Arg Val Pro Leu Arg Arg His Pro Ser Leu
            20   25   30
Lys Lys Lys Leu Arg Ala Arg Ser Gln Leu Ser Glu Phe Trp Lys Ser
        35   40   45

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


<210> 93
<211> 343
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶E同功異型物

<400> 93
Ile Gln Phe Thr Glu Ser Cys Ser Met Asp Gln Ser Ala Lys Glu Pro
 1               5                  10                  15
Leu Ile Asn Tyr Leu Asp Met Glu Tyr Phe Gly Thr Ile Ser Ile Gly
            20                  25                  30
Ser Pro Pro Gln Asn Phe Thr Val Ile Phe Asp Thr Gly Ser Ser Asn
        35                  40                  45
Leu Trp Val Pro Ser Val Tyr Cys Thr Ser Pro Ala Cys Lys Thr His
    50                  55                  60
Ser Arg Phe Gln Pro Ser Gln Ser Ser Thr Tyr Ser Gln Pro Gly Gln
65                  70                  75                  80
```

```
Ser Phe Ser Ile Gln Tyr Gly Thr Gly Ser Leu Ser Gly Ile Ile Gly
                85                  90                  95
Ala Asp Gln Val Ser Val Glu Gly Leu Thr Val Val Gly Gln Gln Phe
            100                 105                 110
Gly Glu Ser Val Thr Glu Pro Gly Gln Thr Phe Val Asp Ala Glu Phe
        115                 120                 125
Asp Gly Ile Leu Gly Leu Gly Tyr Pro Ser Leu Ala Val Gly Gly Val
    130                 135                 140
Thr Pro Val Phe Asp Asn Met Met Ala Gln Asn Leu Val Asp Leu Pro
145                 150                 155                 160
Met Phe Ser Val Tyr Met Ser Ser Asn Pro Glu Gly Gly Ala Gly Ser
                165                 170                 175
Glu Leu Ile Phe Gly Gly Tyr Asp His Ser His Phe Ser Gly Ser Leu
            180                 185                 190
Asn Trp Val Pro Val Thr Lys Gln Ala Tyr Trp Gln Ile Ala Leu Asp
        195                 200                 205
Asn Ile Gln Val Gly Gly Thr Val Met Phe Cys Ser Glu Gly Cys Gln
    210                 215                 220
Ala Ile Val Asp Thr Gly Thr Ser Leu Ile Thr Gly Pro Ser Asp Lys
225                 230                 235                 240
Ile Lys Gln Leu Gln Asn Ala Ile Gly Ala Ala Pro Val Asp Gly Glu
                245                 250                 255
Tyr Ala Val Glu Cys Ala Asn Leu Asn Val Met Pro Asp Val Thr Phe
            260                 265                 270
Thr Ile Asn Gly Val Pro Tyr Thr Leu Ser Pro Thr Ala Tyr Thr Leu
        275                 280                 285
Leu Asp Phe Val Asp Gly Met Gln Phe Cys Ser Ser Gly Phe Gln Gly
    290                 295                 300
Leu Asp Ile His Pro Pro Ala Gly Pro Leu Trp Ile Leu Gly Asp Val
305                 310                 315                 320
Phe Ile Arg Gln Phe Tyr Ser Val Phe Asp Arg Gly Asn Asn Arg Val
                325                 330                 335
Gly Leu Ala Pro Ala Val Pro
            340
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<210> 94
<211> 2086
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶E轉錄變異體2

<400> 94

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atcattcggc cctcagactg ggctgggcag gtctgagagt tagggaaagt ccgttcccac 60
tgccctcggg gagagaagaa aggaggggc aagggagaag ctgctggtcg gactcacaat 120
gaaaacgctc cttcttttgc tgctggtgct cctggagctg ggagaggccc aaggatccct 180
tcacagggtg cccctcagga ggcatccgtc cctcaagaag aagctgcggg cacggagcca 240
gctctctgag ttctggaaat cccataattt ggacatgatc cagttcaccg agtcctgctc 300
aatggaccag agtgccaagg aacccctcat caactacttg gatatggaat acttcggcac 360
tatctccatt ggctccccac cacagaactt cactgtcatc ttcgacactg gctcctccaa 420
cctctgggtc ccctctgtgt actgcactag cccagcctgc aagacgcaca gcaggttcca 480
gccttcccag tccagcacat acagccagcc aggtcaatct ttctccattc agtatggaac 540
cgggagcttg tccgggatca ttggagccga ccaagtctct gtggaaggac taaccgtggt 600
tggccagcag tttggagaaa gtgtcacaga gccaggccag acctttgtgg atgcagagtt 660
tgatggaatt ctgggcctgg gataccctc cttggctgtg ggaggagtga ctccagtatt 720
tgacaacatg atggctcaga acctggtgga cttgccgatg ttttctgtct acatgagcag 780
taacccagaa ggtggtgcgg ggagcgagct gatttttgga ggctacgacc actcccattt 840
ctctgggagc ctgaattggg tcccagtcac caagcaagct tactggcaga ttgcactgga 900
taatatgctg tggagtgtgc caaccttaac gtcatgccgg atgtcacctt caccattaac 960
ggagtcccct ataccctcag cccaactgcc tacaccctac tggacttcgt ggatggaatg 1020
cagttctgca gcagtggctt tcaaggactt gacatccacc ctccagctgg gcccctctgg 1080
atcctggggg atgtcttcat tcgacagttt tactcagtct ttgaccgtgg gaataaccgt 1140
gtgggactgg ccccagcagt cccctaagga ggggccttgt gtctgtgcct gcctgtctga 1200
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cagaccttga atatgttagg ctggggcatt ctttacacct acaaaaagtt attttccaga 1260
gaatgtagct gtttccaggg ttgcaacttg aattaagacc aaacagaaca tgagaataca 1320
cacacacaca cacatataca cacacacaca cttcacacat acacaccact cccaccaccg 1380
tcatgatgga ggaattacgt tatacattca tattttgtat tgatttttga ttatgaaaat 1440
caaaaatttt cacatttgat tatgaaaatc tccaaacata tgcacaagca gagatcatgg 1500
tataataaat ccctttgcaa ctccactcag ccctgacaac ccatccacac acggccaggc 1560
ctgtttatct acactgctgc ccactcctct ctccagctcc acatgctgta cctggatcat 1620
tctgaagcaa attccgagca ttacatcatt ttgtccataa atatttctaa catccttaaa 1680
tatacaatcg gaattcaagc atctcccatt gtcccacaaa tgtttggctg tttttgtagt 1740
tggattgttt gtattaggat tcaagcaagg cccatatatt gcatttattt gaaatgtctg 1800
taagtctctt tccatctaca gagtttagca catttgaacg ttgctggttg aaatcccgag 1860
gtgtcatttg acatggttct ctgaacttat ctttcctata aaatggtagt tagatctgga 1920
ggtctgattt tgtggcaaaa atacttccta ggtggtgctg ggtacttctt gttgcatcct 1980
gtcaggaggc agataatgct ggtgcctctc tattggtaat gttaagactg ctgggtgggt 2040
ttggagttct tggctttaat cattcattac aaagttcagc atttta                2086
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<210> 95
<211> 363
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶E同功異型物B前驅體

<400> 95

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Met Lys Thr Leu Leu Leu Leu Leu Leu Val Leu Leu Glu Leu Gly Glu
 1               5                  10                  15
Ala Gln Gly Ser Leu His Arg Val Pro Leu Arg Arg His Pro Ser Leu
            20                  25                  30
Lys Lys Lys Leu Arg Ala Arg Ser Gln Leu Ser Glu Phe Trp Lys Ser
        35                  40                  45
His Asn Leu Asp Met Ile Gln Phe Thr Glu Ser Cys Ser Met Asp Gln
    50                  55                  60
Ser Ala Lys Glu Pro Leu Ile Asn Tyr Leu Asp Met Glu Tyr Phe Gly
65                  70                  75                  80
Thr Ile Ser Ile Gly Ser Pro Pro Gln Asn Phe Thr Val Ile Phe Asp
                85                  90                  95
Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Val Tyr Cys Thr Ser Pro
            100                 105                 110
Ala Cys Lys Thr His Ser Arg Phe Gln Pro Ser Gln Ser Ser Thr Tyr
        115                 120                 125
Ser Gln Pro Gly Gln Ser Phe Ser Ile Gln Tyr Gly Thr Gly Ser Leu
    130                 135                 140
Ser Gly Ile Ile Gly Ala Asp Gln Val Ser Val Glu Gly Leu Thr Val
145                 150                 155                 160
Val Gly Gln Gln Phe Gly Glu Ser Val Thr Glu Pro Gly Gln Thr Phe
                165                 170                 175
Val Asp Ala Glu Phe Asp Gly Ile Leu Gly Leu Gly Tyr Pro Ser Leu
            180                 185                 190
Ala Val Gly Gly Val Thr Pro Val Phe Asp Asn Met Met Ala Gln Asn
        195                 200                 205
Leu Val Asp Leu Pro Met Phe Ser Val Tyr Met Ser Ser Asn Pro Glu
    210                 215                 220
Gly Gly Ala Gly Ser Glu Leu Ile Phe Gly Gly Tyr Asp His Ser His
225                 230                 235                 240
Phe Ser Gly Ser Leu Asn Trp Val Pro Val Thr Lys Gln Ala Tyr Trp
                245                 250                 255
Gln Ile Ala Leu Asp Asn Met Leu Trp Ser Val Pro Thr Leu Thr Ser
            260                 265                 270
Cys Arg Met Ser Pro Ser Pro Leu Thr Glu Ser Pro Ile Pro Ser Ala
        275                 280                 285
Gln Leu Pro Thr Pro Tyr Trp Thr Ser Trp Met Glu Cys Ser Ser Ala
    290                 295                 300
Ala Val Ala Phe Lys Asp Leu Thr Ser Thr Leu Gln Leu Gly Pro Ser
305                 310                 315                 320
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```
Gly Ser Trp Gly Met Ser Ser Phe Asp Ser Phe Thr Gln Ser Leu Thr
                325                 330                 335
Val Gly Ile Thr Val Trp Asp Trp Pro Gln Gln Ser Pro Lys Glu Gly
            340                 345                 350
Pro Cys Val Cys Ala Cys Leu Ser Asp Arg Pro
        355                 360
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<210> 96
<211> 310
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶E同功異型物b

<400> 96

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Ile Gln Phe Thr Glu Ser Cys Ser Met Asp Gln Ser Ala Lys Glu Pro
 1               5                  10                  15
Leu Ile Asn Tyr Leu Asp Met Glu Tyr Phe Gly Thr Ile Ser Ile Gly
            20                  25                  30
Ser Pro Pro Gln Asn Phe Thr Val Ile Phe Asp Thr Gly Ser Ser Asn
        35                  40                  45
Leu Trp Val Pro Ser Val Tyr Cys Thr Ser Pro Ala Cys Lys Thr His
    50                  55                  60
Ser Arg Phe Gln Pro Ser Gln Ser Ser Thr Tyr Ser Gln Pro Gly Gln
65                  70                  75                  80
Ser Phe Ser Ile Gln Tyr Gly Thr Gly Ser Leu Ser Gly Ile Ile Gly
                85                  90                  95
Ala Asp Gln Val Ser Val Glu Gly Leu Thr Val Val Gly Gln Gln Phe
            100                 105                 110
Gly Glu Ser Val Thr Glu Pro Gly Gln Thr Phe Val Asp Ala Glu Phe
        115                 120                 125
Asp Gly Ile Leu Gly Leu Gly Tyr Pro Ser Leu Ala Val Gly Gly Val
    130                 135                 140
Thr Pro Val Phe Asp Asn Met Met Ala Gln Asn Leu Val Asp Leu Pro
145                 150                 155                 160
Met Phe Ser Val Tyr Met Ser Ser Asn Pro Glu Gly Gly Ala Gly Ser
                165                 170                 175
Glu Leu Ile Phe Gly Gly Tyr Asp His Ser His Phe Ser Gly Ser Leu
            180                 185                 190
Asn Trp Val Pro Val Thr Lys Gln Ala Tyr Trp Gln Ile Ala Leu Asp
        195                 200                 205
Asn Met Leu Trp Ser Val Pro Thr Leu Thr Ser Cys Arg Met Ser Pro
    210                 215                 220
Ser Pro Leu Thr Glu Ser Pro Ile Pro Ser Ala Gln Leu Pro Thr Pro
225                 230                 235                 240
Tyr Trp Thr Ser Trp Met Glu Cys Ser Ser Ala Ala Val Ala Phe Lys
                245                 250                 255
Asp Leu Thr Ser Thr Leu Gln Leu Gly Pro Ser Gly Ser Trp Gly Met
            260                 265                 270
Ser Ser Phe Asp Ser Phe Thr Gln Ser Leu Thr Val Gly Ile Thr Val
        275                 280                 285
Trp Asp Trp Pro Gln Gln Ser Pro Lys Glu Gly Pro Cys Val Cys Ala
    290                 295                 300
Cys Leu Ser Asp Arg Pro
305                 310
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<210> 97
<211> 1973
<212> DNA
<213> 現代人

<220>

<223> MMP-1前驅體

<400> 97
gggatattgg agtagcaaga ggctgggaag ccatcactta ccttgcactg agaaagaaga 60
caaaggccag tatgcacagc tttcctccac tgctgctgct gctgttctgg ggtgtggtgt 120
ctcacagctt cccagcgact ctagaaacac aagagcaaga tgtggactta gtccagaaat 180
acctggaaaa atactacaac ctgaagaatg atgggaggca agttgaaaag cggagaaata 240
gtggcccagt ggttgaaaaa ttgaagcaaa tgcaggaatt ctttgggctg aaagtgactg 300
ggaaaccaga tgctgaaacc ctgaaggtga tgaagcagcc cagatgtgga gtgcctgatg 360
tggctcagtt tgtcctcact gaggggaacc ctcgctggga gcaaacacat ctgacctaca 420
ggattgaaaa ttacacgcca gatttgccaa gagcagatgt ggaccatgcc attgagaaag 480
ccttccaact ctggagtaat gtcacacctc tgacattcac caaggtctct gagggtcaag 540
cagacatcat gatatctttt gtcaggggag atcatcggga caactctcct tttgatggac 600
ctggaggaaa tcttgctcat gcttttcaac caggcccagg tattggaggg gatgctcatt 660
ttgatgaaga tgaaaggtgg accaacaatt tcagagagta caacttacat cgtgttgcgg 720
ctcatgaact cggccattct cttggactct cccattctac tgatatcggg gctttgatgt 780
accctagcta caccttcagt ggtgatgttc agctagctca ggatgacatt gatggcatcc 840
aagccatata tggacgttcc caaaatcctg tccagcccat cggcccacaa accccaaaag 900
cgtgtgacag taagctaacc tttgatgcta taactacgat tcggggagaa gtgatgttct 960
ttaaagacag attctacatg cgcacaaatc ccttctaccc ggaagttgag ctcaatttca 1020
tttctgtttt ctggccacaa ctgccaaatg ggcttgaagc tgcttacgaa tttgccgaca 1080
gagatgaagt ccggtttttc aaagggaata agtactgggc tgttcaggga cagaatgtgc 1140
tacacggata ccccaaggac atctacagct cctttggctt ccctagaact gtgaagcata 1200
tcgatgctgc tctttctgag gaaaacactg gaaaaaccta cttctttgtt gctaacaaat 1260
actggaggta tgatgaatat aaacgatcta tggatccagg ttatcccaaa atgatagcac 1320
atgactttcc tggaattggc cacaaagttg atgcagtttt catgaaagat ggatttttct 1380
atttctttca tggaacaaga caatacaaat ttgatcctaa aacgaagaga attttgactc 1440
tccagaaagc taatagctgg ttcaactgca ggaaaaattg aacattacta atttgaatgg 1500
aaaacacatg gtgtgagtcc aaagaaggtg ttttcctgaa gaactgtcta ttttctcagt 1560
catttttaac ctctagagtc actgatacac agaatataat cttatttata cctcagtttg 1620
catatttttt tactatttag aatgtagccc tttttgtact gatataattt agttccacaa 1680
atggtgggta caaaaagtca agtttgtggc ttatggattc atataggcca gagttgcaaa 1740
gatcttttcc agagtatgca actctgacgt tgatcccaga gagcagcttc agtgacaaac 1800
atatcctttc aagacagaaa gagacaggag acatgagtct ttgccggagg aaaagcagct 1860
caagaacaca tgtgcagtca ctggtgtcac cctggatagg caagggataa ctcttctaac 1920
acaaaataag tgttttatgt ttggaataaa gtcaaccttg tttctactgt ttt 1973

<210> 98
<211> 469
<212> PRT
<213> 現代人

<220>
<223> MMP-1前驅體

<400> 98
Met His Ser Phe Pro Pro Leu Leu Leu Leu Leu Phe Trp Gly Val Val
 1   5   10   15
Ser His Ser Phe Pro Ala Thr Leu Glu Thr Gln Glu Gln Asp Val Asp
            20   25   30
Leu Val Gln Lys Tyr Leu Glu Lys Tyr Tyr Asn Leu Lys Asn Asp Gly
        35   40   45
Arg Gln Val Glu Lys Arg Arg Asn Ser Gly Pro Val Val Glu Lys Leu
    50   55   60
Lys Gln Met Gln Glu Phe Phe Gly Leu Lys Val Thr Gly Lys Pro Asp
65   70   75   80
Ala Glu Thr Leu Lys Val Met Lys Gln Pro Arg Cys Gly Val Pro Asp
                85   90   95
Val Ala Gln Phe Val Leu Thr Glu Gly Asn Pro Arg Trp Glu Gln Thr
            100   105   110
His Leu Thr Tyr Arg Ile Glu Asn Tyr Thr Pro Asp Leu Pro Arg Ala
        115   120   125
Asp Val Asp His Ala Ile Glu Lys Ala Phe Gln Leu Trp Ser Asn Val
    130   135   140
Thr Pro Leu Thr Phe Thr Lys Val Ser Glu Gly Gln Ala Asp Ile Met

145 150 155 160
Ile Ser Phe Val Arg Gly Asp His Arg Asp Asn Ser Pro Phe Asp Gly
165 170 175
Pro Gly Gly Asn Leu Ala His Ala Phe Gln Pro Gly Pro Gly Ile Gly
180 185 190
Gly Asp Ala His Phe Asp Glu Asp Glu Arg Trp Thr Asn Asn Phe Arg
195 200 205
Glu Tyr Asn Leu His Arg Val Ala Ala His Glu Leu Gly His Ser Leu
210 215 220
Gly Leu Ser His Ser Thr Asp Ile Gly Ala Leu Met Tyr Pro Ser Tyr
225 230 235 240
Thr Phe Ser Gly Asp Val Gln Leu Ala Gln Asp Asp Ile Asp Gly Ile
245 250 255
Gln Ala Ile Tyr Gly Arg Ser Gln Asn Pro Val Gln Pro Ile Gly Pro
260 265 270
Gln Thr Pro Lys Ala Cys Asp Ser Lys Leu Thr Phe Asp Ala Ile Thr
275 280 285
Thr Ile Arg Gly Glu Val Met Phe Phe Lys Asp Arg Phe Tyr Met Arg
290 295 300
Thr Asn Pro Phe Tyr Pro Glu Val Glu Leu Asn Phe Ile Ser Val Phe
305 310 315 320
Trp Pro Gln Leu Pro Asn Gly Leu Glu Ala Ala Tyr Glu Phe Ala Asp
325 330 335
Arg Asp Glu Val Arg Phe Phe Lys Gly Asn Lys Tyr Trp Ala Val Gln
340 345 350
Gly Gln Asn Val Leu His Gly Tyr Pro Lys Asp Ile Tyr Ser Ser Phe
355 360 365
Gly Phe Pro Arg Thr Val Lys His Ile Asp Ala Ala Leu Ser Glu Glu
370 375 380
Asn Thr Gly Lys Thr Tyr Phe Phe Val Ala Asn Lys Tyr Trp Arg Tyr
385 390 395 400
Asp Glu Tyr Lys Arg Ser Met Asp Pro Gly Tyr Pro Lys Met Ile Ala
405 410 415
His Asp Phe Pro Gly Ile Gly His Lys Val Asp Ala Val Phe Met Lys
420 425 430
Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg Gln Tyr Lys Phe Asp
435 440 445
Pro Lys Thr Lys Arg Ile Leu Thr Leu Gln Lys Ala Asn Ser Trp Phe
450 455 460
Asn Cys Arg Lys Asn
465

<210> 99
<211> 370
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-1

<400> 99
Phe Val Leu Thr Glu Gly Asn Pro Arg Trp Glu Gln Thr His Leu Thr
1 5 10 15
Tyr Arg Ile Glu Asn Tyr Thr Pro Asp Leu Pro Arg Ala Asp Val Asp
20 25 30
His Ala Ile Glu Lys Ala Phe Gln Leu Trp Ser Asn Val Thr Pro Leu
35 40 45
Thr Phe Thr Lys Val Ser Glu Gly Gln Ala Asp Ile Met Ile Ser Phe
50 55 60
Val Arg Gly Asp His Arg Asp Asn Ser Pro Phe Asp Gly Pro Gly Gly
65 70 75 80
Asn Leu Ala His Ala Phe Gln Pro Gly Pro Gly Ile Gly Gly Asp Ala
85 90 95
His Phe Asp Glu Asp Glu Arg Trp Thr Asn Asn Phe Arg Glu Tyr Asn

```
            100                 105                 110
Leu His Arg Val Ala Ala His Glu Leu Gly His Ser Leu Gly Leu Ser
        115                 120                 125
His Ser Thr Asp Ile Gly Ala Leu Met Tyr Pro Ser Tyr Thr Phe Ser
    130                 135                 140
Gly Asp Val Gln Leu Ala Gln Asp Asp Ile Asp Gly Ile Gln Ala Ile
145                 150                 155                 160
Tyr Gly Arg Ser Gln Asn Pro Val Gln Pro Ile Gly Pro Gln Thr Pro
                165                 170                 175
Lys Ala Cys Asp Ser Lys Leu Thr Phe Asp Ala Ile Thr Thr Ile Arg
            180                 185                 190
Gly Glu Val Met Phe Phe Lys Asp Arg Phe Tyr Met Arg Thr Asn Pro
        195                 200                 205
Phe Tyr Pro Glu Val Glu Leu Asn Phe Ile Ser Val Phe Trp Pro Gln
    210                 215                 220
Leu Pro Asn Gly Leu Glu Ala Ala Tyr Glu Phe Ala Asp Arg Asp Glu
225                 230                 235                 240
Val Arg Phe Phe Lys Gly Asn Lys Tyr Trp Ala Val Gln Gly Gln Asn
                245                 250                 255
Val Leu His Gly Tyr Pro Lys Asp Ile Tyr Ser Ser Phe Gly Phe Pro
            260                 265                 270
Arg Thr Val Lys His Ile Asp Ala Ala Leu Ser Glu Glu Asn Thr Gly
        275                 280                 285
Lys Thr Tyr Phe Phe Val Ala Asn Lys Tyr Trp Arg Tyr Asp Glu Tyr
    290                 295                 300
Lys Arg Ser Met Asp Pro Gly Tyr Pro Lys Met Ile Ala His Asp Phe
305                 310                 315                 320
Pro Gly Ile Gly His Lys Val Asp Ala Val Phe Met Lys Asp Gly Phe
                325                 330                 335
Phe Tyr Phe Phe His Gly Thr Arg Gln Tyr Lys Phe Asp Pro Lys Thr
            340                 345                 350
Lys Arg Ile Leu Thr Leu Gln Lys Ala Asn Ser Trp Phe Asn Cys Arg
        355                 360                 365
Lys Asn
    370
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<210> 100
<211> 2223
<212> DNA
<213> 現代人

<220>
<223> MMP-8前驅體

<400> 100

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gctcgccagg gaagggccct acccagagga cagaaagaaa gccaggaggg gtagagtttg 60
aagagaagat catgttctcc ctgaagacgc ttccatttct gctcttactc catgtgcaga 120
tttccaaggc ctttcctgta tcttctaaag agaaaaatac aaaaactgtt caggactacc 180
tggaaaagtt ctaccaatta ccaagcaacc agtatcagtc tacaaggaag aatggcacta 240
atgtgatcgt tgaaaagctt aaagaaatgc agcgattttt tgggttgaat gtgacgggga 300
agccaaatga ggaaactctg gacatgatga aaaagcctcg ctgtggagtg cctgacagtg 360
gtggttttat gttaacccca ggaaacccca agtgggaacg cactaacttg acctacagga 420
ttcgaaacta taccccacag ctgtcagagg ctgaggtaga aagagctatc aaggatgcct 480
ttgaactctg gagtgttgca tcacctctca tcttcaccag gatctcacag ggagaggcag 540
atatcaacat tgctttttac caaagagatc acggtgacaa ttctccattt gatggaccca 600
atggaatcct tgctcatgcc tttcagccag gccaaggtat tggaggagat gctcattttg 660
atgccgaaga aacatggacc aacacctccg caaattacaa cttgtttctt gttgctgctc 720
atgaatttgg ccattctttg gggctcgctc actcctctga ccctggtgcc ttgatgtatc 780
ccaactatgc tttcagggaa accagcaact actcactccc tcaagatgac atcgatggca 840
ttcaggccat ctatggactt tcaagcaacc ctatccaacc tactggacca agcacaccca 900
aaccctgtga ccccagtttg acatttgatg ctatcaccac actccgtgga gaaatacttt 960
tctttaaaga caggtacttc tggagaaggc atcctcagct acaaagagtc gaaatgaatt 1020
ttatttctct attctggcca tcccttccaa ctggtataca ggctgcttat gaagattttg 1080
acagagacct cattttccta tttaaaggca accaatactg ggctctgagt ggctatgata 1140
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ttgacgcagc tgttttctac agaagtaaaa catacttctt tgtaaatgac caattctgga 1260
gatatgataa ccaaagacaa ttcatggagc caggttatcc caaaagcata tcaggtgcct 1320
ttccaggaat agagagtaaa gttgatgcag ttttccagca agaacatttc ttccatgtct 1380
tcagtggacc aagatattac gcatttgatc ttattgctca gagagttacc agagttgcaa 1440
gaggcaataa atggcttaac tgtagatatg gctgaagcaa aatcaaatgt ggctgtatcc 1500
actttcagaa tgttgaaggg aagttcagca tgcattttcg ttacattgtg tcctgcttat 1560
acttttctca atattaagtc attgtttccc atcactgtat ccattctacc tgtcctccgt 1620
gaaaatatgt ttggaatatt ccactatttg cagaggctta ttcagttctt acacattcca 1680
tcttacatta gtgattccat caaagagaag gaaagtaagc ctttttgtca cctcaatatt 1740
tactatttca atacttacat atctgacttc taggatttat tgttatatta cttgcctatc 1800
tgacttcata catccctcag tttcttaaaa tgtcctatgt atatcttcta catgcaattt 1860
agaactagat tttggttaga agtaaggatt ataaacaacc tagacagtac ccttggcctt 1920
tacagaaaat atggtgctgt tttctaccct tggaaagaaa tgtagatgat atgtttcgtg 1980
ggttgaattg tgtcccccat aaaagatatg ttgaagttct aaccccaggt acccatgaat 2040
gtgagcttac cagggtcttt gcagatgtaa ttagttaagt taaggtgaga tcacactgaa 2100
ttagggtggg ctctaaatcc attatgactg ttgttcttat aagaagaaga gagcatagcc 2160
acctagggga ggaggccgtg tgaagacaga ggcagagatt ggagtgacgc atctccaagc 2220
caa 2223

<210> 101
<211> 467
<212> PRT
<213> 現代人

<220>
<223> MMP-8前驅體

<400> 101
Met Phe Ser Leu Lys Thr Leu Pro Phe Leu Leu Leu Leu His Val Gln
 1   5   10   15
Ile Ser Lys Ala Phe Pro Val Ser Ser Lys Glu Lys Asn Thr Lys Thr
            20   25   30
Val Gln Asp Tyr Leu Glu Lys Phe Tyr Gln Leu Pro Ser Asn Gln Tyr
        35   40   45
Gln Ser Thr Arg Lys Asn Gly Thr Asn Val Ile Val Glu Lys Leu Lys
    50   55   60
Glu Met Gln Arg Phe Phe Gly Leu Asn Val Thr Gly Lys Pro Asn Glu
65   70   75   80
Glu Thr Leu Asp Met Met Lys Lys Pro Arg Cys Gly Val Pro Asp Ser
                85   90   95
Gly Gly Phe Met Leu Thr Pro Gly Asn Pro Lys Trp Glu Arg Thr Asn
            100   105   110
Leu Thr Tyr Arg Ile Arg Asn Tyr Thr Pro Gln Leu Ser Glu Ala Glu
        115   120   125
Val Glu Arg Ala Ile Lys Asp Ala Phe Glu Leu Trp Ser Val Ala Ser
    130   135   140
Pro Leu Ile Phe Thr Arg Ile Ser Gln Gly Glu Ala Asp Ile Asn Ile
145   150   155   160
Ala Phe Tyr Gln Arg Asp His Gly Asp Asn Ser Pro Phe Asp Gly Pro
                165   170   175
Asn Gly Ile Leu Ala His Ala Phe Gln Pro Gly Gln Gly Ile Gly Gly
            180   185   190
Asp Ala His Phe Asp Ala Glu Glu Thr Trp Thr Asn Thr Ser Ala Asn
        195   200   205
Tyr Asn Leu Phe Leu Val Ala Ala His Glu Phe Gly His Ser Leu Gly
    210   215   220
Leu Ala His Ser Ser Asp Pro Gly Ala Leu Met Tyr Pro Asn Tyr Ala
225   230   235   240
Phe Arg Glu Thr Ser Asn Tyr Ser Leu Pro Gln Asp Asp Ile Asp Gly
                245   250   255
Ile Gln Ala Ile Tyr Gly Leu Ser Ser Asn Pro Ile Gln Pro Thr Gly
            260   265   270
Pro Ser Thr Pro Lys Pro Cys Asp Pro Ser Leu Thr Phe Asp Ala Ile
        275   280   285

```
Thr Thr Leu Arg Gly Glu Ile Leu Phe Phe Lys Asp Arg Tyr Phe Trp
    290                 295                 300
Arg Arg His Pro Gln Leu Gln Arg Val Glu Met Asn Phe Ile Ser Leu
305                 310                 315                 320
Phe Trp Pro Ser Leu Pro Thr Gly Ile Gln Ala Ala Tyr Glu Asp Phe
                325                 330                 335
Asp Arg Asp Leu Ile Phe Leu Phe Lys Gly Asn Gln Tyr Trp Ala Leu
            340                 345                 350
Ser Gly Tyr Asp Ile Leu Gln Gly Tyr Pro Lys Asp Ile Ser Asn Tyr
        355                 360                 365
Gly Phe Pro Ser Ser Val Gln Ala Ile Asp Ala Ala Val Phe Tyr Arg
    370                 375                 380
Ser Lys Thr Tyr Phe Phe Val Asn Asp Gln Phe Trp Arg Tyr Asp Asn
385                 390                 395                 400
Gln Arg Gln Phe Met Glu Pro Gly Tyr Pro Lys Ser Ile Ser Gly Ala
                405                 410                 415
Phe Pro Gly Ile Glu Ser Lys Val Asp Ala Val Phe Gln Gln Glu His
            420                 425                 430
Phe Phe His Val Phe Ser Gly Pro Arg Tyr Tyr Ala Phe Asp Leu Ile
        435                 440                 445
Ala Gln Arg Val Thr Arg Val Ala Arg Gly Asn Lys Trp Leu Asn Cys
    450                 455                 460
Arg Tyr Gly
465
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<210> 102
<211> 367
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-8

<400> 102

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Leu Thr Pro Gly Asn Pro Lys Trp Glu Arg Thr Asn Leu Thr Tyr Arg

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

```
225                 230                 235                 240
Ile Phe Leu Phe Lys Gly Asn Gln Tyr Trp Ala Leu Ser Gly Tyr Asp
                245                 250                 255
Ile Leu Gln Gly Tyr Pro Lys Asp Ile Ser Asn Tyr Gly Phe Pro Ser
            260                 265                 270
Ser Val Gln Ala Ile Asp Ala Ala Val Phe Tyr Arg Ser Lys Thr Tyr
        275                 280                 285
Phe Phe Val Asn Asp Gln Phe Trp Arg Tyr Asp Asn Gln Arg Gln Phe
    290                 295                 300
Met Glu Pro Gly Tyr Pro Lys Ser Ile Ser Gly Ala Phe Pro Gly Ile
305                 310                 315                 320
Glu Ser Lys Val Asp Ala Val Phe Gln Gln Glu His Phe Phe His Val
                325                 330                 335
Phe Ser Gly Pro Arg Tyr Tyr Ala Phe Asp Leu Ile Ala Gln Arg Val
            340                 345                 350
Thr Arg Val Ala Arg Gly Asn Lys Trp Leu Asn Cys Arg Tyr Gly
        355                 360                 365
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<210> 103
<211> 2722
<212> DNA
<213> 現代人

<220>
<223> MMP-13前驅體

<400> 103

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cttgagctgg actcattgtc gggccctgcc ccttcccagt ggtggtgatg aagatgattt 120
gtctgaggaa gacctccagt ttgcagagcg ctacctgaga tcatactacc atcctacaaa 180
tctcgcggga atcctgaagg agaatgcagc aagctccatg actgagaggc tccgagaaat 240

gcagtctttc ttcggcttag aggtgactgg caaacttgac gataacacct tagatgtcat 300
gaaaaagcca agatgcgggg ttcctgatgt gggtgaatac aatgttttcc ctcgaactct 360
taaatggtcc aaaatgaatt taacctacag aattgtgaat tacacccctg atatgactca 420
ttctgaagtc gaaaaggcat tcaaaaaagc cttcaaagtt tggtccgatg taactcctct 480
gaatttacc agacttcacg atggcattgc tgacatcatg atctcttttg gaattaagga 540
gcatggcgac ttctacccat ttgatgggcc ctctggcctg ctggctcatg cttttcctcc 600
tgggccaaat tatggaggag atgcccattt tgatgatgat gaaacctgga caagtagttc 660
caaaggctac aacttgtttc ttgttgctgc gcatgagttc ggccactcct taggtcttga 720
ccactccaag gaccctggag cactcatgtt tcctatctac acctacaccg gcaaaagcca 780
ctttatgctt cctgatgacg atgtacaagg gatccagtct ctctatggtc caggagatga 840
agaccccaac cctaaacatc caaaaacgcc agacaaatgt gacccttcct tatcccttga 900
tgccattacc agtctccgag gagaaacaat gatctttaaa gacagattct tctggcgcct 960
gcatcctcag caggttgatg cggagctgtt tttaacgaaa tcattttggc cagaacttcc 1020
caaccgtatt gatgctgcat atgagcaccc ttctcatgac ctcatcttca tcttcagagg 1080
tagaaaattt tgggctctta atggttatga cattctggaa ggttatccca aaaaaatatc 1140
tgaactgggt cttccaaaag aagttaagaa gataagtgca gctgttcact ttgaggatac 1200
aggcaagact ctcctgttct caggaaacca ggtctggaga tatgatgata ctaaccatat 1260
tatggataaa gactatccga gactaataga agaagacttc ccaggaattg gtgataaagt 1320
agatgctgtc tatgagaaaa atggttatat ctatttttc aacggaccca tacagtttga 1380
atacagcatc tggagtaacc gtattgttcg cgtcatgcca gcaaattcca ttttgtggtg 1440
ttaagtgtct ttttaaaaat tgttatttaa atcctgaaga gcatttgggg taatacttcc 1500
agaagtgcgg ggtaggggaa gaagagctat caggagaaag cttggttctg tgaacaagct 1560
tcagtaagtt atctttgaat atgtagtatc tatatgacta tgcgtggctg gaaccacatt 1620
gaagaatgtt agagtaatga aatggaggat ctctaaagag catctgattc ttgttgctgt 1680
acaaaagcaa tggttgatga tacttcccac accacaaatg ggacacatgg tctgtcaatg 1740
agagcataat ttaaaaatat atttataagg aaatttaca agggcataaa gtaaatacat 1800
gcatataatg aataaatcat tcttactaaa aagtataaaa tagtatgaaa atggaaattt 1860
gggagagcca tacataaaag aaataaacca aaggaaaatg tctgtaataa tagactgtaa 1920
cttccaaata aataattttc attttgcact gaggatattc agatgtatgt gcccttcttc 1980
acacagacac taacgaaata tcaaagtcat taaagacagg agacaaaaga gcagtggtaa 2040
gaatagtaga tgtggccttt gaattctgtt taattttcac ttttggcaat gactcaaagt 2100
ctgctctcat ataagacaaa tattcctttg catattataa aggataaaga aggatgatgt 2160
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cttttttatta aaatatttca ggttcttcag aagtcacaca ttacaaagtt aaaattgtta 2220
tcaaaatagt ctaaggccat ggcatccctt tttcataaat tatttgatta tttaagacta 2280
aaagttgcat tttaacccta ttttacctag ctaattattt aattgtccgg tttgtcttgg 2340
atatataggc tattttctaa agacttgtat agcatgaaat aaaatatatc ttataaagtg 2400
gaagtatgta tattaaaaaa gagacatcca aatttttttt taaagcagtc tactagattg 2460
tgatcccttg agatatggaa ggatgccttt ttttctctgc atttaaaaaa atccccccagc 2520
acttcccaca gtgcctattg atacttgggg agggtgcttg gcacttattg aatatatgat 2580
cggccatcaa gggaagaact attgtgctca gagacactgt tgataaaaac tcaggcaaag 2640
aaaatgaaat gcatatttgc aaagtgtatt aggaagtgtt tatgttgttt ataataaaaa 2700
tatattttca acagaaaaaa aa 2722

<210> 104
<211> 471
<212> PRT
<213> 現代人

<220>
<223> MMP-13前驅體

<400> 104

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

```
Lys Phe Trp Ala Leu Asn Gly Tyr Asp Ile Leu Glu Gly Tyr Pro Lys
        355                 360                 365
Lys Ile Ser Glu Leu Gly Leu Pro Lys Glu Val Lys Lys Ile Ser Ala
    370                 375                 380
Ala Val His Phe Glu Asp Thr Gly Lys Thr Leu Leu Phe Ser Gly Asn
385                 390                 395                 400
Gln Val Trp Arg Tyr Asp Asp Thr Asn His Ile Met Asp Lys Asp Tyr
                405                 410                 415
Pro Arg Leu Ile Glu Glu Asp Phe Pro Gly Ile Gly Asp Lys Val Asp
            420                 425                 430
Ala Val Tyr Glu Lys Asn Gly Tyr Ile Tyr Phe Phe Asn Gly Pro Ile
        435                 440                 445
Gln Phe Glu Tyr Ser Ile Trp Ser Asn Arg Ile Val Arg Val Met Pro
    450                 455                 460
Ala Asn Ser Ile Leu Trp Cys
465                 470
```

<210> 105
<211> 368
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-13

<400> 105

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

                165                 170                 175
Thr Pro Asp Lys Cys Asp Pro Ser Leu Ser Leu Asp Ala Ile Thr Ser
            180                 185                 190
Leu Arg Gly Glu Thr Met Ile Phe Lys Asp Arg Phe Phe Trp Arg Leu
        195                 200                 205
His Pro Gln Gln Val Asp Ala Glu Leu Phe Leu Thr Lys Ser Phe Trp
    210                 215                 220
Pro Glu Leu Pro Asn Arg Ile Asp Ala Ala Tyr Glu His Pro Ser His
225                 230                 235                 240
Asp Leu Ile Phe Ile Phe Arg Gly Arg Lys Phe Trp Ala Leu Asn Gly
                245                 250                 255
Tyr Asp Ile Leu Glu Gly Tyr Pro Lys Lys Ile Ser Glu Leu Gly Leu
            260                 265                 270
Pro Lys Glu Val Lys Lys Ile Ser Ala Ala Val His Phe Glu Asp Thr
        275                 280                 285
Gly Lys Thr Leu Leu Phe Ser Gly Asn Gln Val Trp Arg Tyr Asp Asp
```

```
    290                 295                 300
Thr Asn His Ile Met Asp Lys Asp Tyr Pro Arg Leu Ile Glu Glu Asp
305                 310                 315                 320
Phe Pro Gly Ile Gly Asp Lys Val Asp Ala Val Tyr Glu Lys Asn Gly
                325                 330                 335
Tyr Ile Tyr Phe Phe Asn Gly Pro Ile Gln Phe Glu Tyr Ser Ile Trp
            340                 345                 350
Ser Asn Arg Ile Val Arg Val Met Pro Ala Asn Ser Ile Leu Trp Cys
        355                 360                 365
```

<210> 106
<211> 1609
<212> DNA
<213> 爪蟾

<220>
<223> MMP-18

<400> 106

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accttcaaat cctagaaagc cttagaagaa tgaacagcct cctgctaaag ctgctactat 60
gtgtagccat tactgctgcc ttcccagcag ataaacaaga tgagccccca gcaacaaagg 120
aagaaatggc agagaattac ttgaagagat tttacagtct tggaactgat gggggaccag 180
ttggaagaaa gaaacacatc caacctttca ctgaaaagct cgagcagatg cagaagtttt 240
ttggcttaaa ggtgacagga acattggacc ccaagactgt agaagtaatg gagaaaccca 300

gatgtggagt ctatgatgtt ggccagtaca gcacagtcgc aaaaagttct gcatggcaga 360
agaaggatct gacctacaga attctaaact tcactcctga cctgcctcag gctgatgtgg 420
agactgccat acaaagagct ttcaaagtct ggagtgacgt gacacctttg acctttacca 480

gaatctacaa tgaagtatca gatatagaaa tctcctttac agctggagat cacaaagaca 540
attctccttt tgatggatct ggtggcattt tggcccatgc ctttcagccc ggcaatggca 600
ttggtggaga tgcccatttt gatgaagatg aaacctggac aaagaccagt gaaatataca 660
atctgtttct tgttgctgct catgaatttg gacactcgct ggggctttct cattccactg 720
atcagggtgc tttgatgtat ccaacatact caaataccga ccccaagaca tttcagcttc 780
ctcaagatga tatcaatgct atacagtatc tatatggaaa atcctccaat ccagtccaac 840
caaccggacc atccactcct tccagatgtg atccaaatgt tgttttcaat gctgtcacca 900
ccatgagagg agaactgatt ttctttgtga agaggttttt atggaggaag catccccaag 960
catccgaggc tgaactcatg tttgttcaag cattctggcc atcgctgccc actaatattg 1020
atgcggcgta tgaaaatcct ataacggagc agatccttgt gtttaaagga tcaaaatata 1080
cagctctgga cggcttcgat gtagtacaag gttaccccag gaacatctac agcctgggat 1140
ttccaaagac cgtgaaaaga attgatgcgg ctgttcatat tgaacaacta gggaaaacat 1200
atttctttgc agctaagaaa tactggagtt atgatgaaga taaaaaacaa atggacaaag 1260
gctttccaaa gcaaataagc aacgatttcc cgggaattcc tgataaaatt gatgcagctt 1320
tttattacag aggccgcctg tatttcttca ttggaaggag ccagtttgaa tacaatatca 1380
actctaaaag aatcgtacag gtcttaagaa gcaacagctg gttgggctgt taataagacg 1440
gaccccaagc tctgtaacaa gggcaacgat gaatgtgatg gcagctcatt tctgcacctg 1500
ccgtgtgacc aatattattt aaaatcattt cctttgaatg tttgacttta tttaatcttt 1560
atgaattaat attttgtact catgttgttt taataaaaac gttttgttt              1609
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<210> 107
<211> 467
<212> PRT
<213> 爪蟾

<220>
<223> MMP-18

<400> 107

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Met Asn Ser Leu Leu Leu Lys Leu Leu Leu Cys Val Ala Ile Thr Ala
 1               5                  10                  15
Ala Phe Pro Ala Asp Lys Gln Asp Glu Pro Pro Ala Thr Lys Glu Glu
            20                  25                  30
Met Ala Glu Asn Tyr Leu Lys Arg Phe Tyr Ser Leu Gly Thr Asp Gly
        35                  40                  45
```

```
Gly Pro Val Gly Arg Lys Lys His Ile Gln Pro Phe Thr Glu Lys Leu
    50                  55                  60
Glu Gln Met Gln Lys Phe Phe Gly Leu Lys Val Thr Gly Thr Leu Asp
65                  70                  75                  80
Pro Lys Thr Val Glu Val Met Glu Lys Pro Arg Cys Gly Val Tyr Asp
                85                  90                  95
Val Gly Gln Tyr Ser Thr Val Ala Lys Ser Ser Ala Trp Gln Lys Lys
            100                 105                 110
Asp Leu Thr Tyr Arg Ile Leu Asn Phe Thr Pro Asp Leu Pro Gln Ala
        115                 120                 125
Asp Val Glu Thr Ala Ile Gln Arg Ala Phe Lys Val Trp Ser Asp Val
    130                 135                 140
Thr Pro Leu Thr Phe Thr Arg Ile Tyr Asn Glu Val Ser Asp Ile Glu
145                 150                 155                 160
Ile Ser Phe Thr Ala Gly Asp His Lys Asp Asn Ser Pro Phe Asp Gly
                165                 170                 175
Ser Gly Gly Ile Leu Ala His Ala Phe Gln Pro Gly Asn Gly Ile Gly
            180                 185                 190
Gly Asp Ala His Phe Asp Glu Asp Glu Thr Trp Thr Lys Thr Ser Glu
        195                 200                 205
Ile Tyr Asn Leu Phe Leu Val Ala Ala His Glu Phe Gly His Ser Leu
    210                 215                 220
Gly Leu Ser His Ser Thr Asp Gln Gly Ala Leu Met Tyr Pro Thr Tyr
225                 230                 235                 240
Ser Asn Thr Asp Pro Lys Thr Phe Gln Leu Pro Gln Asp Asp Ile Asn
                245                 250                 255
Ala Ile Gln Tyr Leu Tyr Gly Lys Ser Ser Asn Pro Val Gln Pro Thr
            260                 265                 270
Gly Pro Ser Thr Pro Ser Arg Cys Asp Pro Asn Val Val Phe Asn Ala
        275                 280                 285
Val Thr Thr Met Arg Gly Glu Leu Ile Phe Phe Val Lys Arg Phe Leu
    290                 295                 300
Trp Arg Lys His Pro Gln Ala Ser Glu Ala Glu Leu Met Phe Val Gln
305                 310                 315                 320
Ala Phe Trp Pro Ser Leu Pro Thr Asn Ile Asp Ala Ala Tyr Glu Asn

                325                 330                 335
Pro Ile Thr Glu Gln Ile Leu Val Phe Lys Gly Ser Lys Tyr Thr Ala
            340                 345                 350
Leu Asp Gly Phe Asp Val Val Gln Gly Tyr Pro Arg Asn Ile Tyr Ser
        355                 360                 365
Leu Gly Phe Pro Lys Thr Val Lys Arg Ile Asp Ala Ala Val His Ile
    370                 375                 380
Glu Gln Leu Gly Lys Thr Tyr Phe Phe Ala Ala Lys Lys Tyr Trp Ser
385                 390                 395                 400
Tyr Asp Glu Asp Lys Lys Gln Met Asp Lys Gly Phe Pro Lys Gln Ile
                405                 410                 415
Ser Asn Asp Phe Pro Gly Ile Pro Asp Lys Ile Asp Ala Ala Phe Tyr
            420                 425                 430
Tyr Arg Gly Arg Leu Tyr Phe Phe Ile Gly Arg Ser Gln Phe Glu Tyr
        435                 440                 445
Asn Ile Asn Ser Lys Arg Ile Val Gln Val Leu Arg Ser Asn Ser Trp
    450                 455                 460
Leu Gly Cys
465
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<210> 108
<211> 368
<212> PRT
<213> 爪蟾

<220>
<223> 成熟MMP-18

<400> 108

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

Met Arg Gly Glu Leu Ile Phe Phe Val Lys Arg Phe Leu Trp Arg Lys
        195                 200                 205
His Pro Gln Ala Ser Glu Ala Glu Leu Met Phe Val Gln Ala Phe Trp
    210                 215                 220
Pro Ser Leu Pro Thr Asn Ile Asp Ala Ala Tyr Glu Asn Pro Ile Thr
225                 230                 235                 240
Glu Gln Ile Leu Val Phe Lys Gly Ser Lys Tyr Thr Ala Leu Asp Gly
                245                 250                 255
Phe Asp Val Val Gln Gly Tyr Pro Arg Asn Ile Tyr Ser Leu Gly Phe
            260                 265                 270
Pro Lys Thr Val Lys Arg Ile Asp Ala Ala Val His Ile Glu Gln Leu
        275                 280                 285
Gly Lys Thr Tyr Phe Phe Ala Ala Lys Lys Tyr Trp Ser Tyr Asp Glu
    290                 295                 300
Asp Lys Lys Gln Met Asp Lys Gly Phe Pro Lys Gln Ile Ser Asn Asp
305                 310                 315                 320
Phe Pro Gly Ile Pro Asp Lys Ile Asp Ala Ala Phe Tyr Tyr Arg Gly
                325                 330                 335
Arg Leu Tyr Phe Phe Ile Gly Arg Ser Gln Phe Glu Tyr Asn Ile Asn
            340                 345                 350
Ser Lys Arg Ile Val Gln Val Leu Arg Ser Asn Ser Trp Leu Gly Cys
        355                 360                 365
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<210> 109
<211> 3546
<212> DNA
<213> 現代人

<220>
<223> MMP-2

<400> 109

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cgaggcggcc acacgcaccg agccagcgac ccccgggcga cgcgcggggc cagggagcgc 300
tacgatggag gcgctaatgg cccggggcgc gctcacgggt cccctgaggg cgctctgtct 360
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ttccaaccac ataaataaaa aaggccatta ttagttgaat cttattgatg aagagaaaaa 3540
aaaaaa 3546

<210> 110
<211> 660
<212> PRT
<213> 現代人

<220>
<223> MMP-2前驅體

<400> 110
Met Glu Ala Leu Met Ala Arg Gly Ala Leu Thr Gly Pro Leu Arg Ala

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Leu Cys Leu Leu Gly Cys Leu Leu Ser His Ala Ala Ala Ala Pro Ser
            20                  25                  30
Pro Ile Ile Lys Phe Pro Gly Asp Val Ala Pro Lys Thr Asp Lys Glu
        35                  40                  45
Leu Ala Val Gln Tyr Leu Asn Thr Phe Tyr Gly Cys Pro Lys Glu Ser
    50                  55                  60
Cys Asn Leu Phe Val Leu Lys Asp Thr Leu Lys Lys Met Gln Lys Phe
65                  70                  75                  80
Phe Gly Leu Pro Gln Thr Gly Asp Leu Asp Gln Asn Thr Ile Glu Thr
                85                  90                  95
Met Arg Lys Pro Arg Cys Gly Asn Pro Asp Val Ala Asn Tyr Asn Phe
            100                 105                 110
Phe Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr Tyr Arg Ile
        115                 120                 125
Ile Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp Asp Ala Phe
    130                 135                 140
Ala Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu Arg Phe Ser
145                 150                 155                 160
Arg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe Gly Arg Trp
                165                 170                 175
Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala
            180                 185                 190
His Ala Phe Ala Pro Gly Thr Gly Val Gly Gly Asp Ser His Phe Asp
        195                 200                 205
Asp Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val Arg Val Lys
    210                 215                 220
Tyr Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe Leu Phe Asn
225                 230                 235                 240
Gly Lys Glu Tyr Asn Ser Cys Thr Asp Thr Gly Arg Ser Asp Gly Phe
                245                 250                 255
Leu Trp Cys Ser Thr Thr Tyr Asn Phe Glu Lys Asp Gly Lys Tyr Gly
            260                 265                 270
Phe Cys Pro His Glu Ala Leu Phe Thr Met Gly Gly Asn Ala Glu Gly
        275                 280                 285
Gln Pro Cys Lys Phe Pro Phe Arg Phe Gln Gly Thr Ser Tyr Asp Ser
    290                 295                 300
Cys Thr Thr Glu Gly Arg Thr Asp Gly Tyr Arg Trp Cys Gly Thr Thr
305                 310                 315                 320
Glu Asp Tyr Asp Arg Asp Lys Lys Tyr Gly Phe Cys Pro Glu Thr Ala
                325                 330                 335
Met Ser Thr Val Gly Gly Asn Ser Glu Gly Ala Pro Cys Val Phe Pro
            340                 345                 350
Phe Thr Phe Leu Gly Asn Lys Tyr Glu Ser Cys Thr Ser Ala Gly Arg
        355                 360                 365
Ser Asp Gly Lys Met Trp Cys Ala Thr Thr Ala Asn Tyr Asp Asp Asp
    370                 375                 380
Arg Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val
385                 390                 395                 400
Ala Ala His Glu Phe Gly His Ala Met Gly Leu Glu His Ser Gln Asp
                405                 410                 415
Pro Gly Ala Leu Met Ala Pro Ile Tyr Thr Tyr Thr Lys Asn Phe Arg
            420                 425                 430
Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Glu Leu Tyr Gly Ala Ser
        435                 440                 445
Pro Asp Ile Asp Leu Gly Thr Gly Pro Thr Pro Thr Leu Gly Pro Val
    450                 455                 460
Thr Pro Glu Ile Cys Lys Gln Asp Ile Val Phe Asp Gly Ile Ala Gln
465                 470                 475                 480
Ile Arg Gly Glu Ile Phe Phe Phe Lys Asp Arg Phe Ile Trp Arg Thr
                485                 490                 495
Val Thr Pro Arg Asp Lys Pro Met Gly Pro Leu Leu Val Ala Thr Phe
            500                 505                 510
Trp Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu Ala Pro Gln
        515                 520                 525
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Glu Glu Lys Ala Val Phe Phe Ala Gly Asn Glu Tyr Trp Ile Tyr Ser
    530                 535                 540
Ala Ser Thr Leu Glu Arg Gly Tyr Pro Lys Pro Leu Thr Ser Leu Gly
545                 550                 555                 560
Leu Pro Pro Asp Val Gln Arg Val Asp Ala Ala Phe Asn Trp Ser Lys
                565                 570                 575
Asn Lys Lys Thr Tyr Ile Phe Ala Gly Asp Lys Phe Trp Arg Tyr Asn
            580                 585                 590
Glu Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu Ile Ala Asp
        595                 600                 605
Ala Trp Asn Ala Ile Pro Asp Asn Leu Asp Ala Val Val Asp Leu Gln
    610                 615                 620
Gly Gly Gly His Ser Tyr Phe Phe Lys Gly Ala Tyr Tyr Leu Lys Leu
625                 630                 635                 640
Glu Asn Gln Ser Leu Lys Ser Val Lys Phe Gly Ser Ile Lys Ser Asp
                645                 650                 655
Trp Leu Gly Cys
            660
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<210> 111
<211> 551
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-2

<400> 111

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Tyr Asn Phe Phe Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr
 1               5                  10                  15
Tyr Arg Ile Ile Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp
            20                  25                  30
Asp Ala Phe Ala Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu
        35                  40                  45
Arg Phe Ser Arg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe
    50                  55                  60
Gly Arg Trp Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly
65                  70                  75                  80
Leu Leu Ala His Ala Phe Ala Pro Gly Thr Gly Val Gly Gly Asp Ser
                85                  90                  95
His Phe Asp Asp Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val
            100                 105                 110
Arg Val Lys Tyr Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe
        115                 120                 125
Leu Phe Asn Gly Lys Glu Tyr Asn Ser Cys Thr Asp Thr Gly Arg Ser
    130                 135                 140
Asp Gly Phe Leu Trp Cys Ser Thr Thr Tyr Asn Phe Glu Lys Asp Gly
145                 150                 155                 160
Lys Tyr Gly Phe Cys Pro His Glu Ala Leu Phe Thr Met Gly Gly Asn
                165                 170                 175
Ala Glu Gly Gln Pro Cys Lys Phe Pro Phe Arg Phe Gln Gly Thr Ser
            180                 185                 190
Tyr Asp Ser Cys Thr Thr Glu Gly Arg Thr Asp Gly Tyr Arg Trp Cys
        195                 200                 205
Gly Thr Thr Glu Asp Tyr Asp Arg Asp Lys Lys Tyr Gly Phe Cys Pro
    210                 215                 220
Glu Thr Ala Met Ser Thr Val Gly Gly Asn Ser Glu Gly Ala Pro Cys
225                 230                 235                 240
Val Phe Pro Phe Thr Phe Leu Gly Asn Lys Tyr Glu Ser Cys Thr Ser
                245                 250                 255
Ala Gly Arg Ser Asp Gly Lys Met Trp Cys Ala Thr Thr Ala Asn Tyr
            260                 265                 270
Asp Asp Asp Arg Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu
        275                 280                 285
```

```
Phe Leu Val Ala Ala His Glu Phe Gly His Ala Met Gly Leu Glu His
    290                 295                 300
Ser Gln Asp Pro Gly Ala Leu Met Ala Pro Ile Tyr Thr Tyr Thr Lys
305                 310                 315                 320
Asn Phe Arg Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Glu Leu Tyr
                325                 330                 335
Gly Ala Ser Pro Asp Ile Asp Leu Gly Thr Gly Pro Thr Pro Thr Leu
            340                 345                 350
Gly Pro Val Thr Pro Glu Ile Cys Lys Gln Asp Ile Val Phe Asp Gly
        355                 360                 365
Ile Ala Gln Ile Arg Gly Glu Ile Phe Phe Phe Lys Asp Arg Phe Ile
    370                 375                 380
Trp Arg Thr Val Thr Pro Arg Asp Lys Pro Met Gly Pro Leu Leu Val
385                 390                 395                 400
Ala Thr Phe Trp Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu
                405                 410                 415
Ala Pro Gln Glu Glu Lys Ala Val Phe Phe Ala Gly Asn Glu Tyr Trp
            420                 425                 430
Ile Tyr Ser Ala Ser Thr Leu Glu Arg Gly Tyr Pro Lys Pro Leu Thr
        435                 440                 445
Ser Leu Gly Leu Pro Pro Asp Val Gln Arg Val Asp Ala Ala Phe Asn
    450                 455                 460
Trp Ser Lys Asn Lys Lys Thr Tyr Ile Phe Ala Gly Asp Lys Phe Trp
465                 470                 475                 480
Arg Tyr Asn Glu Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu
                485                 490                 495
Ile Ala Asp Ala Trp Asn Ala Ile Pro Asp Asn Leu Asp Ala Val Val
            500                 505                 510
Asp Leu Gln Gly Gly Gly His Ser Tyr Phe Phe Lys Gly Ala Tyr Tyr
        515                 520                 525
Leu Lys Leu Glu Asn Gln Ser Leu Lys Ser Val Lys Phe Gly Ser Ile
    530                 535                 540
Lys Ser Asp Trp Leu Gly Cys
545                 550
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<210> 112
<211> 2387
<212> DNA
<213> 現代人

<220>
<223> MMP-9

<400> 112

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gggctgctgc tttgctgccc ccagacagcg ccagtccacc cttgtgctct tccctggaga 120
cctgagaacc aatctcaccg acaggcagct ggcagaggaa tacctgtacc gctatggtta 180
cactcgggtg gcagagatgc gtggagagtc gaaatctctg gggcctgcgc tgctgcttct 240
ccagaagcaa ctgtccctgc ccgagaccgg tgagctggat agcgccacgc tgaaggccat 300
gcgaacccca cggtgcgggg tcccagacct gggcagattc caaacctttg agggcgacct 360
caagtggcac caccacaaca tcacctattg gatccaaaac tactcggaag acttgccgcg 420
ggcggtgatt gacgacgcct ttgcccgcgc cttcgcactg tggagcgcgg tgacgccgct 480
caccttcact cgcgtgtaca gccgggacgc agacatcgtc atccagtttg gtgtcgcgga 540
gcacggagac gggtatccct tcgacgggaa ggacgggctc ctggcacacg cctttcctcc 600
tggccccggc attcagggag acgcccattt cgacgatgac gagttgtggt ccctgggcaa 660
gggcgtcgtg gttccaactc ggtttggaaa cgcagatggc gcggcctgcc acttcccctt 720
catcttcgag ggccgctcct actctgcctg caccaccgac ggtcgctccg acggcttgcc 780
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taccacctcg aactttgaca gcgacaagaa gtggggcttc tgcccggacc aaggatacag 1200
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cgacgtgaat ggcatccggc acctctatgg tcctcgccct gaacctgagc cacggcctcc 1380
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa              2387
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<210> 113
<211> 707
<212> PRT
<213> 現代人

<220>
<223> MMP-9前驅體

<400> 113

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Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys
 1               5                  10                  15
Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro
            20                  25                  30
Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
        35                  40                  45

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

385                 390                 395                 400
His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
                405                 410                 415
Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
            420                 425                 430
Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
        435                 440                 445
Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro
    450                 455                 460
Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
465                 470                 475                 480
Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
                485                 490                 495
Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
            500                 505                 510
Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
        515                 520                 525
Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
    530                 535                 540
Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
545                 550                 555                 560
Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Arg Leu Ser
                565                 570                 575
Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
            580                 585                 590
Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
        595                 600                 605
Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
    610                 615                 620
Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
625                 630                 635                 640
Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
                645                 650                 655
Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
            660                 665                 670
Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
        675                 680                 685
Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys
    690                 695                 700
Pro Glu Asp
705
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<210> 114
<211> 614
<212> PRT
<213> 現代人

<220>

<223> 成熟MMP-9

<400> 114

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Met Arg Thr Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr
 1               5                  10                  15
Phe Glu Gly Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile
            20                  25                  30
Gln Asn Tyr Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe
        35                  40                  45
Ala Arg Ala Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr
    50                  55                  60
Arg Val Tyr Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala
65                  70                  75                  80
Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala
                85                  90                  95
His Ala Phe Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp
            100                 105                 110
Asp Asp Glu Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg
        115                 120                 125
Phe Gly Asn Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu
    130                 135                 140
Gly Arg Ser Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu
145                 150                 155                 160
Pro Trp Cys Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly
                165                 170                 175
Phe Cys Pro Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly
            180                 185                 190
Lys Pro Cys Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala
        195                 200                 205
Cys Thr Thr Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr
    210                 215                 220
Ala Asn Tyr Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala
225                 230                 235                 240
Asp Ser Thr Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe
                245                 250                 255
Pro Phe Thr Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly
            260                 265                 270
Arg Gly Asp Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser
        275                 280                 285
Asp Lys Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu
    290                 295                 300
Val Ala Ala His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser
305                 310                 315                 320
Val Pro Glu Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro
                325                 330                 335
Pro Leu His Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro
            340                 345                 350
Arg Pro Glu Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro
        355                 360                 365
Thr Ala Pro Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro
    370                 375                 380
Ser Glu Arg Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro
385                 390                 395                 400
Thr Gly Pro Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu
                405                 410                 415
Ser Pro Val Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala
            420                 425                 430
Glu Ile Gly Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg
        435                 440                 445
Phe Ser Glu Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala
    450                 455                 460
Asp Lys Trp Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu
465                 470                 475                 480
Pro Leu Ser Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val
                485                 490                 495
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Tyr Thr Gly Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly
            500                 505                 510
Leu Gly Ala Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg
        515                 520                 525
Gly Lys Met Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val
    530                 535                 540
Lys Ala Gln Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met
545                 550                 555                 560
Phe Pro Gly Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu
                565                 570                 575
Lys Ala Tyr Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg
            580                 585                 590
Ser Glu Leu Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile
        595                 600                 605
Leu Gln Cys Pro Glu Asp
    610
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<210> 115
<211> 1828
<212> DNA
<213> 現代人

<220>
<223> MMP-3

<400> 115

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cattggatgg agctgcaagg ggtgaggaca ccagcatgaa ccttgttcag aaatatctag 180
aaaactacta cgacctcaaa aaagatgtga aacagtttgt taggagaaag gacagtggtc 240
ctgttgttaa aaaaatccga gaaatgcaga agttccttgg attggaggtg acggggaagc 300
tggactccga cactctggag gtgatgcgca agcccaggtg tggagttcct gatgttggtc 360
acttcagaac ctttcctggc atcccgaagt ggaggaaaac ccaccttaca tacaggattg 420
tgaattatac accagatttg ccaaaagatg ctgttgattc tgctgttgag aaagctctga 480
aagtctggga agaggtgact ccactcacat tctccaggct gtatgaagga gaggctgata 540
taatgatctc ttttgcagtt agagaacatg gagactttta ccctttgat ggacctggaa 600
atgttttggc ccatgcctat gcccctgggc cagggattaa tggagatgcc cactttgatg 660
atgatgaaca atggacaaag gatacaacag ggaccaattt atttctcgtt gctgctcatg 720
aaattggcca ctccctgggt ctctttcact cagccaacac tgaagctttg atgtacccac 780
tctatcactc actcacagac ctgactcggt tccgcctgtc tcaagatgat ataaatggca 840
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tcaggaagct tgaacctgaa ttgcatttga tctcttcatt ttggccatct cttccttcag 1080
gcgtggatgc cgcatatgaa gttactagca aggacctcgt tttcattttt aaaggaaatc 1140
aattctgggc tatcagagga aatgaggtac gagctggata cccaagaggc atccacaccc 1200
taggtttccc tccaaccgtg aggaaaatcg atgcagccat ttctgataag gaaaagaaca 1260
aaacatattt ctttgtagag gacaaatact ggagatttga tgagaagaga aattccatgg 1320
agccaggctt tcccaagcaa atagctgaag actttccagg gattgactca aagattgatg 1380
ctgtttttga agaatttggg ttcttttatt tctttactgg atcttcacag ttggagtttg 1440
acccaaatgc aaagaaagtg acacacactt tgaagagtaa cagctggctt aattgttgaa 1500
agagatatgt agaaggcaca atatgggcac tttaaatgaa gctaataatt cttcacctaa 1560
gtctctgtga attgaaatgt tcgttttctc ctgcctgtgc tgtgactcga gtcacactca 1620
agggaacttg agcgtgaatc tgtatcttgc cggtcatttt tatgttatta cagggcattc 1680
aaatgggctg ctgcttagct tgcaccttgt cacatagagt gatctttccc aagagaaggg 1740
gaagcactcg tgtgcaacag acaagtgact gtatctgtgt agactatttg cttatttaat 1800
aaagacgatt tgtcagttat tttatctt                                    1828
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<210> 116
<211> 477
<212> PRT
<213> 現代人

<220>

<223> MMP-3前驅體

<400> 116

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Met Lys Ser Leu Pro Ile Leu Leu Leu Leu Cys Val Ala Val Cys Ser
 1               5                  10                  15
Ala Tyr Pro Leu Asp Gly Ala Ala Arg Gly Glu Asp Thr Ser Met Asn
            20                  25                  30
Leu Val Gln Lys Tyr Leu Glu Asn Tyr Tyr Asp Leu Lys Lys Asp Val
        35                  40                  45
Lys Gln Phe Val Arg Arg Lys Asp Ser Gly Pro Val Val Lys Lys Ile
    50                  55                  60
Arg Glu Met Gln Lys Phe Leu Gly Leu Glu Val Thr Gly Lys Leu Asp
65                  70                  75                  80
Ser Asp Thr Leu Glu Val Met Arg Lys Pro Arg Cys Gly Val Pro Asp
                85                  90                  95
Val Gly His Phe Arg Thr Phe Pro Gly Ile Pro Lys Trp Arg Lys Thr
            100                 105                 110
His Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp Leu Pro Lys Asp
        115                 120                 125
Ala Val Asp Ser Ala Val Glu Lys Ala Leu Lys Val Trp Glu Glu Val
    130                 135                 140
Thr Pro Leu Thr Phe Ser Arg Leu Tyr Glu Gly Glu Ala Asp Ile Met
145                 150                 155                 160
Ile Ser Phe Ala Val Arg Glu His Gly Asp Phe Tyr Pro Phe Asp Gly
                165                 170                 175
Pro Gly Asn Val Leu Ala His Ala Tyr Ala Pro Gly Pro Gly Ile Asn
            180                 185                 190
Gly Asp Ala His Phe Asp Asp Asp Glu Gln Trp Thr Lys Asp Thr Thr
        195                 200                 205
Gly Thr Asn Leu Phe Leu Val Ala Ala His Glu Ile Gly His Ser Leu
    210                 215                 220
Gly Leu Phe His Ser Ala Asn Thr Glu Ala Leu Met Tyr Pro Leu Tyr
225                 230                 235                 240
His Ser Leu Thr Asp Leu Thr Arg Phe Arg Leu Ser Gln Asp Asp Ile
                245                 250                 255
Asn Gly Ile Gln Ser Leu Tyr Gly Pro Pro Pro Asp Ser Pro Glu Thr
            260                 265                 270
Pro Leu Val Pro Thr Glu Pro Val Pro Pro Glu Pro Gly Thr Pro Ala
        275                 280                 285
Asn Cys Asp Pro Ala Leu Ser Phe Asp Ala Val Ser Thr Leu Arg Gly
    290                 295                 300
Glu Ile Leu Ile Phe Lys Asp Arg His Phe Trp Arg Lys Ser Leu Arg
305                 310                 315                 320
Lys Leu Glu Pro Glu Leu His Leu Ile Ser Ser Phe Trp Pro Ser Leu
                325                 330                 335
Pro Ser Gly Val Asp Ala Ala Tyr Glu Val Thr Ser Lys Asp Leu Val
            340                 345                 350
Phe Ile Phe Lys Gly Asn Gln Phe Trp Ala Ile Arg Gly Asn Glu Val
        355                 360                 365
Arg Ala Gly Tyr Pro Arg Gly Ile His Thr Leu Gly Phe Pro Pro Thr
    370                 375                 380
Val Arg Lys Ile Asp Ala Ala Ile Ser Asp Lys Glu Lys Asn Lys Thr
385                 390                 395                 400
Tyr Phe Phe Val Glu Asp Lys Tyr Trp Arg Phe Asp Glu Lys Arg Asn
                405                 410                 415
Ser Met Glu Pro Gly Phe Pro Lys Gln Ile Ala Glu Asp Phe Pro Gly
            420                 425                 430
Ile Asp Ser Lys Ile Asp Ala Val Phe Glu Glu Phe Gly Phe Phe Tyr
        435                 440                 445
Phe Phe Thr Gly Ser Ser Gln Leu Glu Phe Asp Pro Asn Ala Lys Lys
    450                 455                 460
Val Thr His Thr Leu Lys Ser Asn Ser Trp Leu Asn Cys
465                 470                 475
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<210> 117
<211> 378
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-3

<400> 117

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

            340                 345                 350
Gly Ser Ser Gln Leu Glu Phe Asp Pro Asn Ala Lys Lys Val Thr His
        355                 360                 365
Thr Leu Lys Ser Asn Ser Trp Leu Asn Cys
    370                 375
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<210> 118
<211> 1743
<212> DNA

<213> 現代人

<220>
<223> MMP-10

<400> 118
aaagaaggta agggcagtga gaatgatgca tcttgcattc cttgtgctgt tgtgtctgcc 60
agtctgctct gcctatcctc tgagtggggc agcaaaagag gaggactcca acaaggatct 120
tgcccagcaa tacctagaaa agtactacaa cctcgaaaag gatgtgaaac agtttagaag 180
aaaggacagt aatctcattg ttaaaaaaat ccaaggaatg cagaagttcc ttgggttgga 240
ggtgacaggg aagctagaca ctgacactct ggaggtgatg cgcaagccca ggtgtggagt 300
tcctgacgtt ggtcacttca gctcctttcc tggcatgccg aagtggagga aaacccacct 360
tacatacagg attgtgaatt atacaccaga tttgccaaga gatgctgttg attctgccat 420
tgagaaagct ctgaaagtct gggaagaggt gactccactc acattctcca ggctgtatga 480
aggagaggct gatataatga tctctttcgc agttaaagaa catggagact tttactcttt 540
tgatggccca ggacacagtt tggctcatgc ctacccacct ggacctgggc tttatggaga 600
tattcacttt gatgatgatg aaaaatggac agaagatgca tcaggcacca atttattcct 660
cgttgctgct catgaacttg gccactccct ggggctcttt cactcagcca acactgaagc 720
tttgatgtac ccactctaca actcattcac agagctcgcc cagttccgcc tttcgcaaga 780
tgatgtgaat ggcattcagt ctctctacgg acctcccccct gcctctactg aggaacccct 840
ggtgcccaca aaatctgttc cttcgggatc tgagatgcca gccaagtgtg atcctgcttt 900
gtccttcgat gccatcagca ctctgagggg agaatatctg ttctttaaag acagatattt 960
ttggcgaaga tcccactgga accctgaacc tgaatttcat ttgatttctg cattttggcc 1020
ctctcttcca tcatatttgg atgctgcata tgaagttaac agcagggaca ccgtttttat 1080
ttttaaagga aatgagttct gggccatcag aggaaatgag gtacaagcag gttatccaag 1140
aggcatccat accctgggtt ttcctccaac cataaggaaa attgatgcag ctgtttctga 1200
caaggaaaag aagaaaacat acttctttgc agcggacaaa tactggagat ttgatgaaaa 1260
tagccagtcc atggagcaag gcttccctag actaatagct gatgactttc caggagttga 1320
gcctaaggtt gatgctgtat tacaggcatt tggatttttc tacttcttca gtggatcatc 1380
acagtttgag tttgacccca atgccaggat ggtgacacac atattaaaga gtaacagctg 1440
gttacattgc taggcgagat agggggaaga cagatatggg tgtttttaat aaatctaata 1500
attattcatc taatgtatta tgagccaaaa tggttaattt ttcctgcatg ttctgtgact 1560
gaagaagatg agccttgcag atatctgcat gtgtcatgaa gaatgtttct ggaattcttc 1620
acttgctttt gaattgcact gaacagaatt aagaaatact catgtgcaat aggtgagaga 1680
atgtattttc atagatgtgt tattacttcc tcaataaaaa gttttatttt gggcctgttc 1740
ctt 1743

<210> 119
<211> 476
<212> PRT
<213> 現代人

<220>
<223> MMP-10前驅體

<400> 119
Met Met His Leu Ala Phe Leu Val Leu Leu Cys Leu Pro Val Cys Ser
 1   5   10   15
Ala Tyr Pro Leu Ser Gly Ala Ala Lys Glu Glu Asp Ser Asn Lys Asp

            20   25   30
Leu Ala Gln Gln Tyr Leu Glu Lys Tyr Tyr Asn Leu Glu Lys Asp Val
        35   40   45
Lys Gln Phe Arg Arg Lys Asp Ser Asn Leu Ile Val Lys Lys Ile Gln
    50   55   60
Gly Met Gln Lys Phe Leu Gly Leu Glu Val Thr Gly Lys Leu Asp Thr
65   70   75   80

Asp Thr Leu Glu Val Met Arg Lys Pro Arg Cys Gly Val Pro Asp Val
                85   90   95
Gly His Phe Ser Ser Phe Pro Gly Met Pro Lys Trp Arg Lys Thr His
            100   105   110
Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp Leu Pro Arg Asp Ala
        115   120   125
Val Asp Ser Ala Ile Glu Lys Ala Leu Lys Val Trp Glu Glu Val Thr

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

            420                 425                 430
Glu Pro Lys Val Asp Ala Val Leu Gln Ala Phe Gly Phe Phe Tyr Phe
        435                 440                 445
Phe Ser Gly Ser Ser Gln Phe Glu Phe Asp Pro Asn Ala Arg Met Val
    450                 455                 460
Thr His Ile Leu Lys Ser Asn Ser Trp Leu His Cys
465                 470                 475


<210> 120
<211> 378
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-10

<400> 120
Phe Ser Ser Phe Pro Gly Met Pro Lys Trp Arg Lys Thr His Leu Thr
 1               5                  10                  15
Tyr Arg Ile Val Asn Tyr Thr Pro Asp Leu Pro Arg Asp Ala Val Asp
            20                  25                  30
Ser Ala Ile Glu Lys Ala Leu Lys Val Trp Glu Glu Val Thr Pro Leu
        35                  40                  45
Thr Phe Ser Arg Leu Tyr Glu Gly Glu Ala Asp Ile Met Ile Ser Phe
    50                  55                  60
Ala Val Lys Glu His Gly Asp Phe Tyr Ser Phe Asp Gly Pro Gly His
65                  70                  75                  80
```

```
Ser Leu Ala His Ala Tyr Pro Pro Gly Pro Gly Leu Tyr Gly Asp Ile
                85                  90                  95
His Phe Asp Asp Asp Glu Lys Trp Thr Glu Asp Ala Ser Gly Thr Asn
            100                 105                 110
Leu Phe Leu Val Ala Ala His Glu Leu Gly His Ser Leu Gly Leu Phe
        115                 120                 125
His Ser Ala Asn Thr Glu Ala Leu Met Tyr Pro Leu Tyr Asn Ser Phe
    130                 135                 140
Thr Glu Leu Ala Gln Phe Arg Leu Ser Gln Asp Asp Val Asn Gly Ile
145                 150                 155                 160
Gln Ser Leu Tyr Gly Pro Pro Pro Ala Ser Thr Glu Glu Pro Leu Val
                165                 170                 175
Pro Thr Lys Ser Val Pro Ser Gly Ser Glu Met Pro Ala Lys Cys Asp
            180                 185                 190
Pro Ala Leu Ser Phe Asp Ala Ile Ser Thr Leu Arg Gly Glu Tyr Leu
        195                 200                 205
Phe Phe Lys Asp Arg Tyr Phe Trp Arg Arg Ser His Trp Asn Pro Glu
    210                 215                 220
Pro Glu Phe His Leu Ile Ser Ala Phe Trp Pro Ser Leu Pro Ser Tyr
225                 230                 235                 240
Leu Asp Ala Ala Tyr Glu Val Asn Ser Arg Asp Thr Val Phe Ile Phe
                245                 250                 255
Lys Gly Asn Glu Phe Trp Ala Ile Arg Gly Asn Glu Val Gln Ala Gly
            260                 265                 270
Tyr Pro Arg Gly Ile His Thr Leu Gly Phe Pro Pro Thr Ile Arg Lys
        275                 280                 285
Ile Asp Ala Ala Val Ser Asp Lys Glu Lys Lys Lys Thr Tyr Phe Phe
    290                 295                 300
Ala Ala Asp Lys Tyr Trp Arg Phe Asp Glu Asn Ser Gln Ser Met Glu
305                 310                 315                 320
Gln Gly Phe Pro Arg Leu Ile Ala Asp Asp Phe Pro Gly Val Glu Pro
                325                 330                 335
Lys Val Asp Ala Val Leu Gln Ala Phe Gly Phe Phe Tyr Phe Phe Ser
            340                 345                 350
Gly Ser Ser Gln Phe Glu Phe Asp Pro Asn Ala Arg Met Val Thr His
        355                 360                 365
Ile Leu Lys Ser Asn Ser Trp Leu His Cys
    370                 375
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<210> 121
<211> 2247
<212> DNA
<213> 現代人

<220>
<223> MMP-11

<400> 121

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ccggggcgga tggctccggc cgcctggctc cgcagcgcgg ccgcgcgcgc cctcctgccc 60
ccgatgctgc tgctgctgct ccagccgccg ccgctgctgg cccgggctct gccgccggac 120
gtccaccacc tccatgccga gaggaggggg ccacagccct ggcatgcagc cctgcccagt 180
agcccggcac ctgcccctgc cacgcaggaa gccccccggc ctgccagcag cctcaggcct 240
ccccgctgtg gcgtgcccga cccatctgat gggctgagtg cccgcaaccg acagaagagg 300
ttcgtgcttt ctggcgggcg ctgggagaag acggacctca cctacaggat ccttcggttc 360
ccatggcagt tggtgcagga gcaggtgcgg cagacgatgg cagaggccct aaaggtatgg 420
agcgatgtga cgccactcac ctttactgag gtgcacgagg gccgtgctga catcatgatc 480
gacttcgcca ggtactggca tggggacgac ctgccgtttg atgggcctgg gggcatcctg 540
gcccatgcct tcttccccaa gactcaccga gaaggggatg tccacttcga ctatgatgag 600
acctggacta tcggggatga ccagggcaca gacctgctgc aggtggcagc ccatgaattt 660
ggccacgtgc tggggctgca gcacacaaca gcagccaagg ccctgatgtc cgccttctac 720
acctttcgct acccactgag tctcagccca gatgactgca ggggcgttca acacctatat 780
ggccagccct ggcccactgt cacctccagg accccagccc tgggccccca ggctgggata 840
gacaccaatg agattgcacc gctggagcca gacgccccgc cagatgcctg tgaggcctcc 900
tttgacgcgg tctccaccat ccgaggcgag ctctttttct tcaaagcggg ctttgtgtgg 960
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cgcctccgtg ggggccagct gcagcccggc tacccagcat tggcctctcg ccactggcag 1020
ggactgccca gccctgtgga cgctgccttc gaggatgccc agggccacat ttggttcttc 1080
caaggtgctc agtactgggt gtacgacggt gaaaagccag tcctgggccc cgcacccctc 1140
accgagctgg gcctggtgag gttcccggtc catgctgcct tggtctgggg tcccgagaag 1200
aacaagatct acttcttccg aggcagggac tactggcgtt tccaccccag cacccggcgt 1260
gtagacagtc ccgtgccccg cagggccact gactggagag gggtgccctc tgagatcgac 1320
gctgccttcc aggatgctga tggctatgcc tacttcctgc gcggccgcct ctactggaag 1380
tttgaccctg tgaaggtgaa ggctctggaa ggcttccccc gtctcgtggg tcctgacttc 1440
tttggctgtg ccgagcctgc caacactttc ctctgaccat ggcttggatg ccctcagggg 1500
tgctgacccc tgccaggcca cgaatatcag gctagagacc catggccatc tttgtggctg 1560
tgggcaccag gcatgggact gagcccatgt ctcctgcagg gggatggggt ggggtacaac 1620
caccatgaca actgccggga gggccacgca ggtcgtggtc acctgccagc gactgtctca 1680
gactgggcag ggaggctttg gcatgactta agaggaaggg cagtcttggg acccgctatg 1740
caggtcctgg caaacctggc tgccctgtct catccctgtc cctcagggta gcaccatggc 1800
aggactgggg gaactggagt gtccttgctg tatccctgtt gtgaggttcc ttccaggggc 1860
tggcactgaa gcaagggtgc tggggcccca tggccttcag ccctggctga gcaactgggc 1920
tgtagggcag ggccacttcc tgaggtcagg tcttggtagg tgcctgcatc tgtctgcctt 1980
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tggggagggg tattcttcat gcaggagacc ccaggccctg gaggctgcaa catacctcaa 2100
tcctgtccca ggccggatcc tcctgaagcc cttttcgcag cactgctatc ctccaaagcc 2160
attgtaaatg tgtgtacagt gtgtataaac cttcttcttc ttttttttt ttaaactgag 2220
gattgtcatt aaacacagtt gttttct 2247

<210> 122
<211> 488
<212> PRT
<213> 現代人

<220>
<223> MMP-11前驅體

<400> 122
Met Ala Pro Ala Ala Trp Leu Arg Ser Ala Ala Ala Arg Ala Leu Leu
 1   5   10   15
Pro Pro Met Leu Leu Leu Leu Leu Gln Pro Pro Pro Leu Leu Ala Arg
            20   25   30
Ala Leu Pro Pro Asp Val His His Leu His Ala Glu Arg Arg Gly Pro
        35   40   45
Gln Pro Trp His Ala Ala Leu Pro Ser Ser Pro Ala Pro Ala Pro Ala
    50   55   60
Thr Gln Glu Ala Pro Arg Pro Ala Ser Ser Leu Arg Pro Pro Arg Cys
65   70   75   80
Gly Val Pro Asp Pro Ser Asp Gly Leu Ser Ala Arg Asn Arg Gln Lys
                85   90   95
Arg Phe Val Leu Ser Gly Gly Arg Trp Glu Lys Thr Asp Leu Thr Tyr
            100   105   110
Arg Ile Leu Arg Phe Pro Trp Gln Leu Val Gln Glu Gln Val Arg Gln
        115   120   125
Thr Met Ala Glu Ala Leu Lys Val Trp Ser Asp Val Thr Pro Leu Thr
    130   135   140
Phe Thr Glu Val His Glu Gly Arg Ala Asp Ile Met Ile Asp Phe Ala
145   150   155   160
Arg Tyr Trp His Gly Asp Asp Leu Pro Phe Asp Gly Pro Gly Gly Ile
                165   170   175
Leu Ala His Ala Phe Phe Pro Lys Thr His Arg Glu Gly Asp Val His
            180   185   190
Phe Asp Tyr Asp Glu Thr Trp Thr Ile Gly Asp Asp Gln Gly Thr Asp
        195   200   205
Leu Leu Gln Val Ala Ala His Glu Phe Gly His Val Leu Gly Leu Gln
    210   215   220
His Thr Thr Ala Ala Lys Ala Leu Met Ser Ala Phe Tyr Thr Phe Arg
225   230   235   240
Tyr Pro Leu Ser Leu Ser Pro Asp Asp Cys Arg Gly Val Gln His Leu
                245   250   255
Tyr Gly Gln Pro Trp Pro Thr Val Thr Ser Arg Thr Pro Ala Leu Gly

```
            260                 265                 270
Pro Gln Ala Gly Ile Asp Thr Asn Glu Ile Ala Pro Leu Glu Pro Asp
        275                 280                 285
Ala Pro Pro Asp Ala Cys Glu Ala Ser Phe Asp Ala Val Ser Thr Ile
    290                 295                 300
Arg Gly Glu Leu Phe Phe Phe Lys Ala Gly Phe Val Trp Arg Leu Arg
305                 310                 315                 320
Gly Gly Gln Leu Gln Pro Gly Tyr Pro Ala Leu Ala Ser Arg His Trp
                325                 330                 335
Gln Gly Leu Pro Ser Pro Val Asp Ala Ala Phe Glu Asp Ala Gln Gly
            340                 345                 350
His Ile Trp Phe Phe Gln Gly Ala Gln Tyr Trp Val Tyr Asp Gly Glu
        355                 360                 365
Lys Pro Val Leu Gly Pro Ala Pro Leu Thr Glu Leu Gly Leu Val Arg
    370                 375                 380
Phe Pro Val His Ala Ala Leu Val Trp Gly Pro Glu Lys Asn Lys Ile
385                 390                 395                 400
Tyr Phe Phe Arg Gly Arg Asp Tyr Trp Arg Phe His Pro Ser Thr Arg
                405                 410                 415
Arg Val Asp Ser Pro Val Pro Arg Arg Ala Thr Asp Trp Arg Gly Val
            420                 425                 430
Pro Ser Glu Ile Asp Ala Ala Phe Gln Asp Ala Asp Gly Tyr Ala Tyr
        435                 440                 445
Phe Leu Arg Gly Arg Leu Tyr Trp Lys Phe Asp Pro Val Lys Val Lys
    450                 455                 460
Ala Leu Glu Gly Phe Pro Arg Leu Val Gly Pro Asp Phe Phe Gly Cys
465                 470                 475                 480
Ala Glu Pro Ala Asn Thr Phe Leu
                485
```

<210> 123
<211> 391
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-11

<400> 123

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

```
          195                 200                 205

Gly Glu Leu Phe Phe Phe Lys Ala Gly Phe Val Trp Arg Leu Arg Gly
    210                 215                 220
Gly Gln Leu Gln Pro Gly Tyr Pro Ala Leu Ala Ser Arg His Trp Gln
225                 230                 235                 240
Gly Leu Pro Ser Pro Val Asp Ala Ala Phe Glu Asp Ala Gln Gly His
                245                 250                 255
Ile Trp Phe Phe Gln Gly Ala Gln Tyr Trp Val Tyr Asp Gly Glu Lys
            260                 265                 270
Pro Val Leu Gly Pro Ala Pro Leu Thr Glu Leu Gly Leu Val Arg Phe
        275                 280                 285
Pro Val His Ala Ala Leu Val Trp Gly Pro Glu Lys Asn Lys Ile Tyr
    290                 295                 300
Phe Phe Arg Gly Arg Asp Tyr Trp Arg Phe His Pro Ser Thr Arg Arg
305                 310                 315                 320
Val Asp Ser Pro Val Pro Arg Arg Ala Thr Asp Trp Arg Gly Val Pro
                325                 330                 335
Ser Glu Ile Asp Ala Ala Phe Gln Asp Ala Asp Gly Tyr Ala Tyr Phe
            340                 345                 350
Leu Arg Gly Arg Leu Tyr Trp Lys Phe Asp Pro Val Lys Val Lys Ala
        355                 360                 365
Leu Glu Gly Phe Pro Arg Leu Val Gly Pro Asp Phe Phe Gly Cys Ala
    370                 375                 380
Glu Pro Ala Asn Thr Phe Leu
385                 390
```

<210> 124
<211> 1147
<212> DNA
<213> 現代人

<220>
<223> MMP-7

<400> 124

```
accaaatcaa ccataggtcc aagaacaatt gtctctggac ggcagctatg cgactcaccg 60
tgctgtgtgc tgtgtgcctg ctgcctggca gcctggccct gccgctgcct caggaggcgg 120
gaggcatgag tgagctacag tgggaacagg ctcaggacta tctcaagaga ttttatctct 180
atgactcaga aacaaaaaat gccaacagtt tagaagccaa actcaaggag atgcaaaaat 240
tctttggcct acctataact ggaatgttaa actcccgcgt catagaaata atgcagaagc 300
ccagatgtgg agtgccagat gttgcagaat actcactatt tccaaatagc ccaaaatgga 360
cttccaaagt ggtcacctac aggatcgtat catatactcg agacttaccg catattacag 420
tggatcgatt agtgtcaaag gctttaaaca tgtggggcaa agagatcccc ctgcatttca 480
ggaaagttgt atggggaact gctgacatca tgattggctt tgcgcgagga gctcatgggg 540
actcctaccc atttgatggg ccaggaaaca cgctggctca tgcctttgcg cctgggacag 600
gtctcggagg agatgctcac ttcgatgagg atgaacgctg gacggatggt agcagtctag 660
ggattaactt cctgtatgct gcaactcatg aacttggcca ttctttgggt atgggacatt 720
cctctgatcc taatgcagtg atgtatccaa cctatggaaa tggagatccc caaaatttta 780
aactttccca ggatgatatt aaaggcattc agaaactata tggaaagaga agtaattcaa 840
gaaagaaata gaaacttcag gcagaacatc cattcattca ttcattggat tgtatatcat 900
tgttgcacaa tcagaattga taagcactgt tcctccactc catttagcaa ttatgtcacc 960
ctttttttatt gcagttggtt tttgaatgtc tttcactcct tttaaggata aactccttta 1020
tggtgtgact gtgtcttatt catctatact tgcagtgggt agatgtcaat aaatgttaca 1080
tacacaaata aataaaatgt ttattccatg gtaaatttaa aaaaaaaaaa aaaaaaaaaa 1140
aaaaaaa                                                          1147
```

<210> 125
<211> 267
<212> PRT
<213> 現代人

<220>

<223> MMP-7前驅體

<400> 125

```
Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu
 1               5                  10                  15
Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp
            20                  25                  30
Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu
        35                  40                  45
Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys
    50                  55                  60
Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu
65                  70                  75                  80
Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser
                85                  90                  95
Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg
            100                 105                 110
Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu
        115                 120                 125
Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe
    130                 135                 140
Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg
145                 150                 155                 160
Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu
                165                 170                 175
Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
            180                 185                 190
Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
        195                 200                 205
Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
    210                 215                 220
Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp
225                 230                 235                 240
Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys
                245                 250                 255
Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys
            260                 265
```

<210> 126
<211> 173
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-7

<400> 126

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

```
    130                 135                 140
Gly Asp Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile
145                 150                 155                 160
Gln Lys Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys
                165                 170
```

<210> 127
<211> 998
<212> DNA
<213> 現代人

<220>
<223> MMP-26

<400> 127

```
gacaaatgag ggtttggcat gcagctcgtc atcttaagag ttactatctt cttgccctgg 60
tgtttcgccg ttccagtgcc ccctgctgca gaccataaag gatgggactt tgttgagggc 120
tatttccatc aatttttcct gaccaagaag gagtcgccac tccttaccca ggagacacaa 180
acacagctcc tgcaacaatt ccatcggaat gggacagacc tacttgacat gcagatgcat 240
gctctgctac accagcccca ctgtggggtg cctgatgggt ccgacacctc catctcgcca 300
ggaagatgca agtggaataa gcacactcta acttacagga ttatcaatta cccacatgat 360
atgaagccat ccgcagtgaa agacagtata tataatgcag tttccatctg gagcaatgtg 420
acccctttga tattccagca agtgcagaat ggagatgcag acatcaaggt ttctttctgg 480
cagtgggccc atgaagatgg ttggcccttt gatgggccag gtggtatctt aggccatgcc 540
ttttaccaa attctggaaa tcctggagtt gtccattttg acaagaatga acactggtca 600
gcttcagaca ctggatataa tctgttcctg gttgcaactc atgagattgg gcattctttg 660
ggcctgcagc actctgggaa tcagagctcc ataatgtacc ccacttactg gtatcacgac 720
cctagaacct tccagctcag tgccgatgat atccaaagga tccagcattt gtatggagaa 780
aaatgttcat ctgacatacc ttaatgttag cacagaggac ttattcaacc tgtcctttca 840
gggagtttat tggaggatca aagaactgaa agcactagag cagccttggg gactgctagg 900
atgaagccct aaagaatgca acctagtcag gttagctgaa ccgacactca aaacgctact 960
gagtcacaat aaagattgtt ttaaagagta aaaaaaaa                         998
```

<210> 128
<211> 261
<212> PRT
<213> 現代人

<220>
<223> MMP-26前驅體

<400> 128

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

```
Pro Asn Ser Gly Asn Pro Gly Val Val His Phe Asp Lys Asn Glu His
            180                 185                 190
Trp Ser Ala Ser Asp Thr Gly Tyr Asn Leu Phe Leu Val Ala Thr His
        195                 200                 205

Glu Ile Gly His Ser Leu Gly Leu Gln His Ser Gly Asn Gln Ser Ser
    210                 215                 220
Ile Met Tyr Pro Thr Tyr Trp Tyr His Asp Pro Arg Thr Phe Gln Leu
225                 230                 235                 240
Ser Ala Asp Asp Ile Gln Arg Ile Gln His Leu Tyr Gly Glu Lys Cys
                245                 250                 255
Ser Ser Asp Ile Pro
            260
```

<210> 129
<211> 172
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-26

<400> 129

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

<210> 130
<211> 1825
<212> DNA
<213> 現代人

<220>
<223> MMP-12

<400> 130

```
agaaaggaac acagtaaact gaattgatcc gtttagaagt ttacaatgaa gtttcttcta 60
atactgctcc tgcaggccac tgcttctgga gctcttcccc tgaacagctc tacaagcctg 120
gaaaaaaata atgtgctatt tggtgaaaga tacttagaaa aattttatgg ccttgagata 180
aacaaacttc cagtgacaaa aatgaaatat agtggaaact taatgaagga aaaaatccaa 240
gaaatgcagc acttcttggg tctgaaagtg accgggcaac tggacacatc taccctggag 300
atgatgcacg cacctcgatg tggagtcccc gatgtccatc atttcaggga aatgccaggg 360
gggcccgtat ggaggaaaca ttatatcacc tacagaatca ataattacac acctgacatg 420
aaccgtgagg atgttgacta cgcaatccgg aaagctttcc aagtatggag taatgttacc 480
```

```
cccttgaaat tcagcaagat taacacaggc atggctgaca ttttggtggt ttttgcccgt 540
ggagctcatg gagacttcca tgcttttgat ggcaaaggtg gaatcctagc ccatgctttt 600
ggacctggat ctggcattgg aggggatgca catttcgatg aggacgaatt ctggactaca 660
cattcaggag gcaccaactt gttcctcact gctgttcacg agattggcca ttccttaggt 720
cttggccatt ctagtgatcc aaaggccgta atgttcccca cctacaaata tgttgacatc 780
aacacatttc gcctctctgc tgatgacata cgtggcattc agtccctgta tggagaccca 840
aaagagaacc aacgcttgcc aaatcctgac aattcagaac cagctctctg tgaccccaat 900
ttgagttttg atgctgtcac taccgtggga ataagatct ttttcttcaa agacaggttc 960
ttctggctga aggtttctga gagaccaaag accagtgtta atttaatttc ttccttatgg 1020
ccaaccttgc catctggcat tgaagctgct tatgaaattg aagccagaaa tcaagttttt 1080
ctttttaaag atgacaaata ctggttaatt agcaatttaa gaccagagcc aaattatccc 1140
aagagcatac attcttttgg ttttcctaac tttgtgaaaa aaattgatgc agctgttttt 1200
aacccacgtt tttataggac ctacttcttt gtagataacc agtattggag gtatgatgaa 1260
aggagacaga tgatggaccc tggttatccc aaactgatta ccaagaactt ccaaggaatc 1320
gggcctaaaa ttgatgcagt cttctactct aaaaacaaat actactattt cttccaagga 1380
tctaaccaat ttgaatatga cttcctactc caacgtatca ccaaaacact gaaaagcaat 1440
agctggtttg gttgttagaa atggtgtaat taatggtttt tgttagttca cttcagctta 1500
ataagtattt attgcatatt tgctatgtcc tcagtgtacc actacttaga gatatgtatc 1560
ataaaaataa aatctgtaaa ccataggtaa tgattatata aaatacataa tatttttcaa 1620
ttttgaaaac tctaattgtc cattcttgct tgactctact attaagtttg aaaatagtta 1680
ccttcaaagg ccaagagaat tctatttgaa gcatgctctg taagttgctt cctaacatcc 1740
ttggactgag aaattatact tacttctggc ataactaaaa ttaagtatat atattttggc 1800
tcaaataaaa ttgaaaaaaa aatca                                       1825
```

<210> 131
<211> 470
<212> PRT
<213> 現代人

<220>
<223> MMP-12前驅體

<400> 131

```
Met Lys Phe Leu Leu Ile Leu Leu Leu Gln Ala Thr Ala Ser Gly Ala
 1               5                  10                  15
Leu Pro Leu Asn Ser Ser Thr Ser Leu Glu Lys Asn Asn Val Leu Phe
            20                  25                  30
Gly Glu Arg Tyr Leu Glu Lys Phe Tyr Gly Leu Glu Ile Asn Lys Leu
        35                  40                  45
Pro Val Thr Lys Met Lys Tyr Ser Gly Asn Leu Met Lys Glu Lys Ile
    50                  55                  60
Gln Glu Met Gln His Phe Leu Gly Leu Lys Val Thr Gly Gln Leu Asp
65                  70                  75                  80
Thr Ser Thr Leu Glu Met Met His Ala Pro Arg Cys Gly Val Pro Asp
                85                  90                  95
Val His His Phe Arg Glu Met Pro Gly Gly Pro Val Trp Arg Lys His
            100                 105                 110
Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr Thr Pro Asp Met Asn Arg Glu
        115                 120                 125
Asp Val Asp Tyr Ala Ile Arg Lys Ala Phe Gln Val Trp Ser Asn Val
    130                 135                 140
Thr Pro Leu Lys Phe Ser Lys Ile Asn Thr Gly Met Ala Asp Ile Leu
145                 150                 155                 160
Val Val Phe Ala Arg Gly Ala His Gly Asp Phe His Ala Phe Asp Gly
                165                 170                 175
Lys Gly Gly Ile Leu Ala His Ala Phe Gly Pro Gly Ser Gly Ile Gly
            180                 185                 190
Gly Asp Ala His Phe Asp Glu Asp Glu Phe Trp Thr Thr His Ser Gly
        195                 200                 205
Gly Thr Asn Leu Phe Leu Thr Ala Val His Glu Ile Gly His Ser Leu
    210                 215                 220
Gly Leu Gly His Ser Ser Asp Pro Lys Ala Val Met Phe Pro Thr Tyr
225                 230                 235                 240
Lys Tyr Val Asp Ile Asn Thr Phe Arg Leu Ser Ala Asp Asp Ile Arg
                245                 250                 255
```

```
Gly Ile Gln Ser Leu Tyr Gly Asp Pro Lys Glu Asn Gln Arg Leu Pro
            260                 265                 270
Asn Pro Asp Asn Ser Glu Pro Ala Leu Cys Asp Pro Asn Leu Ser Phe
        275                 280                 285
Asp Ala Val Thr Thr Val Gly Asn Lys Ile Phe Phe Phe Lys Asp Arg
    290                 295                 300
Phe Phe Trp Leu Lys Val Ser Glu Arg Pro Lys Thr Ser Val Asn Leu

305                 310                 315                 320
Ile Ser Ser Leu Trp Pro Thr Leu Pro Ser Gly Ile Glu Ala Ala Tyr
                325                 330                 335
Glu Ile Glu Ala Arg Asn Gln Val Phe Leu Phe Lys Asp Asp Lys Tyr
            340                 345                 350
Trp Leu Ile Ser Asn Leu Arg Pro Glu Pro Asn Tyr Pro Lys Ser Ile
        355                 360                 365
His Ser Phe Gly Phe Pro Asn Phe Val Lys Lys Ile Asp Ala Ala Val
    370                 375                 380
Phe Asn Pro Arg Phe Tyr Arg Thr Tyr Phe Phe Val Asp Asn Gln Tyr
385                 390                 395                 400
Trp Arg Tyr Asp Glu Arg Arg Gln Met Met Asp Pro Gly Tyr Pro Lys
                405                 410                 415
Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val
            420                 425                 430
Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln
        435                 440                 445
Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser
    450                 455                 460
Asn Ser Trp Phe Gly Cys
465                 470
```

<210> 132
<211> 365
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-12

<400> 132

```
Gly Pro Val Trp Arg Lys His Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr
 1                   5                  10                  15
Thr Pro Asp Met Asn Arg Glu Asp Val Asp Tyr Ala Ile Arg Lys Ala

            20                  25                  30
Phe Gln Val Trp Ser Asn Val Thr Pro Leu Lys Phe Ser Lys Ile Asn
        35                  40                  45

Thr Gly Met Ala Asp Ile Leu Val Val Phe Ala Arg Gly Ala His Gly
    50                  55                  60
Asp Phe His Ala Phe Asp Gly Lys Gly Gly Ile Leu Ala His Ala Phe
65                  70                  75                  80
Gly Pro Gly Ser Gly Ile Gly Gly Asp Ala His Phe Asp Glu Asp Glu
                85                  90                  95
Phe Trp Thr Thr His Ser Gly Gly Thr Asn Leu Phe Leu Thr Ala Val
            100                 105                 110
His Glu Ile Gly His Ser Leu Gly Leu Gly His Ser Ser Asp Pro Lys
        115                 120                 125
Ala Val Met Phe Pro Thr Tyr Lys Tyr Val Asp Ile Asn Thr Phe Arg
    130                 135                 140
Leu Ser Ala Asp Asp Ile Arg Gly Ile Gln Ser Leu Tyr Gly Asp Pro
145                 150                 155                 160
Lys Glu Asn Gln Arg Leu Pro Asn Pro Asp Asn Ser Glu Pro Ala Leu
                165                 170                 175
Cys Asp Pro Asn Leu Ser Phe Asp Ala Val Thr Thr Val Gly Asn Lys
```

```
            180                 185                 190
Ile Phe Phe Phe Lys Asp Arg Phe Phe Trp Leu Lys Val Ser Glu Arg
        195                 200                 205
Pro Lys Thr Ser Val Asn Leu Ile Ser Ser Leu Trp Pro Thr Leu Pro
    210                 215                 220
Ser Gly Ile Glu Ala Ala Tyr Glu Ile Glu Ala Arg Asn Gln Val Phe
225                 230                 235                 240
Leu Phe Lys Asp Asp Lys Tyr Trp Leu Ile Ser Asn Leu Arg Pro Glu
                245                 250                 255
Pro Asn Tyr Pro Lys Ser Ile His Ser Phe Gly Phe Pro Asn Phe Val
            260                 265                 270
Lys Lys Ile Asp Ala Ala Val Phe Asn Pro Arg Phe Tyr Arg Thr Tyr
        275                 280                 285
Phe Phe Val Asp Asn Gln Tyr Trp Arg Tyr Asp Glu Arg Arg Gln Met
    290                 295                 300
Met Asp Pro Gly Tyr Pro Lys Leu Ile Thr Lys Asn Phe Gln Gly Ile
305                 310                 315                 320
Gly Pro Lys Ile Asp Ala Val Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr
                325                 330                 335
Phe Phe Gln Gly Ser Asn Gln Phe Glu Tyr Asp Phe Leu Leu Gln Arg
            340                 345                 350
Ile Thr Lys Thr Leu Lys Ser Asn Ser Trp Phe Gly Cys
        355                 360                 365
```

<210> 133
<211> 3558
<212> DNA
<213> 現代人

<220>
<223> MMP-14

<400> 133

```
cagaccccag ttcgccgact aagcagaaga aagatcaaaa accggaaaag aggagaagag 60
caaacaggca ctttgaggaa caatcccctt taactccaag ccgacagcgg tctaggaatt 120
caagttcagt gcctaccgaa gacaaaggcg ccccgaggga gtggcggtgc gaccccaggg 180
cgtgggcccg gccgcggagc ccacactgcc cggctgaccc ggtggtctcg gaccatgtct 240
cccgccccaa gacccccccg ttgtctcctg ctccccctgc tcacgctcgg caccgcgctc 300
gcctccctcg gctcggccca aagcagcagc ttcagccccg aagcctggct acagcaatat 360
ggctacctgc ctcccgggga cctacgtacc cacacacagc gctcacccca gtcactctca 420
gcggccatcg ctgccatgca gaagttttac ggcttgcaag taacaggcaa agctgatgca 480
gacaccatga aggccatgag gcgccccccga tgtggtgttc cagacaagtt tggggctgag 540
atcaaggcca atgttcgaag gaagcgctac gccatccagg gtctcaaatg gcaacataat 600
gaaatcactt tctgcatcca gaattacacc cccaaggtgg gcgagtatgc cacatacgag 660
gccattcgca aggcgttccg cgtgtgggag agtgccacac cactgcgctt ccgcgaggtg 720
ccctatgcct acatccgtga gggccatgag aagcaggccg acatcatgat cttctttgcc 780
gagggcttcc atggcgacag cacgcccttc gatggtgagg gcggcttcct ggcccatgcc 840
tacttcccag gccccaacat tggaggagac acccactttg actctgccga gccttggact 900
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<210> 134
<211> 582
<212> PRT
<213> 現代人

<220>
<223> MMP-14前驅體

<400> 134
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Thr Leu Gly Thr Ala Leu Ala Ser Leu Gly Ser Ala Gln Ser Ser Ser
            20   25   30
Phe Ser Pro Glu Ala Trp Leu Gln Gln Tyr Gly Tyr Leu Pro Pro Gly
        35   40   45
Asp Leu Arg Thr His Thr Gln Arg Ser Pro Gln Ser Leu Ser Ala Ala
    50   55   60
Ile Ala Ala Met Gln Lys Phe Tyr Gly Leu Gln Val Thr Gly Lys Ala
65   70   75   80
Asp Ala Asp Thr Met Lys Ala Met Arg Arg Pro Arg Cys Gly Val Pro
                85   90   95
Asp Lys Phe Gly Ala Glu Ile Lys Ala Asn Val Arg Arg Lys Arg Tyr
            100   105   110
Ala Ile Gln Gly Leu Lys Trp Gln His Asn Glu Ile Thr Phe Cys Ile
        115   120   125
Gln Asn Tyr Thr Pro Lys Val Gly Glu Tyr Ala Thr Tyr Glu Ala Ile
    130   135   140
Arg Lys Ala Phe Arg Val Trp Glu Ser Ala Thr Pro Leu Arg Phe Arg
145   150   155   160
Glu Val Pro Tyr Ala Tyr Ile Arg Glu Gly His Glu Lys Gln Ala Asp
                165   170   175
Ile Met Ile Phe Phe Ala Glu Gly Phe His Gly Asp Ser Thr Pro Phe
            180   185   190
Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Asn

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        195                 200                 205
Ile Gly Gly Asp Thr His Phe Asp Ser Ala Glu Pro Trp Thr Val Arg
    210                 215                 220
Asn Glu Asp Leu Asn Gly Asn Asp Ile Phe Leu Val Ala Val His Glu
225                 230                 235                 240
Leu Gly His Ala Leu Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile
                245                 250                 255
Met Ala Pro Phe Tyr Gln Trp Met Asp Thr Glu Asn Phe Val Leu Pro
            260                 265                 270
Asp Asp Asp Arg Arg Gly Ile Gln Gln Leu Tyr Gly Gly Glu Ser Gly
        275                 280                 285
Phe Pro Thr Lys Met Pro Pro Gln Pro Arg Thr Thr Ser Arg Pro Ser
    290                 295                 300
Val Pro Asp Lys Pro Lys Asn Pro Thr Tyr Gly Pro Asn Ile Cys Asp
305                 310                 315                 320
Gly Asn Phe Asp Thr Val Ala Met Leu Arg Gly Glu Met Phe Val Phe
                325                 330                 335
Lys Glu Arg Trp Phe Trp Arg Val Arg Asn Asn Gln Val Met Asp Gly
            340                 345                 350
Tyr Pro Met Pro Ile Gly Gln Phe Trp Arg Gly Leu Pro Ala Ser Ile

        355                 360                 365
Asn Thr Ala Tyr Glu Arg Lys Asp Gly Lys Phe Val Phe Phe Lys Gly
    370                 375                 380
Asp Lys His Trp Val Phe Asp Glu Ala Ser Leu Glu Pro Gly Tyr Pro
385                 390                 395                 400
Lys His Ile Lys Glu Leu Gly Arg Gly Leu Pro Thr Asp Lys Ile Asp
                405                 410                 415
Ala Ala Leu Phe Trp Met Pro Asn Gly Lys Thr Tyr Phe Phe Arg Gly
            420                 425                 430
Asn Lys Tyr Tyr Arg Phe Asn Glu Glu Leu Arg Ala Val Asp Ser Glu
        435                 440                 445
Tyr Pro Lys Asn Ile Lys Val Trp Glu Gly Ile Pro Glu Ser Pro Arg
    450                 455                 460
Gly Ser Phe Met Gly Ser Asp Glu Val Phe Thr Tyr Phe Tyr Lys Gly
465                 470                 475                 480
Asn Lys Tyr Trp Lys Phe Asn Asn Gln Lys Leu Lys Val Glu Pro Gly
                485                 490                 495
Tyr Pro Lys Ser Ala Leu Arg Asp Trp Met Gly Cys Pro Ser Gly Gly
            500                 505                 510
Arg Pro Asp Glu Gly Thr Glu Glu Glu Thr Glu Val Ile Ile Ile Glu
        515                 520                 525
Val Asp Glu Glu Gly Gly Gly Ala Val Ser Ala Ala Ala Val Val Leu
    530                 535                 540
Pro Val Leu Leu Leu Leu Leu Val Leu Ala Val Gly Leu Ala Val Phe
545                 550                 555                 560
Phe Phe Arg Arg His Gly Thr Pro Arg Arg Leu Leu Tyr Cys Gln Arg
                565                 570                 575
Ser Leu Leu Asp Lys Val
            580
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<210> 135
<211> 471
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-14

<400> 135

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Tyr Ala Ile Gln Gly Leu Lys Trp Gln His Asn Glu Ile Thr Phe Cys
 1               5                  10                  15
Ile Gln Asn Tyr Thr Pro Lys Val Gly Glu Tyr Ala Thr Tyr Glu Ala
            20                  25                  30
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Ile Arg Lys Ala Phe Arg Val Trp Glu Ser Ala Thr Pro Leu Arg Phe
        35                  40                  45
Arg Glu Val Pro Tyr Ala Tyr Ile Arg Glu Gly His Glu Lys Gln Ala
    50                  55                  60
Asp Ile Met Ile Phe Phe Ala Glu Gly Phe His Gly Asp Ser Thr Pro
65                  70                  75                  80
Phe Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro
                85                  90                  95
Asn Ile Gly Gly Asp Thr His Phe Asp Ser Ala Glu Pro Trp Thr Val
            100                 105                 110
Arg Asn Glu Asp Leu Asn Gly Asn Asp Ile Phe Leu Val Ala Val His
        115                 120                 125
Glu Leu Gly His Ala Leu Gly Leu Glu His Ser Ser Asp Pro Ser Ala
    130                 135                 140
Ile Met Ala Pro Phe Tyr Gln Trp Met Asp Thr Glu Asn Phe Val Leu
145                 150                 155                 160
Pro Asp Asp Asp Arg Arg Gly Ile Gln Gln Leu Tyr Gly Gly Glu Ser
                165                 170                 175
Gly Phe Pro Thr Lys Met Pro Pro Gln Pro Arg Thr Thr Ser Arg Pro
            180                 185                 190
Ser Val Pro Asp Lys Pro Lys Asn Pro Thr Tyr Gly Pro Asn Ile Cys
        195                 200                 205
Asp Gly Asn Phe Asp Thr Val Ala Met Leu Arg Gly Glu Met Phe Val
    210                 215                 220
Phe Lys Glu Arg Trp Phe Trp Arg Val Arg Asn Asn Gln Val Met Asp
225                 230                 235                 240
Gly Tyr Pro Met Pro Ile Gly Gln Phe Trp Arg Gly Leu Pro Ala Ser
                245                 250                 255
Ile Asn Thr Ala Tyr Glu Arg Lys Asp Gly Lys Phe Val Phe Phe Lys
            260                 265                 270
Gly Asp Lys His Trp Val Phe Asp Glu Ala Ser Leu Glu Pro Gly Tyr
        275                 280                 285
Pro Lys His Ile Lys Glu Leu Gly Arg Gly Leu Pro Thr Asp Lys Ile
    290                 295                 300
Asp Ala Ala Leu Phe Trp Met Pro Asn Gly Lys Thr Tyr Phe Phe Arg
305                 310                 315                 320
Gly Asn Lys Tyr Tyr Arg Phe Asn Glu Glu Leu Arg Ala Val Asp Ser
                325                 330                 335
Glu Tyr Pro Lys Asn Ile Lys Val Trp Glu Gly Ile Pro Glu Ser Pro
            340                 345                 350
Arg Gly Ser Phe Met Gly Ser Asp Glu Val Phe Thr Tyr Phe Tyr Lys
        355                 360                 365
Gly Asn Lys Tyr Trp Lys Phe Asn Asn Gln Lys Leu Lys Val Glu Pro
    370                 375                 380
Gly Tyr Pro Lys Ser Ala Leu Arg Asp Trp Met Gly Cys Pro Ser Gly
385                 390                 395                 400
Gly Arg Pro Asp Glu Gly Thr Glu Glu Glu Thr Glu Val Ile Ile Ile
                405                 410                 415
Glu Val Asp Glu Glu Gly Gly Gly Ala Val Ser Ala Ala Ala Val Val
            420                 425                 430
Leu Pro Val Leu Leu Leu Leu Leu Val Leu Ala Val Gly Leu Ala Val
        435                 440                 445
Phe Phe Phe Arg Arg His Gly Thr Pro Arg Arg Leu Leu Tyr Cys Gln
    450                 455                 460
Arg Ser Leu Leu Asp Lys Val
465                 470
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<210> 136
<211> 4456
<212> DNA
<213> 現代人

<220>
<223> MMP-15

<400> 136
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gcctcctccc tccgcggggg gtcgcgttgg aggtcacccc cgccccctag gcgctgggtt 180
gggagtgacg cggggtgggc tggagaggtt tcctgccgtc tgggaagcgt aaacggaccg 240
cccacctgtc gggcctcggc cgcccgcacc tgcttgtgag aagcctgcgg ctggggcacc 300
gcccccggtc cccgcccggg tccgcgcatt gggagcacac tggcccttta agagcgcggc 360
ggccgcggcg cgcggggagg agggctggga gcgcccggag ccgcgctgaa ctcgccgggg 420
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<210> 137
<211> 669
<212> PRT
<213> 現代人

<220>
<223> MMP-15前驅體

<400> 137
Met Gly Ser Asp Pro Ser Ala Pro Gly Arg Pro Gly Trp Thr Gly Ser
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Leu Leu Gly Asp Arg Glu Glu Ala Ala Arg Pro Arg Leu Leu Pro Leu
            20   25   30
Leu Leu Val Leu Leu Gly Cys Leu Gly Leu Gly Val Ala Ala Glu Asp
        35   40   45
Ala Glu Val His Ala Glu Asn Trp Leu Arg Leu Tyr Gly Tyr Leu Pro
    50   55   60
Gln Pro Ser Arg His Met Ser Thr Met Arg Ser Ala Gln Ile Leu Ala
65   70   75   80
Ser Ala Leu Ala Glu Met Gln Arg Phe Tyr Gly Ile Pro Val Thr Gly
                85   90   95
Val Leu Asp Glu Glu Thr Lys Glu Trp Met Lys Arg Pro Arg Cys Gly
            100   105   110
Val Pro Asp Gln Phe Gly Val Arg Val Lys Ala Asn Leu Arg Arg Arg
        115   120   125
Arg Lys Arg Tyr Ala Leu Thr Gly Arg Lys Trp Asn Asn His His Leu
    130   135   140
Thr Phe Ser Ile Gln Asn Tyr Thr Glu Lys Leu Gly Trp Tyr His Ser
145   150   155   160
Met Glu Ala Val Arg Arg Ala Phe Arg Val Trp Glu Gln Ala Thr Pro
                165   170   175

Leu Val Phe Gln Glu Val Pro Tyr Glu Asp Ile Arg Leu Arg Arg Gln
            180   185   190
Lys Glu Ala Asp Ile Met Val Leu Phe Ala Ser Gly Phe His Gly Asp
        195   200   205
Ser Ser Pro Phe Asp Gly Thr Gly Gly Phe Leu Ala His Ala Tyr Phe
    210   215   220
Pro Gly Pro Gly Leu Gly Gly Asp Thr His Phe Asp Ala Asp Glu Pro
225   230   235   240
Trp Thr Phe Ser Ser Thr Asp Leu His Gly Asn Asn Leu Phe Leu Val
                245   250   255
Ala Val His Glu Leu Gly His Ala Leu Gly Leu Glu His Ser Ser Asn
            260   265   270
Pro Asn Ala Ile Met Ala Pro Phe Tyr Gln Trp Lys Asp Val Asp Asn
        275   280   285
Phe Lys Leu Pro Glu Asp Asp Leu Arg Gly Ile Gln Gln Leu Tyr Gly
    290   295   300
Thr Pro Asp Gly Gln Pro Gln Pro Thr Gln Pro Leu Pro Thr Val Thr
305   310   315   320

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Pro Arg Arg Pro Gly Arg Pro Asp His Arg Pro Pro Arg Pro Pro Gln
                325                 330                 335
Pro Pro Pro Pro Gly Gly Lys Pro Glu Arg Pro Pro Lys Pro Gly Pro
            340                 345                 350
Pro Val Gln Pro Arg Ala Thr Glu Arg Pro Asp Gln Tyr Gly Pro Asn
        355                 360                 365
Ile Cys Asp Gly Asp Phe Asp Thr Val Ala Met Leu Arg Gly Glu Met
    370                 375                 380
Phe Val Phe Lys Gly Arg Trp Phe Trp Arg Val Arg His Asn Arg Val
385                 390                 395                 400
Leu Asp Asn Tyr Pro Met Pro Ile Gly His Phe Trp Arg Gly Leu Pro
                405                 410                 415
Gly Asp Ile Ser Ala Ala Tyr Glu Arg Gln Asp Gly Arg Phe Val Phe
            420                 425                 430
Phe Lys Gly Asp Arg Tyr Trp Leu Phe Arg Glu Ala Asn Leu Glu Pro
        435                 440                 445
Gly Tyr Pro Gln Pro Leu Thr Ser Tyr Gly Leu Gly Ile Pro Tyr Asp
    450                 455                 460
Arg Ile Asp Thr Ala Ile Trp Trp Glu Pro Thr Gly His Thr Phe Phe
465                 470                 475                 480
Phe Gln Glu Asp Arg Tyr Trp Arg Phe Asn Glu Glu Thr Gln Arg Gly
                485                 490                 495
Asp Pro Gly Tyr Pro Lys Pro Ile Ser Val Trp Gln Gly Ile Pro Ala
            500                 505                 510

Ser Pro Lys Gly Ala Phe Leu Ser Asn Asp Ala Ala Tyr Thr Tyr Phe

        515                 520                 525
Tyr Lys Gly Thr Lys Tyr Trp Lys Phe Asp Asn Glu Arg Leu Arg Met
    530                 535                 540
Glu Pro Gly Tyr Pro Lys Ser Ile Leu Arg Asp Phe Met Gly Cys Gln
545                 550                 555                 560
Glu His Val Glu Pro Gly Pro Arg Trp Pro Asp Val Ala Arg Pro Pro
                565                 570                 575
Phe Asn Pro His Gly Gly Ala Glu Pro Gly Ala Asp Ser Ala Glu Gly
            580                 585                 590
Asp Val Gly Asp Gly Asp Gly Asp Phe Gly Ala Gly Val Asn Lys Asp
        595                 600                 605
Gly Gly Ser Arg Val Val Val Gln Met Glu Glu Val Ala Arg Thr Val
    610                 615                 620
Asn Val Val Met Val Leu Val Pro Leu Leu Leu Leu Leu Cys Val Leu
625                 630                 635                 640
Gly Leu Thr Tyr Ala Leu Val Gln Met Gln Arg Lys Gly Ala Pro Arg
                645                 650                 655
Val Leu Leu Tyr Cys Lys Arg Ser Leu Gln Glu Trp Val
            660                 665
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<210> 138
<211> 529
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-15

<400> 138

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Tyr Ala Leu Thr Gly Arg Lys Trp Asn Asn His His Leu Thr Phe Ser
 1               5                  10                  15
Ile Gln Asn Tyr Thr Glu Lys Leu Gly Trp Tyr His Ser Met Glu Ala
            20                  25                  30
Val Arg Arg Ala Phe Arg Val Trp Glu Gln Ala Thr Pro Leu Val Phe
        35                  40                  45
Gln Glu Val Pro Tyr Glu Asp Ile Arg Leu Arg Arg Gln Lys Glu Ala
    50                  55                  60
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Asp Ile Met Val Leu Phe Ala Ser Gly Phe His Gly Asp Ser Ser Pro
65                  70                  75                  80
Phe Asp Gly Thr Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro
                85                  90                  95
Gly Leu Gly Gly Asp Thr His Phe Asp Ala Asp Glu Pro Trp Thr Phe
            100                 105                 110
Ser Ser Thr Asp Leu His Gly Asn Asn Leu Phe Leu Val Ala Val His
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Glu Leu Gly His Ala Leu Gly Leu Glu His Ser Ser Asn Pro Asn Ala
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Ile Met Ala Pro Phe Tyr Gln Trp Lys Asp Val Asp Asn Phe Lys Leu
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Pro Glu Asp Asp Leu Arg Gly Ile Gln Gln Leu Tyr Gly Thr Pro Asp
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Gly Gln Pro Gln Pro Thr Gln Pro Leu Pro Thr Val Thr Pro Arg Arg
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Pro Gly Arg Pro Asp His Arg Pro Pro Arg Pro Pro Gln Pro Pro Pro
        195                 200                 205
Pro Gly Gly Lys Pro Glu Arg Pro Pro Lys Pro Gly Pro Pro Val Gln
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Pro Arg Ala Thr Glu Arg Pro Asp Gln Tyr Gly Pro Asn Ile Cys Asp
225                 230                 235                 240
Gly Asp Phe Asp Thr Val Ala Met Leu Arg Gly Glu Met Phe Val Phe
                245                 250                 255
Lys Gly Arg Trp Phe Trp Arg Val Arg His Asn Arg Val Leu Asp Asn
            260                 265                 270
Tyr Pro Met Pro Ile Gly His Phe Trp Arg Gly Leu Pro Gly Asp Ile
        275                 280                 285
Ser Ala Ala Tyr Glu Arg Gln Asp Gly Arg Phe Val Phe Phe Lys Gly
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Asp Arg Tyr Trp Leu Phe Arg Glu Ala Asn Leu Glu Pro Gly Tyr Pro
305                 310                 315                 320
Gln Pro Leu Thr Ser Tyr Gly Leu Gly Ile Pro Tyr Asp Arg Ile Asp
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Thr Ala Ile Trp Trp Glu Pro Thr Gly His Thr Phe Phe Phe Gln Glu
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Asp Arg Tyr Trp Arg Phe Asn Glu Glu Thr Gln Arg Gly Asp Pro Gly
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Tyr Pro Lys Pro Ile Ser Val Trp Gln Gly Ile Pro Ala Ser Pro Lys
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Gly Ala Phe Leu Ser Asn Asp Ala Ala Tyr Thr Tyr Phe Tyr Lys Gly
385                 390                 395                 400
Thr Lys Tyr Trp Lys Phe Asp Asn Glu Arg Leu Arg Met Glu Pro Gly
                405                 410                 415
Tyr Pro Lys Ser Ile Leu Arg Asp Phe Met Gly Cys Gln Glu His Val
            420                 425                 430
Glu Pro Gly Pro Arg Trp Pro Asp Val Ala Arg Pro Pro Phe Asn Pro
        435                 440                 445
His Gly Gly Ala Glu Pro Gly Ala Asp Ser Ala Glu Gly Asp Val Gly
    450                 455                 460
Asp Gly Asp Gly Asp Phe Gly Ala Gly Val Asn Lys Asp Gly Gly Ser
465                 470                 475                 480
Arg Val Val Val Gln Met Glu Glu Val Ala Arg Thr Val Asn Val Val
                485                 490                 495
Met Val Leu Val Pro Leu Leu Leu Leu Leu Cys Val Leu Gly Leu Thr
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<211> 6347
<212> DNA
<213> 現代人

<220>
<223> MMP-16

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<212> PRT
<213> 現代人

<220>
<223> MMP-16前驅體

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Thr Val Cys Gly Thr Glu Gln Tyr Phe Asn Val Glu Val Trp Leu Gln
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Lys Tyr Gly Tyr Leu Pro Pro Thr Asp Pro Arg Met Ser Val Leu Arg
    50                  55                  60
Ser Ala Glu Thr Met Gln Ser Ala Leu Ala Ala Met Gln Gln Phe Tyr
65                  70                  75                  80
Gly Ile Asn Met Thr Gly Lys Val Asp Arg Asn Thr Ile Asp Trp Met
                85                  90                  95
Lys Lys Pro Arg Cys Gly Val Pro Asp Gln Thr Arg Gly Ser Ser Lys
            100                 105                 110
Phe His Ile Arg Arg Lys Arg Tyr Ala Leu Thr Gly Gln Lys Trp Gln
        115                 120                 125
His Lys His Ile Thr Tyr Ser Ile Lys Asn Val Thr Pro Lys Val Gly
    130                 135                 140
Asp Pro Glu Thr Arg Lys Ala Ile Arg Arg Ala Phe Asp Val Trp Gln
145                 150                 155                 160
Asn Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr Ser Glu Leu Glu
                165                 170                 175
Asn Gly Lys Arg Asp Val Asp Ile Thr Ile Ile Phe Ala Ser Gly Phe
            180                 185                 190
His Gly Asp Ser Ser Pro Phe Asp Gly Glu Gly Gly Phe Leu Ala His
        195                 200                 205
Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr His Phe Asp Ser
    210                 215                 220
Asp Glu Pro Trp Thr Leu Gly Asn Pro Asn His Asp Gly Asn Asp Leu
225                 230                 235                 240
Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu Gly Leu Glu His
                245                 250                 255
Ser Asn Asp Pro Thr Ala Ile Met Ala Pro Phe Tyr Gln Tyr Met Glu
            260                 265                 270
Thr Asp Asn Phe Lys Leu Pro Asn Asp Asp Leu Gln Gly Ile Gln Lys
        275                 280                 285
Ile Tyr Gly Pro Pro Asp Lys Ile Pro Pro Pro Thr Arg Pro Leu Pro
    290                 295                 300
Thr Val Pro Pro His Arg Ser Ile Pro Pro Ala Asp Pro Arg Lys Asn
305                 310                 315                 320
Asp Arg Pro Lys Pro Pro Arg Pro Pro Thr Gly Arg Pro Ser Tyr Pro
                325                 330                 335
Gly Ala Lys Pro Asn Ile Cys Asp Gly Asn Phe Asn Thr Leu Ala Ile
            340                 345                 350
Leu Arg Arg Glu Met Phe Val Phe Lys Asp Gln Trp Phe Trp Arg Val
        355                 360                 365
Arg Asn Asn Arg Val Met Asp Gly Tyr Pro Met Gln Ile Thr Tyr Phe
    370                 375                 380
Trp Arg Gly Leu Pro Pro Ser Ile Asp Ala Val Tyr Glu Asn Ser Asp
385                 390                 395                 400
Gly Asn Phe Val Phe Phe Lys Gly Asn Lys Tyr Trp Val Phe Lys Asp
                405                 410                 415
Thr Thr Leu Gln Pro Gly Tyr Pro His Asp Leu Ile Thr Leu Gly Ser
            420                 425                 430
Gly Ile Pro Pro His Gly Ile Asp Ser Ala Ile Trp Trp Glu Asp Val
        435                 440                 445
Gly Lys Thr Tyr Phe Phe Lys Gly Asp Arg Tyr Trp Arg Tyr Ser Glu
    450                 455                 460
Glu Met Lys Thr Met Asp Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp
465                 470                 475                 480
Lys Gly Ile Pro Glu Ser Pro Gln Gly Ala Phe Val His Lys Glu Asn
                485                 490                 495
Gly Phe Thr Tyr Phe Tyr Lys Gly Lys Glu Tyr Trp Lys Phe Asn Asn
            500                 505                 510
Gln Ile Leu Lys Val Glu Pro Gly Tyr Pro Arg Ser Ile Leu Lys Asp
        515                 520                 525
Phe Met Gly Cys Asp Gly Pro Thr Asp Arg Val Lys Glu Gly His Ser
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Pro Pro Asp Asp Val Asp Ile Val Ile Lys Leu Asp Asn Thr Ala Ser
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<210> 141
<211> 481
<212> PRT
<213> 現代人

<220>
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<400> 141
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35 40 45
Glu Glu Val Pro Tyr Ser Glu Leu Glu Asn Gly Lys Arg Asp Val Asp
50 55 60
Ile Thr Ile Ile Phe Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe
65 70 75 80
Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly
85 90 95
Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly
100 105 110
Asn Pro Asn His Asp Gly Asn Asp Leu Phe Leu Val Ala Val His Glu
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Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp Pro Thr Ala Ile
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Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr Asp Asn Phe Lys Leu Pro
145 150 155 160
Asn Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly Pro Pro Asp Lys
165 170 175
Ile Pro Pro Pro Thr Arg Pro Leu Pro Thr Val Pro Pro His Arg Ser
180 185 190
Ile Pro Pro Ala Asp Pro Arg Lys Asn Asp Arg Pro Lys Pro Pro Arg
195 200 205
Pro Pro Thr Gly Arg Pro Ser Tyr Pro Gly Ala Lys Pro Asn Ile Cys
210 215 220
Asp Gly Asn Phe Asn Thr Leu Ala Ile Leu Arg Arg Glu Met Phe Val
225 230 235 240
Phe Lys Asp Gln Trp Phe Trp Arg Val Arg Asn Asn Arg Val Met Asp
245 250 255
Gly Tyr Pro Met Gln Ile Thr Tyr Phe Trp Arg Gly Leu Pro Pro Ser
260 265 270
Ile Asp Ala Val Tyr Glu Asn Ser Asp Gly Asn Phe Val Phe Phe Lys
275 280 285
Gly Asn Lys Tyr Trp Val Phe Lys Asp Thr Thr Leu Gln Pro Gly Tyr
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Pro His Asp Leu Ile Thr Leu Gly Ser Gly Ile Pro Pro His Gly Ile
305 310 315 320
Asp Ser Ala Ile Trp Trp Glu Asp Val Gly Lys Thr Tyr Phe Phe Lys
325 330 335
Gly Asp Arg Tyr Trp Arg Tyr Ser Glu Glu Met Lys Thr Met Asp Pro
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Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly Ile Pro Glu Ser Pro
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Gln Gly Ala Phe Val His Lys Glu Asn Gly Phe Thr Tyr Phe Tyr Lys

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Gly Lys Glu Tyr Trp Lys Phe Asn Asn Gln Ile Leu Lys Val Glu Pro
385                 390                 395                 400
Gly Tyr Pro Arg Ser Ile Leu Lys Asp Phe Met Gly Cys Asp Gly Pro
                405                 410                 415
Thr Asp Arg Val Lys Glu Gly His Ser Pro Pro Asp Asp Val Asp Ile
            420                 425                 430
Val Ile Lys Leu Asp Asn Thr Ala Ser Thr Val Lys Ala Ile Ala Ile
        435                 440                 445
Val Ile Pro Cys Ile Leu Ala Leu Cys Leu Leu Val Leu Val Tyr Thr
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Val Phe Gln Phe Lys Arg Lys Gly Thr Pro Arg His Ile Leu Tyr Cys
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<210> 142
<211> 2438
<212> DNA
<213> 現代人

<220>
<223> MMP-17

<400> 142

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tgacctctcc ctgctttgta aaaaaaaaaa aaaaaaaa 2438

<210> 143
<211> 606
<212> PRT
<213> 現代人

<220>
<223> MMP-17前驅體

<400> 143
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1 5 10 15
Gly Leu Ser Arg Leu Pro Leu Leu Pro Leu Pro Leu Leu Leu Leu Leu
20 25 30
Ala Leu Gly Thr Arg Gly Gly Cys Ala Ala Pro Ala Pro Ala Pro Arg
35 40 45
Ala Glu Asp Leu Ser Leu Gly Val Glu Trp Leu Ser Arg Phe Gly Tyr
50 55 60
Leu Pro Pro Ala Asp Pro Thr Thr Gly Gln Leu Gln Thr Gln Glu Glu
65 70 75 80
Leu Ser Lys Ala Ile Thr Ala Met Gln Gln Phe Gly Gly Leu Glu Ala
85 90 95
Thr Gly Ile Leu Asp Glu Ala Thr Leu Ala Leu Met Lys Thr Pro Arg
100 105 110
Cys Ser Leu Pro Asp Leu Pro Val Leu Thr Gln Ala Arg Arg Arg Arg
115 120 125
Gln Ala Pro Ala Pro Thr Lys Trp Asn Lys Arg Asn Leu Ser Trp Arg
130 135 140
Val Arg Thr Phe Pro Arg Asp Ser Pro Leu Gly His Asp Thr Val Arg
145 150 155 160
Ala Leu Met Tyr Tyr Ala Leu Lys Val Trp Ser Asp Ile Ala Pro Leu
165 170 175
Asn Phe His Glu Val Ala Gly Ser Thr Ala Asp Ile Gln Ile Asp Phe
180 185 190
Ser Lys Ala Asp His Asn Asp Gly Tyr Pro Phe Asp Gly Pro Gly Gly
195 200 205

Thr Val Ala His Ala Phe Phe Pro Gly His His His Thr Ala Gly Asp
210 215 220
Thr His Phe Asp Asp Asp Glu Ala Trp Thr Phe Arg Ser Ser Asp Ala
225 230 235 240
His Gly Met Asp Leu Phe Ala Val Ala Val His Glu Phe Gly His Ala
245 250 255
Ile Gly Leu Ser His Val Ala Ala Ala His Ser Ile Met Arg Pro Tyr
260 265 270
Tyr Gln Gly Pro Val Gly Asp Pro Leu Arg Tyr Gly Leu Pro Tyr Glu
275 280 285
Asp Lys Val Arg Val Trp Gln Leu Tyr Gly Val Arg Glu Ser Val Ser
290 295 300
Pro Thr Ala Gln Pro Glu Glu Pro Pro Leu Leu Pro Glu Pro Pro Asp
305 310 315 320
Asn Arg Ser Ser Ala Pro Pro Arg Lys Asp Val Pro His Arg Cys Ser
325 330 335
Thr His Phe Asp Ala Val Ala Gln Ile Arg Gly Glu Ala Phe Phe Phe
340 345 350
Lys Gly Lys Tyr Phe Trp Arg Leu Thr Arg Asp Arg His Leu Val Ser
355 360 365
Leu Gln Pro Ala Gln Met His Arg Phe Trp Arg Gly Leu Pro Leu His
370 375 380
Leu Asp Ser Val Asp Ala Val Tyr Glu Arg Thr Ser Asp His Lys Ile
385 390 395 400
Val Phe Phe Lys Gly Asp Arg Tyr Trp Val Phe Lys Asp Asn Asn Val

```
                405                 410                 415
Glu Glu Gly Tyr Pro Arg Pro Val Ser Asp Phe Ser Leu Pro Pro Gly
            420                 425                 430
Gly Ile Asp Ala Ala Phe Ser Trp Ala His Asn Asp Arg Thr Tyr Phe
        435                 440                 445
Phe Lys Asp Gln Leu Tyr Trp Arg Tyr Asp Asp His Thr Arg His Met
    450                 455                 460
Asp Pro Gly Tyr Pro Ala Gln Ser Pro Leu Trp Arg Gly Val Pro Ser
465                 470                 475                 480
Thr Leu Asp Asp Ala Met Arg Trp Ser Asp Gly Ala Ser Tyr Phe Phe
                485                 490                 495
Arg Gly Gln Glu Tyr Trp Lys Val Leu Asp Gly Glu Leu Glu Val Ala
            500                 505                 510
Pro Gly Tyr Pro Gln Ser Thr Ala Arg Asp Trp Leu Val Cys Gly Asp
        515                 520                 525
Ser Gln Ala Asp Gly Ser Val Ala Ala Gly Val Asp Ala Ala Glu Gly
    530                 535                 540
Pro Arg Ala Pro Pro Gly Gln His Asp Gln Ser Arg Ser Glu Asp Gly

545                 550                 555                 560
Tyr Glu Val Cys Ser Cys Thr Ser Gly Ala Ser Ser Pro Pro Gly Ala
                565                 570                 575
Pro Gly Pro Leu Val Ala Ala Thr Met Leu Leu Leu Leu Pro Pro Leu
            580                 585                 590
Ser Pro Gly Ala Leu Trp Thr Ala Ala Gln Ala Leu Thr Leu
        595                 600                 605
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<210> 144
<211> 478
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-17

<400> 144

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

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Lys Gly Lys Tyr Phe Trp Arg Leu Thr Arg Asp Arg His Leu Val Ser
225                 230                 235                 240
Leu Gln Pro Ala Gln Met His Arg Phe Trp Arg Gly Leu Pro Leu His
                245                 250                 255
Leu Asp Ser Val Asp Ala Val Tyr Glu Arg Thr Ser Asp His Lys Ile
            260                 265                 270
Val Phe Phe Lys Gly Asp Arg Tyr Trp Val Phe Lys Asp Asn Asn Val
        275                 280                 285
Glu Glu Gly Tyr Pro Arg Pro Val Ser Asp Phe Ser Leu Pro Pro Gly
    290                 295                 300
Gly Ile Asp Ala Ala Phe Ser Trp Ala His Asn Asp Arg Thr Tyr Phe
305                 310                 315                 320
Phe Lys Asp Gln Leu Tyr Trp Arg Tyr Asp Asp His Thr Arg His Met
                325                 330                 335
Asp Pro Gly Tyr Pro Ala Gln Ser Pro Leu Trp Arg Gly Val Pro Ser
            340                 345                 350
Thr Leu Asp Asp Ala Met Arg Trp Ser Asp Gly Ala Ser Tyr Phe Phe
        355                 360                 365
Arg Gly Gln Glu Tyr Trp Lys Val Leu Asp Gly Glu Leu Glu Val Ala
    370                 375                 380
Pro Gly Tyr Pro Gln Ser Thr Ala Arg Asp Trp Leu Val Cys Gly Asp
385                 390                 395                 400
Ser Gln Ala Asp Gly Ser Val Ala Ala Gly Val Asp Ala Ala Glu Gly
                405                 410                 415
Pro Arg Ala Pro Pro Gly Gln His Asp Gln Ser Arg Ser Glu Asp Gly
            420                 425                 430
Tyr Glu Val Cys Ser Cys Thr Ser Gly Ala Ser Ser Pro Pro Gly Ala
        435                 440                 445
Pro Gly Pro Leu Val Ala Ala Thr Met Leu Leu Leu Leu Pro Pro Leu
    450                 455                 460
Ser Pro Gly Ala Leu Trp Thr Ala Ala Gln Ala Leu Thr Leu
465                 470                 475
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<210> 145
<211> 3262
<212> DNA
<213> 現代人

<220>
<223> MMP-19

<400> 145

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gctcccagaa atctcaggtc agaggcacgg acagcctctg gagctctcgt ctggtgggac 120
catgaactgc cagcagctgt ggctgggctt cctactcccc atgacagtct caggccgggt 180
cctggggctt gcagaggtgg cgcccgtgga ctacctgtca caatatgggt acctacagaa 240
gcctctagaa ggatctaata acttcaagcc agaagatatc accgaggctc tgagagcttt 300
tcaggaagca tctgaacttc cagtctcagg tcagctggat gatgccacaa gggcccgcat 360
gaggcagcct cgttgtggcc tagaggatcc cttcaaccag aagaccctta aatacctgtt 420
gctgggccgc tggagaaaga agcacctgac tttccgcatc ttgaacctgc cctccaccct 480
tccaccccac acagcccggg cagccctgcg tcaagccttc caggactgga gcaatgtggc 540
tcccttgacc ttccaagagg tgcaggctgg tgcggctgac atccgcctct ccttccatgg 600
ccgccaaagc tcgtactgtt ccaatacttt tgatgggcct gggagagtcc tggcccatgc 660
cgacatccca gagctgggca gtgtgcactt cgacgaagac gagttctgga ctgaggggac 720
ctaccgtggg gtgaacctgc gcatcattgc agcccatgaa gtgggccatg ctctggggct 780
tgggcactcc cgatattccc aggccctcat ggccccagtc tacgagggct accggcccca 840
ctttaagctg cacccagatg atgtggcagg gatccaggct ctctatggca agaagagtcc 900
agtgataagg gatgaggaag aagaagagac agagctgccc actgtgcccc cagtgcccac 960
agaacccagt cccatgccag acccttgcag tagtgaactg gatgccatga tgctggggcc 1020
ccgtgggaag acctatgctt tcaaggggga ctatgtgtgg actgtatcag attcaggacc 1080
gggccccttg ttccgagtgt ctgccctttg ggaggggctc cccggaaacc tggatgctgc 1140
tgtctactcg cctcgaacac aatggattca cttctttaag ggagacaagg tgtggcgcta 1200
cattaatttc aagatgtctc ctggcttccc caagaagctg aatagggtag aacctaacct 1260
ggatgcagct ctctattggc ctctcaacca aaaggtgttc ctctttaagg gctccgggta 1320
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ctggcagtgg gacgagctag cccgaactga cttcagcagc taccccaaac caatcaaggg 1380
tttgtttacg ggagtgccaa accagccctc ggctgctatg agttggcaag atggccgagt 1440
ctacttcttc aagggcaaag tctactggcg cctcaaccag cagcttcgag tagagaaagg 1500
ctatcccaga aatatttccc acaactggat gcactgtcgt ccccggacta tagacactac 1560
cccatcaggt gggaatacca ctccctcagg tacgggcata accttggata ccactctctc 1620
agccacagaa accacgtttg aatactgact gctcacccac agacacaatc ttggacatta 1680
acccctgagg ctccaccacc cacccttttca tttccccccc agaagcctaa ggcctaatag 1740
ctgaatgaaa tacctgtctg ctcagtagaa ccttgcaggt gctgtagcag gcgcaagacc 1800
gtagatctca ggcctctaac acttccaact ccagccacca ctttcctgtg cattttcact 1860
cctgagaagt gctcccctaa ctcagatccc ctaacttaga tttggccccc aactccattt 1920
cctgtctgtc ttagacagcc cttccaactg tgtcatctct tctctggagg tcaatggtgg 1980
agggagatgc ctgggtcctg ttcttcctac ataaaatgca agaaaacagc atggccagta 2040
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agctaattaa ccttgttgaa tctcagattc cccatttgca acattaggtt aagaccagta 2160
ctgcaggatt gttgcactaa atgaaatact gtatgtgaag tgcctggcac agtgtctggt 2220
acatttgtgt ttaataaaag ctaactccat gttcataaga gaggactgaa cagctcttcc 2280
tctagctgtc tggctgtata actcttacag tagtctgtat aataagggca tctctattag 2340
atctttaggg gacagaggat ttgtcaagat ggttagctct ttgttttggg gtgcagagaa 2400
agaaaagagc agcaacagca gaggctggac tccctggttc agtatttaat gccattttat 2460
tcacatgctc ccatgttctc cctccctccc attgtagcct tgctgcccag gggagggata 2520
tgtcttcctt tatgcatctg ggaaaccagg aacagaccct gcgcaggaga gtcagagggg 2580
gaagagttag aatgggtcag tggctggaac aaagttctgg ttaaggagga aattagtgcc 2640
acccacggtg agaagcagag aaggcacttg catcctatgc agccctgaag accaggctcc 2700
tttgggcaaa aggcaagact ctggcaggtg ggtcaatgct ctctccttgg agcaagaagc 2760
cagcttttgg ggaaggcagg tcctgaggca ggcactgccc tgtggtcttc cccaggttga 2820
ggagagaagt ggaagcccca tggaagacag tgctcccagc tgaggtagga ggcggaggtg 2880
ggggtggggg tagtttaagc ctatggggcc caggggggaaa ggccaaacag aaacccaact 2940
acccccctaat gaagggcctg gaggttgggg tatcttggag ctcctcagag cccttcttcc 3000
catcaaaaag gtatcaaatg ccttggaagc tccctgatcc tacaaaacaa aaaaatgctt 3060
atttttacca ctgtgaggca agctgaggtg aacatttaaa aggctatttc aagacgaggt 3120
gcggtggcta taatcctagc actttgggag gctgaagcag gaggatcact tgagcccagg 3180
agttcaagac cagcttgggc aacataggga gaccctgtct ctgcaaaaaa ataaaaacga 3240
atacataaaa attaaaaaaa aa 3262

<210> 146
<211> 508
<212> PRT
<213> 現代人

<220>
<223> MMP-19前驅體

<400> 146

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

```
Leu Ala His Ala Asp Ile Pro Glu Leu Gly Ser Val His Phe Asp Glu
            180                 185                 190
Asp Glu Phe Trp Thr Glu Gly Thr Tyr Arg Gly Val Asn Leu Arg Ile
        195                 200                 205
Ile Ala Ala His Glu Val Gly His Ala Leu Gly Leu Gly His Ser Arg
    210                 215                 220
Tyr Ser Gln Ala Leu Met Ala Pro Val Tyr Glu Gly Tyr Arg Pro His

225                 230                 235                 240
Phe Lys Leu His Pro Asp Asp Val Ala Gly Ile Gln Ala Leu Tyr Gly
                245                 250                 255
Lys Lys Ser Pro Val Ile Arg Asp Glu Glu Glu Glu Glu Thr Glu Leu
            260                 265                 270
Pro Thr Val Pro Pro Val Pro Thr Glu Pro Ser Pro Met Pro Asp Pro
        275                 280                 285
Cys Ser Ser Glu Leu Asp Ala Met Met Leu Gly Pro Arg Gly Lys Thr
    290                 295                 300
Tyr Ala Phe Lys Gly Asp Tyr Val Trp Thr Val Ser Asp Ser Gly Pro
305                 310                 315                 320
Gly Pro Leu Phe Arg Val Ser Ala Leu Trp Glu Gly Leu Pro Gly Asn
                325                 330                 335
Leu Asp Ala Ala Val Tyr Ser Pro Arg Thr Gln Trp Ile His Phe Phe
            340                 345                 350
Lys Gly Asp Lys Val Trp Arg Tyr Ile Asn Phe Lys Met Ser Pro Gly
        355                 360                 365
Phe Pro Lys Lys Leu Asn Arg Val Glu Pro Asn Leu Asp Ala Ala Leu
    370                 375                 380
Tyr Trp Pro Leu Asn Gln Lys Val Phe Leu Phe Lys Gly Ser Gly Tyr
385                 390                 395                 400
Trp Gln Trp Asp Glu Leu Ala Arg Thr Asp Phe Ser Ser Tyr Pro Lys
                405                 410                 415
Pro Ile Lys Gly Leu Phe Thr Gly Val Pro Asn Gln Pro Ser Ala Ala
            420                 425                 430
Met Ser Trp Gln Asp Gly Arg Val Tyr Phe Phe Lys Gly Lys Val Tyr
        435                 440                 445
Trp Arg Leu Asn Gln Gln Leu Arg Val Glu Lys Gly Tyr Pro Arg Asn
    450                 455                 460
Ile Ser His Asn Trp Met His Cys Arg Pro Arg Thr Ile Asp Thr Thr
465                 470                 475                 480
Pro Ser Gly Gly Asn Thr Thr Pro Ser Gly Thr Gly Ile Thr Leu Asp
                485                 490                 495
Thr Thr Leu Ser Ala Thr Glu Thr Thr Phe Glu Tyr
            500                 505
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<210> 147
<211> 411
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-19

<400> 147

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

```
                85                  90                  95
Glu Phe Trp Thr Glu Gly Thr Tyr Arg Gly Val Asn Leu Arg Ile Ile
            100                 105                 110
Ala Ala His Glu Val Gly His Ala Leu Gly Leu Gly His Ser Arg Tyr
        115                 120                 125
Ser Gln Ala Leu Met Ala Pro Val Tyr Glu Gly Tyr Arg Pro His Phe
    130                 135                 140
Lys Leu His Pro Asp Asp Val Ala Gly Ile Gln Ala Leu Tyr Gly Lys
145                 150                 155                 160
Lys Ser Pro Val Ile Arg Asp Glu Glu Glu Glu Glu Thr Glu Leu Pro
                165                 170                 175
Thr Val Pro Pro Val Pro Thr Glu Pro Ser Pro Met Pro Asp Pro Cys
            180                 185                 190
Ser Ser Glu Leu Asp Ala Met Met Leu Gly Pro Arg Gly Lys Thr Tyr
        195                 200                 205
Ala Phe Lys Gly Asp Tyr Val Trp Thr Val Ser Asp Ser Gly Pro Gly
    210                 215                 220
Pro Leu Phe Arg Val Ser Ala Leu Trp Glu Gly Leu Pro Gly Asn Leu
225                 230                 235                 240
Asp Ala Ala Val Tyr Ser Pro Arg Thr Gln Trp Ile His Phe Phe Lys
                245                 250                 255
Gly Asp Lys Val Trp Arg Tyr Ile Asn Phe Lys Met Ser Pro Gly Phe
            260                 265                 270
Pro Lys Lys Leu Asn Arg Val Glu Pro Asn Leu Asp Ala Ala Leu Tyr
        275                 280                 285
Trp Pro Leu Asn Gln Lys Val Phe Leu Phe Lys Gly Ser Gly Tyr Trp
    290                 295                 300
Gln Trp Asp Glu Leu Ala Arg Thr Asp Phe Ser Ser Tyr Pro Lys Pro
305                 310                 315                 320
Ile Lys Gly Leu Phe Thr Gly Val Pro Asn Gln Pro Ser Ala Ala Met
                325                 330                 335
Ser Trp Gln Asp Gly Arg Val Tyr Phe Phe Lys Gly Lys Val Tyr Trp
            340                 345                 350
Arg Leu Asn Gln Gln Leu Arg Val Glu Lys Gly Tyr Pro Arg Asn Ile
        355                 360                 365
Ser His Asn Trp Met His Cys Arg Pro Arg Thr Ile Asp Thr Thr Pro
    370                 375                 380
Ser Gly Gly Asn Thr Thr Pro Ser Gly Thr Gly Ile Thr Leu Asp Thr
385                 390                 395                 400
Thr Leu Ser Ala Thr Glu Thr Thr Phe Glu Tyr
                405                 410
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<210> 148
<211> 1674
<212> DNA
<213> 現代人

<220>
<223> MMP-20

<400> 148
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caactaccgc ctcgcacagg cgtatcttga caaatattac acaaataaag aaggacacca 180
gattggtgag atggttgcaa gaggaagcaa ttccatgata aggaagatta aggagctaca 240
agcgttcttt ggcctccaag tcaccgggaa gttagaccag accacaatga acgtgatcaa 300
gaagcctcgc tgtggagttc ctgatgtggc caattatcgc ctcttccctg gtgaacccaa 360
atggaaaaaa aatactttga catacagaat atctaaatac acaccttcca tgagttctgt 420
cgaggtggac aaagcagtgg agatggcctt gcaggcctgg agtagcgccg tccctctgag 480
ctttgtcaga ataaactcag gagaagcgga tattatgata tcttttgaaa atggagatca 540
cggggattcc tatccattcg atgggcctcg ggggactcta gcccatgcat ttgctcctgg 600
agaaggcctg ggaggagata cacatttcga caatcctgag aagtggacta tgggaacgaa 660
tggttttaat ttgtttaccg ttgctgctca tgaatttggc catgccctgg gcctggccca 720
ttccacagac ccatcagcac tgatgtaccc aacttataag tacaagaatc cctatggatt 780

ccacctcccc aaagatgatg tgaaagggat ccaggcatta tacggacctc ggaaagtatt 840
cctggggaag cccactctgc cccatgcccc ccatcacaag ccatccatcc ctgacctctg 900
tgactccagc tcatcctttg acgctgtgac aatgctgggg aaggagctcc tgctcttcaa 960
ggaccggatt ttctggagac ggcaggttca cttgcggaca ggaattcggc ccagcactat 1020
taccagctcc ttcccccagc tcatgtccaa tgtggatgca gcttacgaag tggctgagag 1080
gggcactgct tacttcttca aaggtcccca ctactggata acaagaggat tccaaatgca 1140
aggtcctcct cggactattt atgactttgg atttccaagg cacgtgcagc aaatagatgc 1200
tgctgtctac ctcagggagc cacagaagac ccttttcttt gtgggagatg aatactacag 1260
ctacgacgaa aggaaaagga aaatggaaaa agactatcca aagaatactg aagaagaatt 1320
ttcaggagta aatggccaaa tcgatgctgc tgtagaatta aatggctaca tttacttctt 1380
ttcaggacca aaaacataca agtatgacac agagaaggaa gatgtggtta gtgtggtgaa 1440
atctagttcc tggattggtt gctaaataga aaagcctagt cttctcaagc aatgaggatg 1500
actacaagca gcctctaact ggatcttaag gactaaagca gaatgtagga gagggattct 1560
tccaaaggcc ttcaaatcaa attagaattc actgagaata ataatacttc caatttttt 1620
catagttgta taatcagaat ttcaatccac attagaaaag tttttatatg ggca 1674

<210> 149
<211> 483
<212> PRT
<213> 現代人

<220>
<223> MMP-20前驅體

<400> 149
Met Lys Val Leu Pro Ala Ser Gly Leu Ala Val Phe Leu Ile Met Ala
 1   5   10   15
Leu Lys Phe Ser Thr Ala Ala Pro Ser Leu Val Ala Ala Ser Pro Arg
            20   25   30
Thr Trp Arg Asn Asn Tyr Arg Leu Ala Gln Ala Tyr Leu Asp Lys Tyr
        35   40   45
Tyr Thr Asn Lys Glu Gly His Gln Ile Gly Glu Met Val Ala Arg Gly
    50   55   60

Ser Asn Ser Met Ile Arg Lys Ile Lys Glu Leu Gln Ala Phe Phe Gly
65   70   75   80
Leu Gln Val Thr Gly Lys Leu Asp Gln Thr Thr Met Asn Val Ile Lys
                85   90   95
Lys Pro Arg Cys Gly Val Pro Asp Val Ala Asn Tyr Arg Leu Phe Pro
            100   105   110
Gly Glu Pro Lys Trp Lys Lys Asn Thr Leu Thr Tyr Arg Ile Ser Lys
        115   120   125
Tyr Thr Pro Ser Met Ser Ser Val Glu Val Asp Lys Ala Val Glu Met
    130   135   140
Ala Leu Gln Ala Trp Ser Ser Ala Val Pro Leu Ser Phe Val Arg Ile
145   150   155   160
Asn Ser Gly Glu Ala Asp Ile Met Ile Ser Phe Glu Asn Gly Asp His
                165   170   175
Gly Asp Ser Tyr Pro Phe Asp Gly Pro Arg Gly Thr Leu Ala His Ala
            180   185   190
Phe Ala Pro Gly Glu Gly Leu Gly Gly Asp Thr His Phe Asp Asn Pro
        195   200   205
Glu Lys Trp Thr Met Gly Thr Asn Gly Phe Asn Leu Phe Thr Val Ala
    210   215   220
Ala His Glu Phe Gly His Ala Leu Gly Leu Ala His Ser Thr Asp Pro
225   230   235   240
Ser Ala Leu Met Tyr Pro Thr Tyr Lys Tyr Lys Asn Pro Tyr Gly Phe
                245   250   255
His Leu Pro Lys Asp Asp Val Lys Gly Ile Gln Ala Leu Tyr Gly Pro
            260   265   270
Arg Lys Val Phe Leu Gly Lys Pro Thr Leu Pro His Ala Pro His His
        275   280   285
Lys Pro Ser Ile Pro Asp Leu Cys Asp Ser Ser Ser Ser Phe Asp Ala
    290   295   300
Val Thr Met Leu Gly Lys Glu Leu Leu Leu Phe Lys Asp Arg Ile Phe

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305                 310                 315                 320
Trp Arg Arg Gln Val His Leu Arg Thr Gly Ile Arg Pro Ser Thr Ile
                325                 330                 335
Thr Ser Ser Phe Pro Gln Leu Met Ser Asn Val Asp Ala Ala Tyr Glu
            340                 345                 350
Val Ala Glu Arg Gly Thr Ala Tyr Phe Phe Lys Gly Pro His Tyr Trp
        355                 360                 365
Ile Thr Arg Gly Phe Gln Met Gln Gly Pro Pro Arg Thr Ile Tyr Asp
    370                 375                 380
Phe Gly Phe Pro Arg His Val Gln Gln Ile Asp Ala Ala Val Tyr Leu
385                 390                 395                 400
Arg Glu Pro Gln Lys Thr Leu Phe Phe Val Gly Asp Glu Tyr Tyr Ser

                405                 410                 415
Tyr Asp Glu Arg Lys Arg Lys Met Glu Lys Asp Tyr Pro Lys Asn Thr
            420                 425                 430
Glu Glu Glu Phe Ser Gly Val Asn Gly Gln Ile Asp Ala Ala Val Glu
        435                 440                 445
Leu Asn Gly Tyr Ile Tyr Phe Phe Ser Gly Pro Lys Thr Tyr Lys Tyr
    450                 455                 460
Asp Thr Glu Lys Glu Asp Val Val Ser Val Val Lys Ser Ser Ser Trp
465                 470                 475                 480
Ile Gly Cys
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<210> 150
<211> 373
<212> PRT
<213> 現代人

<220>
<223> 成熟MMP-20

<400> 150

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Tyr Arg Leu Phe Pro Gly Glu Pro Lys Trp Lys Lys Asn Thr Leu Thr
 1                5                  10                  15
Tyr Arg Ile Ser Lys Tyr Thr Pro Ser Met Ser Ser Val Glu Val Asp
            20                  25                  30
Lys Ala Val Glu Met Ala Leu Gln Ala Trp Ser Ser Ala Val Pro Leu
        35                  40                  45
Ser Phe Val Arg Ile Asn Ser Gly Glu Ala Asp Ile Met Ile Ser Phe
    50                  55                  60
Glu Asn Gly Asp His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Arg Gly
65                  70                  75                  80
Thr Leu Ala His Ala Phe Ala Pro Gly Glu Gly Leu Gly Gly Asp Thr
                85                  90                  95
His Phe Asp Asn Ala Glu Lys Trp Thr Met Gly Thr Asn Gly Phe Asn
            100                 105                 110
Leu Phe Thr Val Ala Ala His Glu Phe Gly His Ala Leu Gly Leu Ala
        115                 120                 125
His Ser Thr Asp Pro Ser Ala Leu Met Tyr Pro Thr Tyr Lys Tyr Lys
    130                 135                 140
Asn Pro Tyr Gly Phe His Leu Pro Lys Asp Asp Val Lys Gly Ile Gln
145                 150                 155                 160
Ala Leu Tyr Gly Pro Arg Lys Val Phe Leu Gly Lys Pro Thr Leu Pro
                165                 170                 175
His Ala Pro His His Lys Pro Ser Ile Pro Asp Leu Cys Asp Ser Ser
            180                 185                 190
Ser Ser Phe Asp Ala Val Thr Met Leu Gly Lys Glu Leu Leu Leu Phe
        195                 200                 205
Lys Asp Arg Ile Phe Trp Arg Arg Gln Val His Leu Arg Thr Gly Ile
    210                 215                 220
Arg Pro Ser Thr Ile Thr Ser Ser Phe Pro Gln Leu Met Ser Asn Val
225                 230                 235                 240
```

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Asp Ala Ala Tyr Glu Val Ala Glu Arg Gly Thr Ala Tyr Phe Phe Lys
                245                 250                 255
Gly Pro His Tyr Trp Ile Thr Arg Gly Phe Gln Met Gln Gly Pro Pro
            260                 265                 270
Arg Thr Ile Tyr Asp Phe Gly Phe Pro Arg His Val Gln Gln Ile Asp
        275                 280                 285
Ala Ala Val Tyr Leu Arg Glu Pro Gln Lys Thr Leu Phe Phe Val Gly
    290                 295                 300
Asp Glu Tyr Tyr Ser Tyr Asp Glu Arg Lys Arg Lys Met Glu Lys Asp
305                 310                 315                 320
Tyr Pro Lys Asn Thr Glu Glu Glu Phe Ser Gly Val Asn Gly Gln Ile

                325                 330                 335
Asp Ala Ala Val Glu Leu Asn Gly Tyr Ile Tyr Phe Phe Ser Gly Pro
            340                 345                 350
Lys Thr Tyr Lys Tyr Asp Thr Glu Lys Glu Asp Val Val Ser Val Val
        355                 360                 365
Lys Ser Ser Ser Trp
    370
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<210> 151
<211> 3127
<212> DNA
<213> 爪蟾

<220>
<223> XMMP

<400> 151

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atcatatgag gccaccatgc cttctatcaa gcttctggtt tggtgctgct tgtgtgtgat 120
atcccccagg ctgtgccatt ctgagaagct cttccacagt cgggatcggt cagaccttca 180
gccctcagca attgaacagg cagaactggt caaggatatg ctctctgccc agcaattcct 240
ggcaaaatat gggtggacac aaccagttat ttgggatcca tcaagtacca atgaaaacga 300
acctctaaaa gatttcagtc tgatgcaaga gggagtttgt aacccaaggc aagaagtggc 360
tgagccaaca aaaagccccc aattcattga cgcgctcaaa aagtttcaga agctaaacaa 420
cttgccagtg acaggaaccc ttgatgatgc caccatcaac gccatgaaca agccacggtg 480
cggcgtgcca gacaaccaaa tggcaaagaa agagacggag aaaccgacag cagcacagtc 540
acttgaaaac aagactaagg attctgagaa tgttactcaa caaaacccag acccccccaa 600
gattcggagg aagaggttct tagatatgtt aatgtactca aacaagtaca gggaagaaca 660
ggaggcgctt cagaaatcca caggcaaagt cttcaccaaa aagctgctga aatggagaat 720
gattggagaa ggctacagca atcagctttc catcaacgag caaagatatg tcttcaggct 780
ggctttccgc atgtggagtg aagtcatgcc actggacttt gaagaagata acacctcccc 840

tctatcccaa attgatatca aacttggatt cggacgaggt cgccatttag gctgtagccg 900
ggcattcgat ggctctgggc aggagttcgc ccacgcttgg tttctggggg acattcactt 960
tgacgacgat gaacatttta ctgctcccag tagtgagcat gggattagtc tgctgaaggt 1020
ggcagcccat gaaattggcc atgttcttgg attatctcac atccacaggg tgggatcaat 1080
aatgcagccc aattacattc cgcaggactc tggctttgag ctggacttgt ctgacaggag 1140
agccatacag aacctatacg gctcatgtga aggccccttt gacacagcgt ttgactggat 1200
ctataaagag aagaaccaat acggggagct tgttgttcga tacaacacct actttttttcg 1260
caacagctgg tactggatgt atgagaatcg gagcaacagg acccgatacg gggatccact 1320
tgcaattgcc aacggctggc acggaattcc cgtacagaat attgatgctt ttgttcatgt 1380
ctggacctgg acaagagacg cctcctactt ttttaaaggt actcagtact ggcgctacga 1440
tagtgaaaat gacaaagcct atgctgaaga tgcacaggga aagagctacc ctcgcctaat 1500
ctcagaaggg tttcctggaa tcccaagccc catcaatgct gcctattttg acaggagaag 1560
acagtacatt tacttcttca gggactccca ggtttttgcc tttgatatca acagaaacag 1620
agttgcgcca gacttcccca aaagaatctt ggacttttttc ccagccgtcg cagcaaacaa 1680
tcaccccaag ggcaacatag acgtggccta ttattcctac acatacagct ccttatttct 1740
cttcaaagga aaagagtttt ggaaagtcgt cagcgacaag gacaggaggc aaaacccgtc 1800
tcttccatac aatggattgt tccccagaag agcaatatct cagcagtggt ttgatatctg 1860
caacgtacac ccttcattgc tgaaaatttg atttgcccaa aatagcccag cctgaataat 1920
agtcatgcac tgaggttttc taaagtcttc ttctgccctt gtcccacctg tgcactcacc 1980
tgtagcatgg acagcccaaa atagcccagc ctgaataata gtcatccact gaggttttct 2040
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aaagtcttct tctgcccttg tcccacctgt gcactcacct gtagcatgga catactccca 2100
gatgattgac ctttctacaa ctctacttcc agagtgtcca tgtctaagaa tttcttagta 2160
aaagagttga ctagactatt gtattgtttc ctaaacgcag ccataaagga gctccaacag 2220
cacaagattc caggaagcca ttccctcaat tcataaagga caggagtgtg cgctccaata 2280
atggctaata tatgtacatt attaaacaca agaatgggag aaatccattc gagaaaaaag 2340
tatttattag ttgagatgaa tcccaatttg ggaagattga gagttgaaca aggatcctta 2400
ttatgtatct gcttaaatgt tttatttatc cattttgct tgagtttctg cttcgattag 2460
gaagtattgg agcatgattc ataatgattg aactgatgtg aacttctcca gaatgcactt 2520
ctaaacacaa acataatact gatggaggag gaataattgt atggggatag aggctccata 2580
gaaggcaaac tttaaggctg caataatatc gtggtcaaat atgtgctttc tcattggtgg 2640
taaaggttta ttgaaggccc tttgcttctt ctgctcaaca gtggaccatg tgctcaaagt 2700
aagctcccta cacaatggtt gatggaaatg tgactggtct gcatgaagcc ctcaacccaa 2760
ctgaacaact gtgggatgaa ttggaccatg gattaaggga gccaggccgg atcattgaag 2820
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ctctatagct cttaaaggcc gtgcatgttt gatttagaaa gatacacttg atgttattac 3060
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aaaaaaa 3127

<210> 152
<211> 604
<212> PRT
<213> 爪蟾

<220>
<223> XMMP前驅體

<400> 152

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

```
Phe Leu Gly Asp Ile His Phe Asp Asp Asp Glu His Phe Thr Ala Pro
    290                 295                 300
Ser Ser Glu His Gly Ile Ser Leu Leu Lys Val Ala Ala His Glu Ile
305                 310                 315                 320
Gly His Val Leu Gly Leu Ser His Ile His Arg Val Gly Ser Ile Met
                325                 330                 335
Gln Pro Asn Tyr Ile Pro Gln Asp Ser Gly Phe Glu Leu Asp Leu Ser
            340                 345                 350
Asp Arg Arg Ala Ile Gln Asn Leu Tyr Gly Ser Cys Glu Gly Pro Phe
        355                 360                 365
Asp Thr Ala Phe Asp Trp Ile Tyr Lys Glu Lys Asn Gln Tyr Gly Glu
    370                 375                 380
Leu Val Val Arg Tyr Asn Thr Tyr Phe Phe Arg Asn Ser Trp Tyr Trp
385                 390                 395                 400
Met Tyr Glu Asn Arg Ser Asn Arg Thr Arg Tyr Gly Asp Pro Leu Ala
                405                 410                 415
Ile Ala Asn Gly Trp His Gly Ile Pro Val Gln Asn Ile Asp Ala Phe
            420                 425                 430
Val His Val Trp Thr Trp Thr Arg Asp Ala Ser Tyr Phe Phe Lys Gly
        435                 440                 445
Thr Gln Tyr Trp Arg Tyr Asp Ser Glu Asn Asp Lys Ala Tyr Ala Glu
    450                 455                 460
Asp Ala Gln Gly Lys Ser Tyr Pro Arg Leu Ile Ser Glu Gly Phe Pro
465                 470                 475                 480
Gly Ile Pro Ser Pro Ile Asn Ala Ala Tyr Phe Asp Arg Arg Arg Gln
                485                 490                 495
Tyr Ile Tyr Phe Phe Arg Asp Ser Gln Val Phe Ala Phe Asp Ile Asn
            500                 505                 510
Arg Asn Arg Val Ala Pro Asp Phe Pro Lys Arg Ile Leu Asp Phe Phe
        515                 520                 525
Pro Ala Val Ala Ala Asn Asn His Pro Lys Gly Asn Ile Asp Val Ala
    530                 535                 540
Tyr Tyr Ser Tyr Thr Tyr Ser Ser Leu Phe Leu Phe Lys Gly Lys Glu
545                 550                 555                 560
Phe Trp Lys Val Val Ser Asp Lys Asp Arg Arg Gln Asn Pro Ser Leu
                565                 570                 575
Pro Tyr Asn Gly Leu Phe Pro Arg Arg Ala Ile Ser Gln Gln Trp Phe
            580                 585                 590
Asp Ile Cys Asn Val His Pro Ser Leu Leu Lys Ile
        595                 600
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<210> 153
<211> 420
<212> PRT
<213> 爪蟾

<220>
<223> 成熟XMMP

<400> 153

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Phe Leu Asp Met Leu Met Tyr Ser Asn Lys Tyr Arg Glu Glu Gln Glu
 1               5                  10                  15
Ala Leu Gln Lys Ser Thr Gly Lys Val Phe Thr Lys Lys Leu Leu Lys
            20                  25                  30
Trp Arg Met Ile Gly Glu Gly Tyr Ser Asn Gln Leu Ser Ile Asn Glu
        35                  40                  45
Gln Arg Tyr Val Phe Arg Leu Ala Phe Arg Met Trp Ser Glu Val Met
    50                  55                  60
Pro Leu Asp Phe Glu Glu Asp Asn Thr Ser Pro Leu Ser Gln Ile Asp
65                  70                  75                  80
Ile Lys Leu Gly Phe Gly Arg Gly Arg His Leu Gly Cys Ser Arg Ala
                85                  90                  95
Phe Asp Gly Ser Gly Gln Glu Phe Ala His Ala Trp Phe Leu Gly Asp
            100                 105                 110
```

```
Ile His Phe Asp Asp Asp Glu His Phe Thr Ala Pro Ser Ser Glu His
        115                 120                 125
Gly Ile Ser Leu Leu Lys Val Ala Ala His Glu Ile Gly His Val Leu
    130                 135                 140
Gly Leu Ser His Ile His Arg Val Gly Ser Ile Met Gln Pro Asn Tyr
145                 150                 155                 160
Ile Pro Gln Asp Ser Gly Phe Glu Leu Asp Leu Ser Asp Arg Arg Ala
                165                 170                 175
Ile Gln Asn Leu Tyr Gly Ser Cys Glu Gly Pro Phe Asp Thr Ala Phe
            180                 185                 190
Asp Trp Ile Tyr Lys Glu Lys Asn Gln Tyr Gly Glu Leu Val Val Arg
        195                 200                 205
Tyr Asn Thr Tyr Phe Phe Arg Asn Ser Trp Tyr Trp Met Tyr Glu Asn
    210                 215                 220
Arg Ser Asn Arg Thr Arg Tyr Gly Asp Pro Leu Ala Ile Ala Asn Gly
225                 230                 235                 240
Trp His Gly Ile Pro Val Gln Asn Ile Asp Ala Phe Val His Val Trp
                245                 250                 255
Thr Trp Thr Arg Asp Ala Ser Tyr Phe Phe Lys Gly Thr Gln Tyr Trp
            260                 265                 270
Arg Tyr Asp Ser Glu Asn Asp Lys Ala Tyr Ala Glu Asp Ala Gln Gly
        275                 280                 285
Lys Ser Tyr Pro Arg Leu Ile Ser Glu Gly Phe Pro Gly Ile Pro Ser
    290                 295                 300
Pro Ile Asn Ala Ala Tyr Phe Asp Arg Arg Arg Gln Tyr Ile Tyr Phe
305                 310                 315                 320
Phe Arg Asp Ser Gln Val Phe Ala Phe Asp Ile Asn Arg Asn Arg Val
                325                 330                 335
Ala Pro Asp Phe Pro Lys Arg Ile Leu Asp Phe Phe Pro Ala Val Ala
            340                 345                 350
Ala Asn Asn His Pro Lys Gly Asn Ile Asp Val Ala Tyr Tyr Ser Tyr
        355                 360                 365
Thr Tyr Ser Ser Leu Phe Leu Phe Lys Gly Lys Glu Phe Trp Lys Val
    370                 375                 380
Val Ser Asp Lys Asp Arg Arg Gln Asn Pro Ser Leu Pro Tyr Asn Gly
385                 390                 395                 400
Leu Phe Pro Arg Arg Ala Ile Ser Gln Gln Trp Phe Asp Ile Cys Asn
                405                 410                 415
Val His Pro Ser
            420
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<210> 154
<211> 1694
<212> DNA
<213> 現代人

<220>
<223> 肝素酶

<400> 154

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gggcaccagc caagatgctg ctgcgctcga agcctgcgct gccgccgccg ctgatgctgc 60
tgctcctggg gccgctgggt cccctctccc ctggcgccct gccccgacct gcgcaagcac 120
aggacgtcgt ggacctggac ttcttcaccc aggagccgct gcacctggtg agcccctcgt 180
tcctgtccgt caccattgac gccaacctgg ccacggaccc gcggttcctc atcctcctgg 240
gttctccaaa gcttcgtacc ttggccagag gcttgtctcc tgcgtacctg aggtttggtg 300
gcaccaagac agacttccta attttcgatc ccaagaagga atcaaccttt gaagagagaa 360
gttactggca atctcaagtc aaccaggata tttgcaaata tggatccatc cctcctgatg 420
tggaggagaa gttacggttg gaatggccct accaggagca attgctactc cgagaacact 480
accagaaaaa gttcaagaac agcacctact caagaagctc tgtagatgtg ctatacactt 540
ttgcaaactg ctcaggactg gacttgatct ttggcctaaa tgcgttatta agaacagcag 600
atttgcagtg gaacagttct aatgctcagt tgctcctgga ctactgctct tccaaggggt 660
ataacatttc ttgggaacta ggcaatgaac ctaacagttt ccttaagaag gctgatattt 720
tcatcaatgg gtcgcagtta ggagaagatt ttattcaatt gcataaactt ctaagaaagt 780
ccaccttcaa aaatgcaaaa ctctatggtc ctgatgttgg tcagcctcga agaaagacgg 840
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```
ctaagatgct gaagagcttc ctgaaggctg gtggagaagt gattgattca gttacatggc 900
atcactacta tttgaatgga cggactgcta ccagggaaga ttttctaaac cctgatgtat 960
tggacatttt tatttcatct gtgcaaaaag ttttccaggt ggttgagagc accaggcctg 1020
gcaagaaggt ctggttagga gaaacaagct ctgcatatgg aggcggagcg cccttgctat 1080
ccgacacctt tgcagctggc tttatgtggc tggataaatt gggcctgtca gcccgaatgg 1140
gaatagaagt ggtgatgagg caagtattct ttggagcagg aaactaccat ttagtggatg 1200
aaaacttcga tcctttacct gattattggc tatctcttct gttcaagaaa ttggtgggca 1260
ccaaggtgtt aatggcaagc gtgcaaggtt caaagagaag gaagcttcga gtataccttc 1320
attgcacaaa cactgacaat ccaaggtata aagaaggaga tttaactctg tatgccataa 1380
acctccataa tgtcaccaag tacttgcggt tacctatcc ttttctaac aagcaagtgg 1440
ataaatacct tctaagacct ttgggacctc atggattact ttccaaatct gtccaactca 1500
atggtctaac tctaaagatg gtggatgatc aaaccttgcc acctttaatg gaaaaacctc 1560
tccggccagg aagttcactg ggcttgccag ctttctcata tagtttttt gtgataagaa 1620
atgccaaagt tgctgcttgc atctgaaaat aaaatatact agtcctgaca ctgaaaaaaa 1680
aaaaaaaaaa aaaa                                                  1694
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<210> 155
<211> 543
<212> PRT
<213> 現代人

<220>
<223> 肝素酶前驅體

<400> 155

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

305 310 315 320
Ser Ser Val Gln Lys Val Phe Gln Val Val Glu Ser Thr Arg Pro Gly
325 330 335
Lys Lys Val Trp Leu Gly Glu Thr Ser Ser Ala Tyr Gly Gly Gly Ala
340 345 350
Pro Leu Leu Ser Asp Thr Phe Ala Ala Gly Phe Met Trp Leu Asp Lys
355 360 365
Leu Gly Leu Ser Ala Arg Met Gly Ile Glu Val Val Met Arg Gln Val
370 375 380
Phe Phe Gly Ala Gly Asn Tyr His Leu Val Asp Glu Asn Phe Asp Pro
385 390 395 400
Leu Pro Asp Tyr Trp Leu Ser Leu Leu Phe Lys Lys Leu Val Gly Thr
405 410 415
Lys Val Leu Met Ala Ser Val Gln Gly Ser Lys Arg Arg Lys Leu Arg
420 425 430
Val Tyr Leu His Cys Thr Asn Thr Asp Asn Pro Arg Tyr Lys Glu Gly
435 440 445
Asp Leu Thr Leu Tyr Ala Ile Asn Leu His Asn Val Thr Lys Tyr Leu
450 455 460
Arg Leu Pro Tyr Pro Phe Ser Asn Lys Gln Val Asp Lys Tyr Leu Leu
465 470 475 480
Arg Pro Leu Gly Pro His Gly Leu Leu Ser Lys Ser Val Gln Leu Asn
485 490 495
Gly Leu Thr Leu Lys Met Val Asp Asp Gln Thr Leu Pro Pro Leu Met
500 505 510
Glu Lys Pro Leu Arg Pro Gly Ser Ser Leu Gly Leu Pro Ala Phe Ser
515 520 525
Tyr Ser Phe Phe Val Ile Arg Asn Ala Lys Val Ala Ala Cys Ile
530 535 540

<210> 156
<211> 460
<212> PRT
<213> 現代人

<220>
<223> 成熟肝素酶

<220>
<223> 肝素酶8 kDa 亞單位

<220>
<223> 肝素酶50 kDa 亞單位

<400> 156
Gln Asp Val Val Asp Leu Asp Phe Phe Thr Gln Glu Pro Leu His Leu
1 5 10 15
Val Ser Pro Ser Phe Leu Ser Val Thr Ile Asp Ala Asn Leu Ala Thr
20 25 30
Asp Pro Arg Phe Leu Ile Leu Leu Gly Ser Pro Lys Leu Arg Thr Leu
35 40 45
Ala Arg Gly Leu Ser Pro Ala Tyr Leu Arg Phe Gly Gly Thr Lys Thr
50 55 60
Asp Phe Leu Ile Phe Asp Pro Lys Lys Glu Lys Lys Phe Lys Asn Ser
65 70 75 80
Thr Tyr Ser Arg Ser Ser Val Asp Val Leu Tyr Thr Phe Ala Asn Cys
85 90 95
Ser Gly Leu Asp Leu Ile Phe Gly Leu Asn Ala Leu Leu Arg Thr Ala
100 105 110
Asp Leu Gln Trp Asn Ser Ser Asn Ala Gln Leu Leu Leu Asp Tyr Cys
115 120 125
Ser Ser Lys Gly Tyr Asn Ile Ser Trp Glu Leu Gly Asn Glu Pro Asn
130 135 140
Ser Phe Leu Lys Lys Ala Asp Ile Phe Ile Asn Gly Ser Gln Leu Gly

```
145                 150                 155                 160
Glu Asp Phe Ile Gln Leu His Lys Leu Leu Arg Lys Ser Thr Phe Lys
                165                 170                 175
Asn Ala Lys Leu Tyr Gly Pro Asp Val Gly Gln Pro Arg Arg Lys Thr
            180                 185                 190
Ala Lys Met Leu Lys Ser Phe Leu Lys Ala Gly Gly Glu Val Ile Asp
        195                 200                 205
Ser Val Thr Trp His His Tyr Tyr Leu Asn Gly Arg Thr Ala Thr Arg
    210                 215                 220
Glu Asp Phe Leu Asn Pro Asp Val Leu Asp Ile Phe Ile Ser Ser Val
225                 230                 235                 240
Gln Lys Val Phe Gln Val Val Glu Ser Thr Arg Pro Gly Lys Lys Val
                245                 250                 255
Trp Leu Gly Glu Thr Ser Ser Ala Tyr Gly Gly Gly Ala Pro Leu Leu
            260                 265                 270
Ser Asp Thr Phe Ala Ala Gly Phe Met Trp Leu Asp Lys Leu Gly Leu
        275                 280                 285
Ser Ala Arg Met Gly Ile Glu Val Val Met Arg Gln Val Phe Phe Gly
    290                 295                 300
Ala Gly Asn Tyr His Leu Val Asp Glu Asn Phe Asp Pro Leu Pro Asp
305                 310                 315                 320
Tyr Trp Leu Ser Leu Leu Phe Lys Lys Leu Val Gly Thr Lys Val Leu
                325                 330                 335
Met Ala Ser Val Gln Gly Ser Lys Arg Arg Lys Leu Arg Val Tyr Leu
            340                 345                 350
His Cys Thr Asn Thr Asp Asn Pro Arg Tyr Lys Glu Gly Asp Leu Thr
        355                 360                 365
Leu Tyr Ala Ile Asn Leu His Asn Val Thr Lys Tyr Leu Arg Leu Pro
    370                 375                 380
Tyr Pro Phe Ser Asn Lys Gln Val Asp Lys Tyr Leu Leu Arg Pro Leu
385                 390                 395                 400
Gly Pro His Gly Leu Leu Ser Lys Ser Val Gln Leu Asn Gly Leu Thr
                405                 410                 415
Leu Lys Met Val Asp Asp Gln Thr Leu Pro Pro Leu Met Glu Lys Pro
            420                 425                 430
Leu Arg Pro Gly Ser Ser Leu Gly Leu Pro Ala Phe Ser Tyr Ser Phe
        435                 440                 445
Phe Val Ile Arg Asn Ala Lys Val Ala Ala Cys Ile
    450                 455                 460
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<210> 157
<211> 4670
<212> DNA
<213> 現代人

<220>
<223> ADAMTS-1

<400> 157

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<211> 967
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<213> 現代人

<220>
<223> ADAMTS-前驅體

<400> 158

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Asp Met Gly Asn Ala Glu Arg Ala Pro Gly Ser Arg Ser Phe Gly Pro
            20                  25                  30
Val Pro Thr Leu Leu Leu Leu Ala Ala Ala Leu Leu Ala Val Ser Asp
        35                  40                  45
Ala Leu Gly Arg Pro Ser Glu Glu Asp Glu Glu Leu Val Val Pro Glu
    50                  55                  60
Leu Glu Arg Ala Pro Gly His Gly Thr Thr Arg Leu Arg Leu His Ala
65                  70                  75                  80
Phe Asp Gln Gln Leu Asp Leu Glu Leu Arg Pro Asp Ser Ser Phe Leu
                85                  90                  95
Ala Pro Gly Phe Thr Leu Gln Asn Val Gly Arg Lys Ser Gly Ser Glu
            100                 105                 110
Thr Pro Leu Pro Glu Thr Asp Leu Ala His Cys Phe Tyr Ser Gly Thr
        115                 120                 125
Val Asn Gly Asp Pro Ser Ser Ala Ala Ala Leu Ser Leu Cys Glu Gly
    130                 135                 140
Val Arg Gly Ala Phe Tyr Leu Leu Gly Glu Ala Tyr Phe Ile Gln Pro
145                 150                 155                 160
Leu Pro Ala Ala Ser Glu Arg Leu Ala Thr Ala Ala Pro Gly Glu Lys
                165                 170                 175
Pro Pro Ala Pro Leu Gln Phe His Leu Leu Arg Arg Asn Arg Gln Gly
            180                 185                 190
Asp Val Gly Gly Thr Cys Gly Val Val Asp Asp Glu Pro Arg Pro Thr
        195                 200                 205
Gly Lys Ala Glu Thr Glu Asp Glu Asp Glu Gly Thr Glu Gly Glu Asp
    210                 215                 220
Glu Gly Ala Gln Trp Ser Pro Gln Asp Pro Ala Leu Gln Gly Val Gly
225                 230                 235                 240
Gln Pro Thr Gly Thr Gly Ser Ile Arg Lys Lys Arg Phe Val Ser Ser
                245                 250                 255
His Arg Tyr Val Glu Thr Met Leu Val Ala Asp Gln Ser Met Ala Glu
            260                 265                 270
Phe His Gly Ser Gly Leu Lys His Tyr Leu Leu Thr Leu Phe Ser Val
        275                 280                 285
Ala Ala Arg Leu Tyr Lys His Pro Ser Ile Arg Asn Ser Val Ser Leu
    290                 295                 300
Val Val Val Lys Ile Leu Val Ile His Asp Glu Gln Lys Gly Pro Glu
305                 310                 315                 320
Val Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln
                325                 330                 335
Lys Gln His Asn Pro Pro Ser Asp Arg Asp Ala Glu His Tyr Asp Thr
            340                 345                 350
Ala Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Ser Gln Thr Cys Asp
        355                 360                 365
Thr Leu Gly Met Ala Asp Val Gly Thr Val Cys Asp Pro Ser Arg Ser
    370                 375                 380
Cys Ser Val Ile Glu Asp Asp Gly Leu Gln Ala Ala Phe Thr Thr Ala
385                 390                 395                 400
His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ala Lys Gln
                405                 410                 415
Cys Ala Ser Leu Asn Gly Val Asn Gln Asp Ser His Met Met Ala Ser
            420                 425                 430
Met Leu Ser Asn Leu Asp His Ser Gln Pro Trp Ser Pro Cys Ser Ala
        435                 440                 445
Tyr Met Ile Thr Ser Phe Leu Asp Asn Gly His Gly Glu Cys Leu Met
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    450                 455                 460
Asp Lys Pro Gln Asn Pro Ile Gln Leu Pro Gly Asp Leu Pro Gly Thr
465                 470                 475                 480
Ser Tyr Asp Ala Asn Arg Gln Cys Gln Phe Thr Phe Gly Glu Asp Ser
                485                 490                 495
Lys His Cys Pro Asp Ala Ala Ser Thr Cys Ser Thr Leu Trp Cys Thr
            500                 505                 510
Gly Thr Ser Gly Gly Val Leu Val Cys Gln Thr Lys His Phe Pro Trp
        515                 520                 525
Ala Asp Gly Thr Ser Cys Gly Glu Gly Lys Trp Cys Ile Asn Gly Lys
    530                 535                 540
Cys Val Asn Lys Thr Asp Arg Lys His Phe Asp Thr Pro Phe His Gly
545                 550                 555                 560
Ser Trp Gly Met Trp Gly Pro Trp Gly Asp Cys Ser Arg Thr Cys Gly
                565                 570                 575
Gly Gly Val Gln Tyr Thr Met Arg Glu Cys Asp Asn Pro Val Pro Lys
            580                 585                 590
Asn Gly Gly Lys Tyr Cys Glu Gly Lys Arg Val Arg Tyr Arg Ser Cys
        595                 600                 605
Asn Leu Glu Asp Cys Pro Asp Asn Asn Gly Lys Thr Phe Arg Glu Glu
    610                 615                 620
Gln Cys Glu Ala His Asn Glu Phe Ser Lys Ala Ser Phe Gly Ser Gly
625                 630                 635                 640
Pro Ala Val Glu Trp Ile Pro Lys Tyr Ala Gly Val Ser Pro Lys Asp
                645                 650                 655
Arg Cys Lys Leu Ile Cys Gln Ala Lys Gly Ile Gly Tyr Phe Phe Val
            660                 665                 670
Leu Gln Pro Lys Val Val Asp Gly Thr Pro Cys Ser Pro Asp Ser Thr
        675                 680                 685
Ser Val Cys Val Gln Gly Gln Cys Val Lys Ala Gly Cys Asp Arg Ile
    690                 695                 700
Ile Asp Ser Lys Lys Lys Phe Asp Lys Cys Gly Val Cys Gly Gly Asn
705                 710                 715                 720
Gly Ser Thr Cys Lys Lys Ile Ser Gly Ser Val Thr Ser Ala Lys Pro
                725                 730                 735
Gly Tyr His Asp Ile Ile Thr Ile Pro Thr Gly Ala Thr Asn Ile Glu
            740                 745                 750
Val Lys Gln Arg Asn Gln Arg Gly Ser Arg Asn Asn Gly Ser Phe Leu
        755                 760                 765
Ala Ile Lys Ala Ala Asp Gly Thr Tyr Ile Leu Asn Gly Asp Tyr Thr
    770                 775                 780
Leu Ser Thr Leu Glu Gln Asp Ile Met Tyr Lys Gly Val Val Leu Arg
785                 790                 795                 800
Tyr Ser Gly Ser Ser Ala Ala Leu Glu Arg Ile Arg Ser Phe Ser Pro
                805                 810                 815
Leu Lys Glu Pro Leu Thr Ile Gln Val Leu Thr Val Gly Asn Ala Leu
            820                 825                 830
Arg Pro Lys Ile Lys Tyr Thr Tyr Phe Val Lys Lys Lys Lys Glu Ser
        835                 840                 845
Phe Asn Ala Ile Pro Thr Phe Ser Ala Trp Val Ile Glu Glu Trp Gly
    850                 855                 860
Glu Cys Ser Lys Ser Cys Glu Leu Gly Trp Gln Arg Arg Leu Val Glu
865                 870                 875                 880
Cys Arg Asp Ile Asn Gly Gln Pro Ala Ser Glu Cys Ala Lys Glu Val
                885                 890                 895
Lys Pro Ala Ser Thr Arg Pro Cys Ala Asp His Pro Cys Pro Gln Trp
            900                 905                 910
Gln Leu Gly Glu Trp Ser Ser Cys Ser Lys Thr Cys Gly Lys Gly Tyr
        915                 920                 925
Lys Lys Arg Ser Leu Lys Cys Leu Ser His Asp Gly Gly Val Leu Ser
    930                 935                 940
His Glu Ser Cys Asp Pro Leu Lys Lys Pro Lys His Phe Ile Asp Phe
945                 950                 955                 960
Cys Thr Met Ala Glu Cys Ser
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<210> 159
<211> 715
<212> PRT
<213> 現代人

<220>
<223> 成熟ADAMTS-1

<400> 159

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Ser Met Ala Glu Phe His Gly Ser Gly Leu Lys His Tyr Leu Leu Thr
            20                  25                  30
Leu Phe Ser Val Ala Ala Arg Leu Tyr Lys His Pro Ser Ile Arg Asn
        35                  40                  45
Ser Val Ser Leu Val Val Val Lys Ile Leu Val Ile His Asp Glu Gln
    50                  55                  60
Lys Gly Pro Glu Val Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe
65                  70                  75                  80
Cys Asn Trp Gln Lys Gln His Asn Pro Pro Ser Asp Arg Asp Ala Glu
                85                  90                  95

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

        435                 440                 445
Cys Asp Arg Ile Ile Asp Ser Lys Lys Lys Phe Asp Lys Cys Gly Val
    450                 455                 460
Cys Gly Gly Asn Gly Ser Thr Cys Lys Lys Ile Ser Gly Ser Val Thr
465                 470                 475                 480
Ser Ala Lys Pro Gly Tyr His Asp Ile Ile Thr Ile Pro Thr Gly Ala
                485                 490                 495
Thr Asn Ile Glu Val Lys Gln Arg Asn Gln Arg Gly Ser Arg Asn Asn
            500                 505                 510
Gly Ser Phe Leu Ala Ile Lys Ala Ala Asp Gly Thr Tyr Ile Leu Asn
        515                 520                 525
Gly Asp Tyr Thr Leu Ser Thr Leu Glu Gln Asp Ile Met Tyr Lys Gly
    530                 535                 540
Val Val Leu Arg Tyr Ser Gly Ser Ser Ala Ala Leu Glu Arg Ile Arg
545                 550                 555                 560
Ser Phe Ser Pro Leu Lys Glu Pro Leu Thr Ile Gln Val Leu Thr Val
                565                 570                 575
Gly Asn Ala Leu Arg Pro Lys Ile Lys Tyr Thr Tyr Phe Val Lys Lys
            580                 585                 590
Lys Lys Glu Ser Phe Asn Ala Ile Pro Thr Phe Ser Ala Trp Val Ile
        595                 600                 605
Glu Glu Trp Gly Glu Cys Ser Lys Ser Cys Glu Leu Gly Trp Gln Arg
    610                 615                 620
Arg Leu Val Glu Cys Arg Asp Ile Asn Gly Gln Pro Ala Ser Glu Cys
625                 630                 635                 640
Ala Lys Glu Val Lys Pro Ala Ser Thr Arg Pro Cys Ala Asp His Pro
                645                 650                 655
Cys Pro Gln Trp Gln Leu Gly Glu Trp Ser Ser Cys Ser Lys Thr Cys
            660                 665                 670
Gly Lys Gly Tyr Lys Lys Arg Ser Leu Lys Cys Leu Ser His Asp Gly
        675                 680                 685
Gly Val Leu Ser His Glu Ser Cys Asp Pro Leu Lys Lys Pro Lys His
    690                 695                 700
Phe Ile Asp Phe Cys Thr Met Ala Glu Cys Ser
705                 710                 715
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<212> DNA
<213> 現代人

<220>
<223> ADAMTS-2

<400> 160

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<212> PRT
<213> 現代人

<220>
<223> ADAMTS-2前驅體

<400> 161
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Pro Pro Ala Asn Ala Arg Leu Ala Ala Ala Ala Asp Pro Pro Gly Gly
        35   40   45
Pro Leu Gly His Gly Ala Glu Arg Ile Leu Ala Val Pro Val Arg Thr
    50   55   60
Asp Ala Gln Gly Arg Leu Val Ser His Val Val Ser Ala Ala Thr Ser
65   70   75   80

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Arg Ala Gly Val Arg Ala Arg Arg Ala Ala Pro Val Arg Thr Pro Ser
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Phe Pro Gly Gly Asn Glu Glu Glu Pro Gly Ser His Leu Phe Tyr Asn
            100                 105                 110
Val Thr Val Phe Gly Arg Asp Leu His Leu Arg Leu Arg Pro Asn Ala
        115                 120                 125
Arg Leu Val Ala Pro Gly Ala Thr Met Glu Trp Gln Gly Glu Lys Gly
    130                 135                 140
Thr Thr Arg Val Glu Pro Leu Leu Gly Ser Cys Leu Tyr Val Gly Asp
145                 150                 155                 160
Val Ala Gly Leu Ala Glu Ala Ser Ser Val Ala Leu Ser Asn Cys Asp
                165                 170                 175
Gly Leu Ala Gly Leu Ile Arg Met Glu Glu Glu Glu Phe Phe Ile Glu
            180                 185                 190
Pro Leu Glu Lys Gly Leu Ala Ala Gln Glu Ala Glu Gln Gly Arg Val
        195                 200                 205
His Val Val Tyr Arg Arg Pro Pro Thr Ser Pro Pro Leu Gly Gly Pro
    210                 215                 220
Gln Ala Leu Asp Thr Gly Ala Ser Leu Asp Ser Leu Asp Ser Leu Ser
225                 230                 235                 240
Arg Ala Leu Gly Val Leu Glu Glu His Ala Asn Ser Ser Arg Arg Arg
                245                 250                 255
Ala Arg Arg His Ala Ala Asp Asp Asp Tyr Asn Ile Glu Val Leu Leu
            260                 265                 270
Gly Val Asp Asp Ser Val Val Gln Phe His Gly Lys Glu His Val Gln
        275                 280                 285
Lys Tyr Leu Leu Thr Leu Met Asn Ile Val Asn Glu Ile Tyr His Asp
    290                 295                 300
Glu Ser Leu Gly Ala His Ile Asn Val Val Leu Val Arg Ile Ile Leu
305                 310                 315                 320
Leu Ser Tyr Gly Lys Ser Met Ser Leu Ile Glu Ile Gly Asn Pro Ser
                325                 330                 335
Gln Ser Leu Glu Asn Val Cys Arg Trp Ala Tyr Leu Gln Gln Lys Pro
            340                 345                 350
Asp Thr Gly His Asp Glu Tyr His Asp His Ala Ile Phe Leu Thr Arg
        355                 360                 365
Gln Asp Phe Gly Pro Ser Gly Met Gln Gly Tyr Ala Pro Val Thr Gly
    370                 375                 380
Met Cys His Pro Val Arg Ser Cys Thr Leu Asn His Glu Asp Gly Phe
385                 390                 395                 400
Ser Ser Ala Phe Val Val Ala His Glu Thr Gly His Val Leu Gly Met
                405                 410                 415
Glu His Asp Gly Gln Gly Asn Arg Cys Gly Asp Glu Val Arg Leu Gly
            420                 425                 430
Ser Ile Met Ala Pro Leu Val Gln Ala Ala Phe His Arg Phe His Trp
        435                 440                 445
Ser Arg Cys Ser Gln Gln Glu Leu Ser Arg Tyr Leu His Ser Tyr Asp
    450                 455                 460
Cys Leu Leu Asp Asp Pro Phe Ala His Asp Trp Pro Ala Leu Pro Gln
465                 470                 475                 480
Leu Pro Gly Leu His Tyr Ser Met Asn Glu Gln Cys Arg Phe Asp Phe
                485                 490                 495
Gly Leu Gly Tyr Met Met Cys Thr Ala Phe Arg Thr Phe Asp Pro Cys
            500                 505                 510
Lys Gln Leu Trp Cys Ser His Pro Asp Asn Pro Tyr Phe Cys Lys Thr
        515                 520                 525
Lys Lys Gly Pro Pro Leu Asp Gly Thr Met Cys Ala Pro Gly Lys His
    530                 535                 540
Cys Phe Lys Gly His Cys Ile Trp Leu Thr Pro Asp Ile Leu Lys Arg
545                 550                 555                 560
Asp Gly Ser Trp Gly Ala Trp Ser Pro Phe Gly Ser Cys Ser Arg Thr
                565                 570                 575
Cys Gly Thr Gly Val Lys Phe Arg Thr Arg Gln Cys Asp Asn Pro His
            580                 585                 590
Pro Ala Asn Gly Gly Arg Thr Cys Ser Gly Leu Ala Tyr Asp Phe Gln
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595 600 605
Leu Cys Ser Arg Gln Asp Cys Pro Asp Ser Leu Ala Asp Phe Arg Glu
610 615 620
Glu Gln Cys Arg Gln Trp Asp Leu Tyr Phe Glu His Gly Asp Ala Gln
625 630 635 640
His His Trp Leu Pro His Glu His Arg Asp Ala Lys Glu Arg Cys His
645 650 655
Leu Tyr Cys Glu Ser Arg Glu Thr Gly Glu Val Val Ser Met Lys Arg
660 665 670
Met Val His Asp Gly Thr Arg Cys Ser Tyr Lys Asp Ala Phe Ser Leu
675 680 685

Cys Val Arg Gly Asp Cys Arg Lys Val Gly Cys Asp Gly Val Ile Gly
690 695 700
Ser Ser Lys Gln Glu Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser
705 710 715 720
His Cys Lys Val Val Lys Gly Thr Phe Thr Arg Ser Pro Lys Lys His
725 730 735
Gly Tyr Ile Lys Met Phe Glu Ile Pro Ala Gly Ala Arg His Leu Leu
740 745 750
Ile Gln Glu Val Asp Ala Thr Ser His His Leu Ala Val Lys Asn Leu
755 760 765
Glu Thr Gly Lys Phe Ile Leu Asn Glu Glu Asn Asp Val Asp Ala Ser
770 775 780
Ser Lys Thr Phe Ile Ala Met Gly Val Glu Trp Glu Tyr Arg Asp Glu
785 790 795 800
Asp Gly Arg Glu Thr Leu Gln Thr Met Gly Pro Leu His Gly Thr Ile
805 810 815
Thr Val Leu Val Ile Pro Val Gly Asp Thr Arg Val Ser Leu Thr Tyr
820 825 830
Lys Tyr Met Ile His Glu Asp Ser Leu Asn Val Asp Asp Asn Asn Val
835 840 845
Leu Glu Glu Asp Ser Val Val Tyr Glu Trp Ala Leu Lys Lys Trp Ser
850 855 860
Pro Cys Ser Lys Pro Cys Gly Gly Gly Ser Gln Phe Thr Lys Tyr Gly
865 870 875 880
Cys Arg Arg Arg Leu Asp His Lys Met Val His Arg Gly Phe Cys Ala
885 890 895
Ala Leu Ser Lys Pro Lys Ala Ile Arg Arg Ala Cys Asn Pro Gln Glu
900 905 910
Cys Ser Gln Pro Val Trp Val Thr Gly Glu Trp Glu Pro Cys Ser Gln
915 920 925
Thr Cys Gly Arg Thr Gly Met Gln Val Arg Ser Val Arg Cys Ile Gln
930 935 940
Pro Leu His Asp Asn Thr Thr Arg Ser Val His Ala Lys His Cys Asn
945 950 955 960
Asp Ala Arg Pro Glu Ser Arg Arg Ala Cys Ser Arg Glu Leu Cys Pro
965 970 975
Gly Arg Trp Arg Ala Gly Pro Trp Ser Gln Cys Ser Val Thr Cys Gly
980 985 990
Asn Gly Thr Gln Glu Arg Pro Val Pro Cys Arg Thr Ala Asp Asp Ser
995 1000 1005
Phe Gly Ile Cys Gln Glu Glu Arg Pro Glu Thr Ala Arg Thr Cys Arg
1010 1015 1020
Leu Gly Pro Cys Pro Arg Asn Ile Ser Asp Pro Ser Lys Lys Ser Tyr

1025 1030 1035 1040
Val Val Gln Trp Leu Ser Arg Pro Asp Pro Asp Ser Pro Ile Arg Lys
1045 1050 1055
Ile Ser Ser Lys Gly His Cys Gln Gly Asp Lys Ser Ile Phe Cys Arg
1060 1065 1070
Met Glu Val Leu Ser Arg Tyr Cys Ser Ile Pro Gly Tyr Asn Lys Leu
1075 1080 1085
Ser Cys Lys Ser Cys Asn Leu Tyr Asn Asn Leu Thr Asn Val Glu Gly
1090 1095 1100

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Arg Ile Glu Pro Pro Pro Gly Lys His Asn Asp Ile Asp Val Phe Met
1105                1110                1115                1120
Pro Thr Leu Pro Val Pro Thr Val Ala Met Glu Val Arg Pro Ser Pro
                1125                1130                1135
Ser Thr Pro Leu Glu Val Pro Leu Asn Ala Ser Ser Thr Asn Ala Thr
            1140                1145                1150
Glu Asp His Pro Glu Thr Asn Ala Val Asp Glu Pro Tyr Lys Ile His
        1155                1160                1165
Gly Leu Glu Asp Glu Val Gln Pro Pro Asn Leu Ile Pro Arg Arg Pro
    1170                1175                1180
Ser Pro Tyr Glu Lys Thr Arg Asn Gln Arg Ile Gln Glu Leu Ile Asp
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Glu Met Arg Lys Lys Glu Met Leu Gly Lys Phe
                1205                1210
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<211> 958
<212> PRT
<213> 現代人

<220>
<223> 成熟ADAMTS-2

<400> 162

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His Val Gln Lys Tyr Leu Leu Thr Leu Met Asn Ile Val Asn Glu Ile
        35                  40                  45
Tyr His Asp Glu Ser Leu Gly Ala His Ile Asn Val Val Leu Val Arg
    50                  55                  60
Ile Ile Leu Leu Ser Tyr Gly Lys Ser Met Ser Leu Ile Glu Ile Gly
65                  70                  75                  80
Asn Pro Ser Gln Ser Leu Glu Asn Val Cys Arg Trp Ala Tyr Leu Gln
                85                  90                  95
Gln Lys Pro Asp Thr Gly His Asp Glu Tyr His Asp His Ala Ile Phe
            100                 105                 110
Leu Thr Arg Gln Asp Phe Gly Pro Ser Gly Met Gln Gly Tyr Ala Pro
        115                 120                 125
Val Thr Gly Met Cys His Pro Val Arg Ser Cys Thr Leu Asn His Glu
    130                 135                 140
Asp Gly Phe Ser Ser Ala Phe Val Val Ala His Glu Thr Gly His Val
145                 150                 155                 160
Leu Gly Met Glu His Asp Gly Gln Gly Asn Arg Cys Gly Asp Glu Val
                165                 170                 175
Arg Leu Gly Ser Ile Met Ala Pro Leu Val Gln Ala Ala Phe His Arg
            180                 185                 190
Phe His Trp Ser Arg Cys Ser Gln Gln Glu Leu Ser Arg Tyr Leu His
        195                 200                 205
Ser Tyr Asp Cys Leu Leu Asp Asp Pro Phe Ala His Asp Trp Pro Ala
    210                 215                 220
Leu Pro Gln Leu Pro Gly Leu His Tyr Ser Met Asn Glu Gln Cys Arg
225                 230                 235                 240
Phe Asp Phe Gly Leu Gly Tyr Met Met Cys Thr Ala Phe Arg Thr Phe
                245                 250                 255
Asp Pro Cys Lys Gln Leu Trp Cys Ser His Pro Asp Asn Pro Tyr Phe
            260                 265                 270
Cys Lys Thr Lys Lys Gly Pro Pro Leu Asp Gly Thr Met Cys Ala Pro
        275                 280                 285
Gly Lys His Cys Phe Lys Gly His Cys Ile Trp Leu Thr Pro Asp Ile
    290                 295                 300
Leu Lys Arg Asp Gly Ser Trp Gly Ala Trp Ser Pro Phe Gly Ser Cys
305                 310                 315                 320
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Ser Arg Thr Cys Gly Thr Gly Val Lys Phe Arg Thr Arg Gln Cys Asp
                325                 330                 335
Asn Pro His Pro Ala Asn Gly Gly Arg Thr Cys Ser Gly Leu Ala Tyr
            340                 345                 350
Asp Phe Gln Leu Cys Ser Arg Gln Asp Cys Pro Asp Ser Leu Ala Asp
        355                 360                 365
Phe Arg Glu Glu Gln Cys Arg Gln Trp Asp Leu Tyr Phe Glu His Gly
    370                 375                 380
Asp Ala Gln His His Trp Leu Pro His Glu His Arg Asp Ala Lys Glu
385                 390                 395                 400
Arg Cys His Leu Tyr Cys Glu Ser Arg Glu Thr Gly Glu Val Val Ser
                405                 410                 415
Met Lys Arg Met Val His Asp Gly Thr Arg Cys Ser Tyr Lys Asp Ala
            420                 425                 430
Phe Ser Leu Cys Val Arg Gly Asp Cys Arg Lys Val Gly Cys Asp Gly
        435                 440                 445
Val Ile Gly Ser Ser Lys Gln Glu Asp Lys Cys Gly Val Cys Gly Gly
    450                 455                 460
Asp Asn Ser His Cys Lys Val Val Lys Gly Thr Phe Thr Arg Ser Pro
465                 470                 475                 480
Lys Lys His Gly Tyr Ile Lys Met Phe Glu Ile Pro Ala Gly Ala Arg
                485                 490                 495
His Leu Leu Ile Gln Glu Val Asp Ala Thr Ser His His Leu Ala Val
            500                 505                 510
Lys Asn Leu Glu Thr Gly Lys Phe Ile Leu Asn Glu Glu Asn Asp Val
        515                 520                 525
Asp Ala Ser Ser Lys Thr Phe Ile Ala Met Gly Val Glu Trp Glu Tyr
    530                 535                 540
Arg Asp Glu Asp Gly Arg Glu Thr Leu Gln Thr Met Gly Pro Leu His
545                 550                 555                 560
Gly Thr Ile Thr Val Leu Val Ile Pro Val Gly Asp Thr Arg Val Ser
                565                 570                 575
Leu Thr Tyr Lys Tyr Met Ile His Glu Asp Ser Leu Asn Val Asp Asp
            580                 585                 590
Asn Asn Val Leu Glu Glu Asp Ser Val Val Tyr Glu Trp Ala Leu Lys
        595                 600                 605
Lys Trp Ser Pro Cys Ser Lys Pro Cys Gly Gly Gly Ser Gln Phe Thr
    610                 615                 620
Lys Tyr Gly Cys Arg Arg Arg Leu Asp His Lys Met Val His Arg Gly
625                 630                 635                 640
Phe Cys Ala Ala Leu Ser Lys Pro Lys Ala Ile Arg Arg Ala Cys Asn
                645                 650                 655
Pro Gln Glu Cys Ser Gln Pro Val Trp Val Thr Gly Glu Trp Glu Pro
            660                 665                 670
Cys Ser Gln Thr Cys Gly Arg Thr Gly Met Gln Val Arg Ser Val Arg
        675                 680                 685
Cys Ile Gln Pro Leu His Asp Asn Thr Thr Arg Ser Val His Ala Lys
    690                 695                 700
His Cys Asn Asp Ala Arg Pro Glu Ser Arg Arg Ala Cys Ser Arg Glu
705                 710                 715                 720
Leu Cys Pro Gly Arg Trp Arg Ala Gly Pro Trp Ser Gln Cys Ser Val
                725                 730                 735
Thr Cys Gly Asn Gly Thr Gln Glu Arg Pro Val Pro Cys Arg Thr Ala
            740                 745                 750
Asp Asp Ser Phe Gly Ile Cys Gln Glu Glu Arg Pro Glu Thr Ala Arg
        755                 760                 765
Thr Cys Arg Leu Gly Pro Cys Pro Arg Asn Ile Ser Asp Pro Ser Lys
    770                 775                 780
Lys Ser Tyr Val Val Gln Trp Leu Ser Arg Pro Asp Pro Asp Ser Pro
785                 790                 795                 800
Ile Arg Lys Ile Ser Ser Lys Gly His Cys Gln Gly Asp Lys Ser Ile
                805                 810                 815
Phe Cys Arg Met Glu Val Leu Ser Arg Tyr Cys Ser Ile Pro Gly Tyr
            820                 825                 830
Asn Lys Leu Ser Cys Lys Ser Cys Asn Leu Tyr Asn Asn Leu Thr Asn
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Val Glu Gly Arg Ile Glu Pro Pro Pro Gly Lys His Asn Asp Ile Asp
    850                 855                 860
Val Phe Met Pro Thr Leu Pro Val Pro Thr Val Ala Met Glu Val Arg
865                 870                 875                 880
Pro Ser Pro Ser Thr Pro Leu Glu Val Pro Leu Asn Ala Ser Ser Thr
                885                 890                 895
Asn Ala Thr Glu Asp His Pro Glu Thr Asn Ala Val Asp Glu Pro Tyr
            900                 905                 910
Lys Ile His Gly Leu Glu Asp Glu Val Gln Pro Pro Asn Leu Ile Pro
        915                 920                 925
Arg Arg Pro Ser Pro Tyr Glu Lys Thr Arg Asn Gln Arg Ile Gln Glu
    930                 935                 940
Leu Ile Asp Glu Met Arg Lys Lys Glu Met Leu Gly Lys Phe
945                 950                 955
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<210> 163
<211> 5821
<212> DNA
<213> 現代人

<220>
<223> ADAMTS-3

<400> 163

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t 5821

<210> 164
<211> 1205
<212> PRT

<213> 現代人

<220>
<223> ADAMTS-3前驅體

<400> 164

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

```
465                 470                 475                 480
Gln Cys Arg Phe Asp Phe Gly Val Gly Tyr Lys Met Cys Thr Ala Phe
                485                 490                 495
Arg Thr Phe Asp Pro Cys Lys Gln Leu Trp Cys Ser His Pro Asp Asn
            500                 505                 510
Pro Tyr Phe Cys Lys Thr Lys Lys Gly Pro Pro Leu Asp Gly Thr Glu
        515                 520                 525
Cys Ala Ala Gly Lys Trp Cys Tyr Lys Gly His Cys Met Trp Lys Asn
    530                 535                 540
Ala Asn Gln Gln Lys Gln Asp Gly Asn Trp Gly Ser Trp Thr Lys Phe
545                 550                 555                 560
Gly Ser Cys Ser Arg Thr Cys Gly Thr Gly Val Arg Phe Arg Thr Arg
                565                 570                 575
Gln Cys Asn Asn Pro Met Pro Ile Asn Gly Gly Gln Asp Cys Pro Gly
            580                 585                 590
Val Asn Phe Glu Tyr Gln Leu Cys Asn Thr Glu Glu Cys Gln Lys His
        595                 600                 605
Phe Glu Asp Phe Arg Ala Gln Gln Cys Gln Gln Arg Asn Ser His Phe
    610                 615                 620
Glu Tyr Gln Asn Thr Lys His His Trp Leu Pro Tyr Glu His Pro Asp
625                 630                 635                 640
Pro Lys Lys Arg Cys His Leu Tyr Cys Gln Ser Lys Glu Thr Gly Asp
                645                 650                 655
Val Ala Tyr Met Lys Gln Leu Val His Asp Gly Thr His Cys Ser Tyr
            660                 665                 670
Lys Asp Pro Tyr Ser Ile Cys Val Arg Gly Glu Cys Val Lys Val Gly
        675                 680                 685
Cys Asp Lys Glu Ile Gly Ser Asn Lys Val Glu Asp Lys Cys Gly Val
    690                 695                 700
Cys Gly Gly Asp Asn Ser His Cys Arg Thr Val Lys Gly Thr Phe Thr
705                 710                 715                 720
Arg Thr Pro Arg Lys Leu Gly Tyr Leu Lys Met Phe Asp Ile Pro Pro
                725                 730                 735
Gly Ala Arg His Val Leu Ile Gln Glu Asp Glu Ala Ser Pro His Ile
            740                 745                 750
Leu Ala Ile Lys Asn Gln Ala Thr Gly His Tyr Ile Leu Asn Gly Lys
        755                 760                 765
Gly Glu Glu Ala Lys Ser Arg Thr Phe Ile Asp Leu Gly Val Glu Trp
    770                 775                 780
Asp Tyr Asn Ile Glu Asp Asp Ile Glu Ser Leu His Thr Asp Gly Pro
785                 790                 795                 800
Leu His Asp Pro Val Ile Val Leu Ile Ile Pro Gln Glu Asn Asp Thr
                805                 810                 815
Arg Ser Ser Leu Thr Tyr Lys Tyr Ile Ile His Glu Asp Ser Val Pro
            820                 825                 830
Thr Ile Asn Ser Asn Asn Val Ile Gln Glu Glu Leu Asp Thr Phe Glu
        835                 840                 845
Trp Ala Leu Lys Ser Trp Ser Gln Val Ser Lys Pro Cys Gly Gly Gly
    850                 855                 860
Phe Gln Tyr Thr Lys Tyr Gly Cys Arg Arg Lys Ser Asp Asn Lys Met
865                 870                 875                 880
Val His Arg Ser Phe Cys Glu Ala Asn Lys Lys Pro Lys Pro Ile Arg
                885                 890                 895
Arg Met Cys Asn Ile Gln Glu Cys Thr His Pro Leu Trp Val Ala Glu
            900                 905                 910
Glu Trp Glu His Cys Thr Lys Thr Cys Gly Ser Ser Gly Tyr Gln Leu
        915                 920                 925
Arg Thr Val Arg Cys Leu Gln Pro Leu Leu Asp Gly Thr Asn Arg Ser
    930                 935                 940
Val His Ser Lys Tyr Cys Met Gly Asp Arg Pro Glu Ser Arg Arg Pro
945                 950                 955                 960
Cys Asn Arg Val Pro Cys Pro Ala Gln Trp Lys Thr Gly Pro Trp Ser
                965                 970                 975
Glu Cys Ser Val Thr Cys Gly Glu Gly Thr Glu Val Arg Gln Val Leu
            980                 985                 990
```

```
Cys Arg Ala Gly Asp His Cys Asp Gly Glu Lys Pro Glu Ser Val Arg
        995                 1000                1005
Ala Cys Gln Leu Pro Pro Cys Asn Asp Glu Pro Cys Leu Gly Asp Lys
    1010                1015                1020
Ser Ile Phe Cys Gln Met Glu Val Leu Ala Arg Tyr Cys Ser Ile Pro
1025                1030                1035                1040
Gly Tyr Asn Lys Leu Cys Cys Glu Ser Cys Ser Lys Arg Ser Ser Thr
                1045                1050                1055
Leu Pro Pro Pro Tyr Leu Leu Glu Ala Ala Glu Thr His Asp Asp Val
            1060                1065                1070
Ile Ser Asn Pro Ser Asp Leu Pro Arg Ser Leu Val Met Pro Thr Ser
        1075                1080                1085
Leu Val Pro Tyr His Ser Glu Thr Pro Ala Lys Lys Met Ser Leu Ser
    1090                1095                1100
Ser Ile Ser Ser Val Gly Gly Pro Asn Ala Tyr Ala Ala Phe Arg Pro
1105                1110                1115                1120
Asn Ser Lys Pro Asp Gly Ala Asn Leu Arg Gln Arg Ser Ala Gln Gln
                1125                1130                1135
Ala Gly Ser Lys Thr Val Arg Leu Val Thr Val Pro Ser Ser Pro Pro
            1140                1145                1150
Thr Lys Arg Val His Leu Ser Ser Ala Ser Gln Met Ala Ala Ala Ser
        1155                1160                1165
Phe Phe Ala Ala Ser Asp Ser Ile Gly Ala Ser Ser Gln Ala Arg Thr
    1170                1175                1180
Ser Lys Lys Asp Gly Lys Ile Ile Asp Asn Arg Arg Pro Thr Arg Ser
1185                1190                1195                1200
Ser Thr Leu Glu Arg
                1205
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<210> 165

<400> 165
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<210> 166
<211> 4342
<212> DNA
<213> 現代人

<220>
<223> ADAMTS-4

<400> 166

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gacagagaca aaggcacagc ggaagaaggc agagacaggg caggcacaga agcggcccag 120
acagagtcct acagagggag aggccagaga agctgcagaa gacacaggca gggagagaca 180
aagatccagg aaaggagggc tcaggaggag agtttggaga agccagaccc ctgggcacct 240
ctcccaagcc caaggactaa gttttctcca tttcctttaa cggtcctcag cccttctgaa 300
aactttgcct ctgaccttgg caggagtcca agcccccagg ctacagagag gagctttcca 360
aagctagggt gtggaggact tggtgcccta gacggcctca gtcctcccca gctgcagtac 420
cagtgccatg tcccagacag gctcgcatcc cgggaggggc ttggcagggc gctggctgtg 480
gggagcccaa ccctgcctcc tgctccccat tgtgccgctc tcctggctgg tgtggctgct 540
tctgctactg ctggcctctc tcctgccctc agcccggctg gccagccccc tcccccggga 600
ggaggagatc gtgtttccag agaagctcaa cggcagcgtc ctgcctggct cgggcgcccc 660
tgccaggctg ttgtgccgct tgcaggcctt tggggagacg ctgctactag agctggagca 720
ggactccggt gtgcaggtcg aggggctgac agtgcagtac ctgggccagg cgcctgagct 780
gctgggtgga gcagagcctg gcacctacct gactggcacc atcaatggag atccggagtc 840
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atttgtggag acactggtgg tggcagatga caagatggcc gcattccacg gtgcggggct 1140
aaagcgctac ctgctaacag tgatggcagc agcagccaag gccttcaagc acccaagcat 1200
ccgcaatcct gtcagcttgg tggtgactcg gctagtgatc ctggggtcag gcgaggaggg 1260
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gccccaagtg gggcccagtg ctgcccagac cctgcgcagc ttctgtgcct ggcagcgggg 1320
cctcaacacc cctgaggact cggaccctga ccactttgac acagccattc tgtttacccg 1380
tcaggacctg tgtggagtct ccacttgcga cacgctgggt atggctgatg tgggcaccgt 1440
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cataacactc aaaaaaaaaa aa 4342

<210> 167
<211> 837
<212> PRT
<213> 現代人

<220>
<223> ADAMTS-4前驅體

<400> 167

Met Ser Gln Thr Gly Ser His Pro Gly Arg Gly Leu Ala Gly Arg Trp
 1   5   10   15

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Leu Trp Gly Ala Gln Pro Cys Leu Leu Leu Pro Ile Val Pro Leu Ser
                20                  25                  30
Trp Leu Val Trp Leu Leu Leu Leu Leu Leu Leu Ala Ser Leu Leu Pro Ser
            35                  40                  45
Ala Arg Leu Ala Ser Pro Leu Pro Arg Glu Glu Glu Ile Val Phe Pro
        50                  55                  60
Glu Lys Leu Asn Gly Ser Val Leu Pro Gly Ser Gly Ala Pro Ala Arg
65                  70                  75                  80
Leu Leu Cys Arg Leu Gln Ala Phe Gly Glu Thr Leu Leu Leu Glu Leu
                85                  90                  95
Glu Gln Asp Ser Gly Val Gln Val Glu Gly Leu Thr Val Gln Tyr Leu

            100                 105                 110
Gly Gln Ala Pro Glu Leu Leu Gly Gly Ala Glu Pro Gly Thr Tyr Leu
            115                 120                 125
Thr Gly Thr Ile Asn Gly Asp Pro Glu Ser Val Ala Ser Leu His Trp
        130                 135                 140
Asp Gly Gly Ala Leu Leu Gly Val Leu Gln Tyr Arg Gly Ala Glu Leu
145                 150                 155                 160
His Leu Gln Pro Leu Glu Gly Gly Thr Pro Asn Ser Ala Gly Gly Pro
                165                 170                 175
Gly Ala His Ile Leu Arg Arg Lys Ser Pro Ala Ser Gly Gln Gly Pro
            180                 185                 190
Met Cys Asn Val Lys Ala Pro Leu Gly Ser Pro Ser Pro Arg Pro Arg
            195                 200                 205
Arg Ala Lys Arg Phe Ala Ser Leu Ser Arg Phe Val Glu Thr Leu Val
        210                 215                 220
Val Ala Asp Asp Lys Met Ala Ala Phe His Gly Ala Gly Leu Lys Arg
225                 230                 235                 240
Tyr Leu Leu Thr Val Met Ala Ala Ala Ala Lys Ala Phe Lys His Pro
                245                 250                 255
Ser Ile Arg Asn Pro Val Ser Leu Val Val Thr Arg Leu Val Ile Leu
            260                 265                 270
Gly Ser Gly Glu Glu Gly Pro Gln Val Gly Pro Ser Ala Ala Gln Thr
            275                 280                 285
Leu Arg Ser Phe Cys Ala Trp Gln Arg Gly Leu Asn Thr Pro Glu Asp
        290                 295                 300
Ser Asp Pro Asp His Phe Asp Thr Ala Ile Leu Phe Thr Arg Gln Asp
305                 310                 315                 320
Leu Cys Gly Val Ser Thr Cys Asp Thr Leu Gly Met Ala Asp Val Gly
                325                 330                 335
Thr Val Cys Asp Pro Ala Arg Ser Cys Ala Ile Val Glu Asp Asp Gly
            340                 345                 350
Leu Gln Ser Ala Phe Thr Ala Ala His Glu Leu Gly His Val Phe Asn
            355                 360                 365
Met Leu His Asp Asn Ser Lys Pro Cys Ile Ser Leu Asn Gly Pro Leu
        370                 375                 380
Ser Thr Ser Arg His Val Met Ala Pro Val Met Ala His Val Asp Pro
385                 390                 395                 400
Glu Glu Pro Trp Ser Pro Cys Ser Ala Arg Phe Ile Thr Asp Phe Leu
                405                 410                 415
Asp Asn Gly Tyr Gly His Cys Leu Leu Asp Lys Pro Glu Ala Pro Leu
            420                 425                 430
His Leu Pro Val Thr Phe Pro Gly Lys Asp Tyr Asp Ala Asp Arg Gln
            435                 440                 445
Cys Gln Leu Thr Phe Gly Pro Asp Ser Arg His Cys Pro Gln Leu Pro
        450                 455                 460
Pro Pro Cys Ala Ala Leu Trp Cys Ser Gly His Leu Asn Gly His Ala
465                 470                 475                 480
Met Cys Gln Thr Lys His Ser Pro Trp Ala Asp Gly Thr Pro Cys Gly
                485                 490                 495
Pro Ala Gln Ala Cys Met Gly Gly Arg Cys Leu His Met Asp Gln Leu
            500                 505                 510
Gln Asp Phe Asn Ile Pro Gln Ala Gly Gly Trp Gly Pro Trp Gly Pro
            515                 520                 525
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Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Phe Ser Ser
    530                 535                 540
Arg Asp Cys Thr Arg Pro Val Pro Arg Asn Gly Gly Lys Tyr Cys Glu
545                 550                 555                 560
Gly Arg Arg Thr Arg Phe Arg Ser Cys Asn Thr Glu Asp Cys Pro Thr
                565                 570                 575
Gly Ser Ala Leu Thr Phe Arg Glu Glu Gln Cys Ala Ala Tyr Asn His
            580                 585                 590
Arg Thr Asp Leu Phe Lys Ser Phe Pro Gly Pro Met Asp Trp Val Pro
        595                 600                 605
Arg Tyr Thr Gly Val Ala Pro Gln Asp Gln Cys Lys Leu Thr Cys Gln
    610                 615                 620
Ala Arg Ala Leu Gly Tyr Tyr Tyr Val Leu Glu Pro Arg Val Val Asp
625                 630                 635                 640
Gly Thr Pro Cys Ser Pro Asp Ser Ser Ser Val Cys Val Gln Gly Arg
                645                 650                 655
Cys Ile His Ala Gly Cys Asp Arg Ile Ile Gly Ser Lys Lys Lys Phe
            660                 665                 670
Asp Lys Cys Met Val Cys Gly Gly Asp Gly Ser Gly Cys Ser Lys Gln
        675                 680                 685
Ser Gly Ser Phe Arg Lys Phe Arg Tyr Gly Tyr Asn Asn Val Val Thr
    690                 695                 700
Ile Pro Ala Gly Ala Thr His Ile Leu Val Arg Gln Gln Gly Asn Pro
705                 710                 715                 720
Gly His Arg Ser Ile Tyr Leu Ala Leu Lys Leu Pro Asp Gly Ser Tyr
                725                 730                 735
Ala Leu Asn Gly Glu Tyr Thr Leu Met Pro Ser Pro Thr Asp Val Val
            740                 745                 750
Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr Ala Ala Ser
        755                 760                 765
Glu Thr Leu Ser Gly His Gly Pro Leu Ala Gln Pro Leu Thr Leu Gln
    770                 775                 780
Val Leu Val Ala Gly Asn Pro Gln Asp Thr Arg Leu Arg Tyr Ser Phe
785                 790                 795                 800
Phe Val Pro Arg Pro Thr Pro Ser Thr Pro Arg Pro Thr Pro Gln Asp
                805                 810                 815
Trp Leu His Arg Arg Ala Gln Ile Leu Glu Ile Leu Arg Arg Arg Pro
            820                 825                 830
Trp Ala Gly Arg Lys
        835
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<210> 168
<211> 625
<212> PRT
<213> 現代人

<220>
<223> 成熟ADAMTS-4

<400> 168

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 1               5                  10                  15
Lys Met Ala Ala Phe His Gly Ala Gly Leu Lys Arg Tyr Leu Leu Thr
            20                  25                  30
Val Met Ala Ala Ala Ala Lys Ala Phe Lys His Pro Ser Ile Arg Asn
        35                  40                  45
Pro Val Ser Leu Val Val Thr Arg Leu Val Ile Leu Gly Ser Gly Glu
    50                  55                  60
Glu Gly Pro Gln Val Gly Pro Ser Ala Ala Gln Thr Leu Arg Ser Phe
65                  70                  75                  80
Cys Ala Trp Gln Arg Gly Leu Asn Thr Pro Glu Asp Ser Asp Pro Asp
                85                  90                  95
His Phe Asp Thr Ala Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Val
            100                 105                 110
```

```
Ser Thr Cys Asp Thr Leu Gly Met Ala Asp Val Gly Thr Val Cys Asp
        115                 120                 125
Pro Ala Arg Ser Cys Ala Ile Val Glu Asp Asp Gly Leu Gln Ser Ala
    130                 135                 140
Phe Thr Ala Ala His Glu Leu Gly His Val Phe Asn Met Leu His Asp
145                 150                 155                 160
Asn Ser Lys Pro Cys Ile Ser Leu Asn Gly Pro Leu Ser Thr Ser Arg
                165                 170                 175
His Val Met Ala Pro Val Met Ala His Val Asp Pro Glu Glu Pro Trp
            180                 185                 190

Ser Pro Cys Ser Ala Arg Phe Ile Thr Asp Phe Leu Asp Asn Gly Tyr
        195                 200                 205
Gly His Cys Leu Leu Asp Lys Pro Glu Ala Pro Leu His Leu Pro Val
    210                 215                 220
Thr Phe Pro Gly Lys Asp Tyr Asp Ala Asp Arg Gln Cys Gln Leu Thr
225                 230                 235                 240
Phe Gly Pro Asp Ser Arg His Cys Pro Gln Leu Pro Pro Pro Cys Ala
                245                 250                 255
Ala Leu Trp Cys Ser Gly His Leu Asn Gly His Ala Met Cys Gln Thr
            260                 265                 270
Lys His Ser Pro Trp Ala Asp Gly Thr Pro Cys Gly Pro Ala Gln Ala
        275                 280                 285
Cys Met Gly Gly Arg Cys Leu His Met Asp Gln Leu Gln Asp Phe Asn
    290                 295                 300
Ile Pro Gln Ala Gly Gly Trp Gly Pro Trp Gly Pro Trp Gly Asp Cys
305                 310                 315                 320
Ser Arg Thr Cys Gly Gly Gly Val Gln Phe Ser Ser Arg Asp Cys Thr
                325                 330                 335
Arg Pro Val Pro Arg Asn Gly Gly Lys Tyr Cys Glu Gly Arg Arg Thr
            340                 345                 350
Arg Phe Arg Ser Cys Asn Thr Glu Asp Cys Pro Thr Gly Ser Ala Leu
        355                 360                 365
Thr Phe Arg Glu Glu Gln Cys Ala Ala Tyr Asn His Arg Thr Asp Leu
    370                 375                 380
Phe Lys Ser Phe Pro Gly Pro Met Asp Trp Val Pro Arg Tyr Thr Gly
385                 390                 395                 400
Val Ala Pro Gln Asp Gln Cys Lys Leu Thr Cys Gln Ala Arg Ala Leu
                405                 410                 415
Gly Tyr Tyr Tyr Val Leu Glu Pro Arg Val Val Asp Gly Thr Pro Cys
            420                 425                 430
Ser Pro Asp Ser Ser Ser Val Cys Val Gln Gly Arg Cys Ile His Ala
        435                 440                 445
Gly Cys Asp Arg Ile Ile Gly Ser Lys Lys Lys Phe Asp Lys Cys Met
    450                 455                 460
Val Cys Gly Gly Asp Gly Ser Gly Cys Ser Lys Gln Ser Gly Ser Phe
465                 470                 475                 480
Arg Lys Phe Arg Tyr Gly Tyr Asn Asn Val Val Thr Ile Pro Ala Gly
                485                 490                 495
Ala Thr His Ile Leu Val Arg Gln Gln Gly Asn Pro Gly His Arg Ser
            500                 505                 510
Ile Tyr Leu Ala Leu Lys Leu Pro Asp Gly Ser Tyr Ala Leu Asn Gly
        515                 520                 525
Glu Tyr Thr Leu Met Pro Ser Pro Thr Asp Val Val Leu Pro Gly Ala

    530                 535                 540
Val Ser Leu Arg Tyr Ser Gly Ala Thr Ala Ala Ser Glu Thr Leu Ser
545                 550                 555                 560
Gly His Gly Pro Leu Ala Gln Pro Leu Thr Leu Gln Val Leu Val Ala
                565                 570                 575
Gly Asn Pro Gln Asp Thr Arg Leu Arg Tyr Ser Phe Phe Val Pro Arg
            580                 585                 590
Pro Thr Pro Ser Thr Pro Arg Pro Thr Pro Gln Asp Trp Leu His Arg
        595                 600                 605
Arg Ala Gln Ile Leu Glu Ile Leu Arg Arg Arg Pro Trp Ala Gly Arg
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610 615 620
Lys
625

<210> 169
<211> 9046
<212> DNA
<213> 現代人

<220>
<223> ADAMTS-5

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Tyr Leu Ala Leu Lys Lys Lys Asn Gly Glu Tyr Leu Ile Asn Gly Lys
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Tyr Met Ile Ser Thr Ser Glu Thr Ile Ile Asp Ile Asn Gly Thr Val
    530                 535                 540
Met Asn Tyr Ser Gly Trp Ser His Arg Asp Asp Phe Leu His Gly Met
545                 550                 555                 560
Gly Tyr Ser Ala Thr Lys Glu Ile Leu Ile Val Gln Ile Leu Ala Thr
                565                 570                 575
Asp Pro Thr Lys Pro Leu Asp Val Arg Tyr Ser Phe Phe Val Pro Lys
            580                 585                 590
Lys Ser Thr Pro Lys Val Asn Ser Val Thr Ser His Gly Ser Asn Lys
        595                 600                 605
Val Gly Ser His Thr Ser Gln Pro Gln Trp Val Thr Gly Pro Trp Leu
    610                 615                 620
Ala Cys Ser Arg Thr Cys Asp Thr Gly Trp His Thr Arg Thr Val Gln
625                 630                 635                 640
Cys Gln Asp Gly Asn Arg Lys Leu Ala Lys Gly Cys Pro Leu Ser Gln
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Arg Pro Ser Ala Phe Lys Gln Cys Leu Leu Lys Lys Cys
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660 665

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<211> 5269
<212> DNA
<213> 現代人

<220>
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<222> (0)...(0)
<223> ADAMTS14轉錄變異體1

<400> 172
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<210> 173
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<212> PRT
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<220>
<223> ADAMTS14同功異型物1前驅體

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            20   25   30
Gly Lys Leu Ser Asp Tyr Gly Val Thr Val Pro Cys Ser Thr Asp Phe
        35   40   45
Arg Gly Arg Phe Leu Ser His Val Val Ser Gly Pro Ala Ala Ala Ser
    50   55   60
Ala Gly Ser Met Val Val Asp Thr Pro Pro Thr Leu Pro Arg His Ser
65   70   75   80
Ser His Leu Arg Val Ala Arg Ser Pro Leu His Pro Gly Gly Thr Leu
                85   90   95
Trp Pro Gly Arg Val Gly Arg His Ser Leu Tyr Phe Asn Val Thr Val
            100   105   110
Phe Gly Lys Glu Leu His Leu Arg Leu Arg Pro Asn Arg Arg Leu Val
        115   120   125

Val Pro Gly Ser Ser Val Glu Trp Gln Glu Asp Phe Arg Glu Leu Phe
130 135 140
Arg Gln Pro Leu Arg Gln Glu Cys Val Tyr Thr Gly Gly Val Thr Gly
145 150 155 160
Met Pro Gly Ala Ala Val Ala Ile Ser Asn Cys Asp Gly Leu Ala Gly
165 170 175
Leu Ile Arg Thr Asp Ser Thr Asp Phe Phe Ile Glu Pro Leu Glu Arg
180 185 190
Gly Gln Gln Glu Lys Glu Ala Ser Gly Arg Thr His Val Val Tyr Arg
195 200 205
Arg Glu Ala Val Gln Gln Glu Trp Ala Glu Pro Asp Gly Asp Leu His
210 215 220
Asn Glu Ala Phe Gly Leu Gly Asp Leu Pro Asn Leu Leu Gly Leu Val
225 230 235 240
Gly Asp Gln Leu Gly Asp Thr Glu Arg Lys Arg Arg His Ala Lys Pro
245 250 255
Gly Ser Tyr Ser Ile Glu Val Leu Leu Val Val Asp Asp Ser Val Val
260 265 270
Arg Phe His Gly Lys Glu His Val Gln Asn Tyr Val Leu Thr Leu Met
275 280 285
Asn Ile Val Asp Glu Ile Tyr His Asp Glu Ser Leu Gly Val His Ile
290 295 300
Asn Ile Ala Leu Val Arg Leu Ile Met Val Gly Tyr Arg Gln Ser Leu
305 310 315 320
Ser Leu Ile Glu Arg Gly Asn Pro Ser Arg Ser Leu Glu Gln Val Cys
325 330 335
Arg Trp Ala His Ser Gln Gln Arg Gln Asp Pro Ser His Ala Glu His
340 345 350

His Asp His Val Val Phe Leu Thr Arg Gln Asp Phe Gly Pro Ser Gly
355 360 365
Met Gln Gly Tyr Ala Pro Val Thr Gly Met Cys His Pro Leu Arg Ser
370 375 380
Cys Ala Leu Asn His Glu Asp Gly Phe Ser Ser Ala Phe Val Ile Ala
385 390 395 400
His Glu Thr Gly His Val Leu Gly Met Glu His Asp Gly Gln Gly Asn
405 410 415
Gly Cys Ala Asp Glu Thr Ser Leu Gly Ser Val Met Ala Pro Leu Val
420 425 430
Gln Ala Ala Phe His Arg Phe His Trp Ser Arg Cys Ser Lys Leu Glu
435 440 445
Leu Ser Arg Tyr Leu Pro Ser Tyr Asp Cys Leu Leu Asp Asp Pro Phe
450 455 460
Asp Pro Ala Trp Pro Gln Pro Pro Glu Leu Pro Gly Ile Asn Tyr Ser
465 470 475 480
Met Asp Glu Gln Cys Arg Phe Asp Phe Gly Ser Gly Tyr Gln Thr Cys
485 490 495
Leu Ala Phe Arg Thr Phe Glu Pro Cys Lys Gln Leu Trp Cys Ser His
500 505 510
Pro Asp Asn Pro Tyr Phe Cys Lys Thr Lys Lys Gly Pro Pro Leu Asp
515 520 525
Gly Thr Glu Cys Ala Pro Gly Lys Trp Cys Phe Lys Gly His Cys Ile
530 535 540
Trp Lys Ser Pro Glu Gln Thr Tyr Gly Gln Asp Gly Gly Trp Ser Ser
545 550 555 560
Trp Thr Lys Phe Gly Ser Cys Ser Arg Ser Cys Gly Gly Gly Val Arg
565 570 575
Ser Arg Ser Arg Ser Cys Asn Asn Pro Ser Pro Ala Tyr Gly Gly Arg
580 585 590
Leu Cys Leu Gly Pro Met Phe Glu Tyr Gln Val Cys Asn Ser Glu Glu
595 600 605
Cys Pro Gly Thr Tyr Glu Asp Phe Arg Ala Gln Gln Cys Ala Lys Arg
610 615 620
Asn Ser Tyr Tyr Val His Gln Asn Ala Lys His Ser Trp Val Pro Tyr
625 630 635 640

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Glu Pro Asp Asp Asp Ala Gln Lys Cys Glu Leu Ile Cys Gln Ser Ala
                645                 650                 655
Asp Thr Gly Asp Val Val Phe Met Asn Gln Val Val His Asp Gly Thr
            660                 665                 670
Arg Cys Ser Tyr Arg Asp Pro Tyr Ser Val Cys Ala Arg Gly Glu Cys
        675                 680                 685
Val Pro Val Gly Cys Asp Lys Glu Val Gly Ser Met Lys Ala Asp Asp

    690                 695                 700
Lys Cys Gly Val Cys Gly Gly Asp Asn Ser His Cys Arg Thr Val Lys
705                 710                 715                 720
Gly Thr Leu Gly Lys Ala Ser Lys Gln Ala Gly Ala Leu Lys Leu Val
                725                 730                 735
Gln Ile Pro Ala Gly Ala Arg His Ile Gln Ile Glu Ala Leu Glu Lys
            740                 745                 750
Ser Pro His Arg Ile Val Val Lys Asn Gln Val Thr Gly Ser Phe Ile
        755                 760                 765
Leu Asn Pro Lys Gly Lys Glu Ala Thr Ser Arg Thr Phe Thr Ala Met
    770                 775                 780
Gly Leu Glu Trp Glu Asp Ala Val Glu Asp Ala Lys Glu Ser Leu Lys
785                 790                 795                 800
Thr Ser Gly Pro Leu Pro Glu Ala Ile Ala Ile Leu Ala Leu Pro Pro
                805                 810                 815
Thr Glu Gly Gly Pro Arg Ser Ser Leu Ala Tyr Lys Tyr Val Ile His
            820                 825                 830
Glu Asp Leu Leu Pro Leu Ile Gly Ser Asn Asn Val Leu Leu Glu Glu
        835                 840                 845
Met Asp Thr Tyr Glu Trp Ala Leu Lys Ser Trp Ala Pro Cys Ser Lys
    850                 855                 860
Ala Cys Gly Gly Gly Ile Gln Phe Thr Lys Tyr Gly Cys Arg Arg Arg
865                 870                 875                 880
Arg Asp His His Met Val Gln Arg His Leu Cys Asp His Lys Lys Arg
                885                 890                 895
Pro Lys Pro Ile Arg Arg Arg Cys Asn Gln His Pro Cys Ser Gln Pro
            900                 905                 910
Val Trp Val Thr Glu Glu Trp Gly Ala Cys Ser Arg Ser Cys Gly Lys
        915                 920                 925
Leu Gly Val Gln Thr Arg Gly Ile Gln Cys Leu Leu Pro Leu Ser Asn
    930                 935                 940
Gly Thr His Lys Val Met Pro Ala Lys Ala Cys Ala Gly Asp Arg Pro
945                 950                 955                 960
Glu Ala Arg Arg Pro Cys Leu Arg Val Pro Cys Pro Ala Gln Trp Arg
                965                 970                 975
Leu Gly Ala Trp Ser Gln Cys Ser Ala Thr Cys Gly Glu Gly Ile Gln
            980                 985                 990
Gln Arg Gln Val Val Cys Arg Thr Asn Ala Asn Ser Leu Gly His Cys
        995                 1000                1005
Glu Gly Asp Arg Pro Asp Thr Val Gln Val Cys Ser Leu Pro Ala Cys
    1010                1015                1020
Gly Gly Asn His Gln Asn Ser Thr Val Arg Ala Asp Val Trp Glu Leu
1025                1030                1035                1040
Gly Thr Pro Glu Gly Gln Trp Val Pro Gln Ser Glu Pro Leu His Pro
                1045                1050                1055
Ile Asn Lys Ile Ser Ser Thr Glu Pro Cys Thr Gly Asp Arg Ser Val
            1060                1065                1070
Phe Cys Gln Met Glu Val Leu Asp Arg Tyr Cys Ser Ile Pro Gly Tyr
        1075                1080                1085
His Arg Leu Cys Cys Val Ser Cys Ile Lys Lys Ala Ser Gly Pro Asn
    1090                1095                1100
Pro Gly Pro Asp Pro Gly Pro Thr Ser Leu Pro Pro Phe Ser Thr Pro
1105                1110                1115                1120
Gly Ser Pro Leu Pro Gly Pro Gln Asp Pro Ala Asp Ala Ala Glu Pro
                1125                1130                1135
Pro Gly Lys Pro Thr Gly Ser Glu Asp His Gln His Gly Arg Ala Thr
            1140                1145                1150
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Gln Leu Pro Gly Ala Leu Asp Thr Ser Ser Pro Gly Thr Gln His Pro
        1155                1160                1165
Phe Ala Pro Glu Thr Pro Ile Pro Gly Ala Ser Trp Ser Ile Ser Pro
    1170                1175                1180
Thr Thr Pro Gly Gly Leu Pro Trp Gly Trp Thr Gln Thr Pro Thr Pro
1185                1190                1195                1200
Val Pro Glu Asp Lys Gly Gln Pro Gly Glu Asp Leu Arg His Pro Gly
                1205                1210                1215
Thr Ser Leu Pro Ala Ala Ser Pro Val Thr
            1220                1225
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<220>
<223> 成熟ADAMTS14同功異型物1

<400> 174

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Asp Ser Val Val Arg Phe His Gly Lys Glu His Val Gln Asn Tyr Val
            20                  25                  30
Leu Thr Leu Met Asn Ile Val Asp Glu Ile Tyr His Asp Glu Ser Leu
        35                  40                  45
Gly Val His Ile Asn Ile Ala Leu Val Arg Leu Ile Met Val Gly Tyr
    50                  55                  60
Arg Gln Ser Leu Ser Leu Ile Glu Arg Gly Asn Pro Ser Arg Ser Leu
65                  70                  75                  80
Glu Gln Val Cys Arg Trp Ala His Ser Gln Gln Arg Gln Asp Pro Ser
                85                  90                  95
His Ala Glu His His Asp His Val Val Phe Leu Thr Arg Gln Asp Phe
            100                 105                 110
Gly Pro Ser Gly Met Gln Gly Tyr Ala Pro Val Thr Gly Met Cys His
        115                 120                 125
Pro Leu Arg Ser Cys Ala Leu Asn His Glu Asp Gly Phe Ser Ser Ala
    130                 135                 140
Phe Val Ile Ala His Glu Thr Gly His Val Leu Gly Met Glu His Asp
145                 150                 155                 160
Gly Gln Gly Asn Gly Cys Ala Asp Glu Thr Ser Leu Gly Ser Val Met
                165                 170                 175
Ala Pro Leu Val Gln Ala Ala Phe His Arg Phe His Trp Ser Arg Cys
            180                 185                 190
Ser Lys Leu Glu Leu Ser Arg Tyr Leu Pro Ser Tyr Asp Cys Leu Leu
        195                 200                 205
Asp Asp Pro Phe Asp Pro Ala Trp Pro Gln Pro Pro Glu Leu Pro Gly
    210                 215                 220
Ile Asn Tyr Ser Met Asp Glu Gln Cys Arg Phe Asp Phe Gly Ser Gly
225                 230                 235                 240
Tyr Gln Thr Cys Leu Ala Phe Arg Thr Phe Glu Pro Cys Lys Gln Leu
                245                 250                 255
Trp Cys Ser His Pro Asp Asn Pro Tyr Phe Cys Lys Thr Lys Lys Gly
            260                 265                 270
Pro Pro Leu Asp Gly Thr Glu Cys Ala Pro Gly Lys Trp Cys Phe Lys
        275                 280                 285
Gly His Cys Ile Trp Lys Ser Pro Glu Gln Thr Tyr Gly Gln Asp Gly
    290                 295                 300
Gly Trp Ser Ser Trp Thr Lys Phe Gly Ser Cys Ser Arg Ser Cys Gly
305                 310                 315                 320
Gly Gly Val Arg Ser Arg Ser Arg Ser Cys Asn Asn Pro Ser Pro Ala
                325                 330                 335
Tyr Gly Gly Arg Leu Cys Leu Gly Pro Met Phe Glu Tyr Gln Val Cys
            340                 345                 350
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Asn Ser Glu Glu Cys Pro Gly Thr Tyr Glu Asp Phe Arg Ala Gln Gln
        355                 360                 365
Cys Ala Lys Arg Asn Ser Tyr Tyr Val His Gln Asn Ala Lys His Ser
    370                 375                 380
Trp Val Pro Tyr Glu Pro Asp Asp Asp Ala Gln Lys Cys Glu Leu Ile
385                 390                 395                 400
Cys Gln Ser Ala Asp Thr Gly Asp Val Val Phe Met Asn Gln Val Val
                405                 410                 415
His Asp Gly Thr Arg Cys Ser Tyr Arg Asp Pro Tyr Ser Val Cys Ala
            420                 425                 430
Arg Gly Glu Cys Val Pro Val Gly Cys Asp Lys Glu Val Gly Ser Met
        435                 440                 445
Lys Ala Asp Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser His Cys
    450                 455                 460
Arg Thr Val Lys Gly Thr Leu Gly Lys Ala Ser Lys Gln Ala Gly Ala
465                 470                 475                 480
Leu Lys Leu Val Gln Ile Pro Ala Gly Ala Arg His Ile Gln Ile Glu
                485                 490                 495
Ala Leu Glu Lys Ser Pro His Arg Ile Val Val Lys Asn Gln Val Thr
            500                 505                 510
Gly Ser Phe Ile Leu Asn Pro Lys Gly Lys Glu Ala Thr Ser Arg Thr
        515                 520                 525
Phe Thr Ala Met Gly Leu Glu Trp Glu Asp Ala Val Glu Asp Ala Lys
    530                 535                 540
Glu Ser Leu Lys Thr Ser Gly Pro Leu Pro Glu Ala Ile Ala Ile Leu
545                 550                 555                 560
Ala Leu Pro Pro Thr Glu Gly Gly Pro Arg Ser Ser Leu Ala Tyr Lys
                565                 570                 575
Tyr Val Ile His Glu Asp Leu Leu Pro Leu Ile Gly Ser Asn Asn Val
            580                 585                 590
Leu Leu Glu Glu Met Asp Thr Tyr Glu Trp Ala Leu Lys Ser Trp Ala
        595                 600                 605
Pro Cys Ser Lys Ala Cys Gly Gly Gly Ile Gln Phe Thr Lys Tyr Gly
    610                 615                 620
Cys Arg Arg Arg Arg Asp His His Met Val Gln Arg His Leu Cys Asp
625                 630                 635                 640
His Lys Lys Arg Pro Lys Pro Ile Arg Arg Arg Cys Asn Gln His Pro
                645                 650                 655
Cys Ser Gln Pro Val Trp Val Thr Glu Glu Trp Gly Ala Cys Ser Arg
            660                 665                 670
Ser Cys Gly Lys Leu Gly Val Gln Thr Arg Gly Ile Gln Cys Leu Leu
        675                 680                 685
Pro Leu Ser Asn Gly Thr His Lys Val Met Pro Ala Lys Ala Cys Ala
    690                 695                 700
Gly Asp Arg Pro Glu Ala Arg Arg Pro Cys Leu Arg Val Pro Cys Pro
705                 710                 715                 720
Ala Gln Trp Arg Leu Gly Ala Trp Ser Gln Cys Ser Ala Thr Cys Gly
                725                 730                 735
Glu Gly Ile Gln Gln Arg Gln Val Val Cys Arg Thr Asn Ala Asn Ser
            740                 745                 750
Leu Gly His Cys Glu Gly Asp Arg Pro Asp Thr Val Gln Val Cys Ser
        755                 760                 765
Leu Pro Ala Cys Gly Gly Asn His Gln Asn Ser Thr Val Arg Ala Asp
    770                 775                 780
Val Trp Glu Leu Gly Thr Pro Glu Gly Gln Trp Val Pro Gln Ser Glu
785                 790                 795                 800
Pro Leu His Pro Ile Asn Lys Ile Ser Ser Thr Glu Pro Cys Thr Gly
                805                 810                 815
Asp Arg Ser Val Phe Cys Gln Met Glu Val Leu Asp Arg Tyr Cys Ser
            820                 825                 830
Ile Pro Gly Tyr His Arg Leu Cys Cys Val Ser Cys Ile Lys Lys Ala
        835                 840                 845
Ser Gly Pro Asn Pro Gly Pro Asp Pro Gly Pro Thr Ser Leu Pro Pro
    850                 855                 860
Phe Ser Thr Pro Gly Ser Pro Leu Pro Gly Pro Gln Asp Pro Ala Asp
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865 870 875 880
Ala Ala Glu Pro Pro Gly Lys Pro Thr Gly Ser Glu Asp His Gln His
885 890 895
Gly Arg Ala Thr Gln Leu Pro Gly Ala Leu Asp Thr Ser Ser Pro Gly
900 905 910
Thr Gln His Pro Phe Ala Pro Glu Thr Pro Ile Pro Gly Ala Ser Trp
915 920 925
Ser Ile Ser Pro Thr Thr Pro Gly Gly Leu Pro Trp Gly Trp Thr Gln
930 935 940
Thr Pro Thr Pro Val Pro Glu Asp Lys Gly Gln Pro Gly Glu Asp Leu
945 950 955 960
Arg His Pro Gly Thr Ser Leu Pro Ala Ala Ser Pro Val Thr
965 970

<210> 175
<211> 5260
<212> DNA
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<220>
<223> ADAMTS14轉錄變異體2

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aattttatgt atttattaac atcgccattg gaccccaaaa 5260

<210> 176
<211> 1223
<212> PRT
<213> 現代人

<220>
<223> ADAMTS14同功異型物b前驅體

<400> 176
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Ala Leu Cys Ala Ala Ala Gly Ser Arg Thr Pro Glu Leu His Leu Ser
            20   25   30
Gly Lys Leu Ser Asp Tyr Gly Val Thr Val Pro Cys Ser Thr Asp Phe
        35   40   45

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Arg Gly Arg Phe Leu Ser His Val Val Ser Gly Pro Ala Ala Ala Ser
    50                  55                  60
Ala Gly Ser Met Val Val Asp Thr Pro Pro Thr Leu Pro Arg His Ser
65                  70                  75                  80
Ser His Leu Arg Val Ala Arg Ser Pro Leu His Pro Gly Gly Thr Leu
                85                  90                  95
Trp Pro Gly Arg Val Gly Arg His Ser Leu Tyr Phe Asn Val Thr Val
            100                 105                 110
Phe Gly Lys Glu Leu His Leu Arg Leu Arg Pro Asn Arg Arg Leu Val

        115                 120                 125
Val Pro Gly Ser Ser Val Glu Trp Gln Glu Asp Phe Arg Glu Leu Phe
    130                 135                 140
Arg Gln Pro Leu Arg Gln Glu Cys Val Tyr Thr Gly Gly Val Thr Gly
145                 150                 155                 160
Met Pro Gly Ala Ala Val Ala Ile Ser Asn Cys Asp Gly Leu Ala Gly
                165                 170                 175
Leu Ile Arg Thr Asp Ser Thr Asp Phe Phe Ile Glu Pro Leu Glu Arg
            180                 185                 190
Gly Gln Gln Glu Lys Glu Ala Ser Gly Arg Thr His Val Val Tyr Arg
        195                 200                 205
Arg Glu Ala Val Gln Gln Glu Trp Ala Glu Pro Asp Gly Asp Leu His
    210                 215                 220
Asn Glu Ala Phe Gly Leu Gly Asp Leu Pro Asn Leu Leu Gly Leu Val
225                 230                 235                 240
Gly Asp Gln Leu Gly Asp Thr Glu Arg Lys Arg Arg His Ala Lys Pro
                245                 250                 255
Gly Ser Tyr Ser Ile Glu Val Leu Leu Val Val Asp Asp Ser Val Val
            260                 265                 270
Arg Phe His Gly Lys Glu His Val Gln Asn Tyr Val Leu Thr Leu Met
        275                 280                 285
Asn Ile Val Asp Glu Ile Tyr His Asp Glu Ser Leu Gly Val His Ile
    290                 295                 300
Asn Ile Ala Leu Val Arg Leu Ile Met Val Gly Tyr Arg Gln Ser Leu
305                 310                 315                 320
Ser Leu Ile Glu Arg Gly Asn Pro Ser Arg Ser Leu Glu Gln Val Cys
                325                 330                 335
Arg Trp Ala His Ser Gln Gln Arg Gln Asp Pro Ser His Ala Glu His
            340                 345                 350
His Asp His Val Val Phe Leu Thr Arg Gln Asp Phe Gly Pro Ser Gly
        355                 360                 365
Tyr Ala Pro Val Thr Gly Met Cys His Pro Leu Arg Ser Cys Ala Leu
    370                 375                 380
Asn His Glu Asp Gly Phe Ser Ser Ala Phe Val Ile Ala His Glu Thr
385                 390                 395                 400
Gly His Val Leu Gly Met Glu His Asp Gly Gln Gly Asn Gly Cys Ala
                405                 410                 415
Asp Glu Thr Ser Leu Gly Ser Val Met Ala Pro Leu Val Gln Ala Ala
            420                 425                 430
Phe His Arg Phe His Trp Ser Arg Cys Ser Lys Leu Glu Leu Ser Arg
        435                 440                 445
Tyr Leu Pro Ser Tyr Asp Cys Leu Leu Asp Asp Pro Phe Asp Pro Ala
    450                 455                 460
Trp Pro Gln Pro Pro Glu Leu Pro Gly Ile Asn Tyr Ser Met Asp Glu
465                 470                 475                 480
Gln Cys Arg Phe Asp Phe Gly Ser Gly Tyr Gln Thr Cys Leu Ala Phe
                485                 490                 495
Arg Thr Phe Glu Pro Cys Lys Gln Leu Trp Cys Ser His Pro Asp Asn
            500                 505                 510
Pro Tyr Phe Cys Lys Thr Lys Lys Gly Pro Pro Leu Asp Gly Thr Glu
        515                 520                 525
Cys Ala Pro Gly Lys Trp Cys Phe Lys Gly His Cys Ile Trp Lys Ser
    530                 535                 540
Pro Glu Gln Thr Tyr Gly Gln Asp Gly Gly Trp Ser Ser Trp Thr Lys
545                 550                 555                 560
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Phe Gly Ser Cys Ser Arg Ser Cys Gly Gly Gly Val Arg Ser Arg Ser
                565                 570                 575
Arg Ser Cys Asn Asn Pro Ser Pro Ala Tyr Gly Gly Arg Leu Cys Leu
            580                 585                 590
Gly Pro Met Phe Glu Tyr Gln Val Cys Asn Ser Glu Glu Cys Pro Gly
        595                 600                 605
Thr Tyr Glu Asp Phe Arg Ala Gln Gln Cys Ala Lys Arg Asn Ser Tyr
    610                 615                 620
Tyr Val His Gln Asn Ala Lys His Ser Trp Val Pro Tyr Glu Pro Asp
625                 630                 635                 640
Asp Asp Ala Gln Lys Cys Glu Leu Ile Cys Gln Ser Ala Asp Thr Gly
                645                 650                 655
Asp Val Val Phe Met Asn Gln Val Val His Asp Gly Thr Arg Cys Ser
            660                 665                 670
Tyr Arg Asp Pro Tyr Ser Val Cys Ala Arg Gly Glu Cys Val Pro Val
        675                 680                 685
Gly Cys Asp Lys Glu Val Gly Ser Met Lys Ala Asp Asp Lys Cys Gly
    690                 695                 700
Val Cys Gly Gly Asp Asn Ser His Cys Arg Thr Val Lys Gly Thr Leu
705                 710                 715                 720
Gly Lys Ala Ser Lys Gln Ala Gly Ala Leu Lys Leu Val Gln Ile Pro
                725                 730                 735
Ala Gly Ala Arg His Ile Gln Ile Glu Ala Leu Glu Lys Ser Pro His
            740                 745                 750
Arg Ile Val Val Lys Asn Gln Val Thr Gly Ser Phe Ile Leu Asn Pro
        755                 760                 765
Lys Gly Lys Glu Ala Thr Ser Arg Thr Phe Thr Ala Met Gly Leu Glu
    770                 775                 780
Trp Glu Asp Ala Val Glu Asp Ala Lys Glu Ser Leu Lys Thr Ser Gly
785                 790                 795                 800
Pro Leu Pro Glu Ala Ile Ala Ile Leu Ala Leu Pro Pro Thr Glu Gly
                805                 810                 815
Gly Pro Arg Ser Ser Leu Ala Tyr Lys Tyr Val Ile His Glu Asp Leu
            820                 825                 830
Leu Pro Leu Ile Gly Ser Asn Asn Val Leu Leu Glu Glu Met Asp Thr
        835                 840                 845
Tyr Glu Trp Ala Leu Lys Ser Trp Ala Pro Cys Ser Lys Ala Cys Gly
    850                 855                 860
Gly Gly Ile Gln Phe Thr Lys Tyr Gly Cys Arg Arg Arg Arg Asp His
865                 870                 875                 880
His Met Val Gln Arg His Leu Cys Asp His Lys Lys Arg Pro Lys Pro
                885                 890                 895
Ile Arg Arg Arg Cys Asn Gln His Pro Cys Ser Gln Pro Val Trp Val
            900                 905                 910
Thr Glu Glu Trp Gly Ala Cys Ser Arg Ser Cys Gly Lys Leu Gly Val
        915                 920                 925
Gln Thr Arg Gly Ile Gln Cys Leu Leu Pro Leu Ser Asn Gly Thr His
    930                 935                 940
Lys Val Met Pro Ala Lys Ala Cys Ala Gly Asp Arg Pro Glu Ala Arg
945                 950                 955                 960
Arg Pro Cys Leu Arg Val Pro Cys Pro Ala Gln Trp Arg Leu Gly Ala
                965                 970                 975
Trp Ser Gln Cys Ser Ala Thr Cys Gly Glu Gly Ile Gln Gln Arg Gln
            980                 985                 990
Val Val Cys Arg Thr Asn Ala Asn Ser Leu Gly His Cys Glu Gly Asp
        995                 1000                1005
Arg Pro Asp Thr Val Gln Val Cys Ser Leu Pro Ala Cys Gly Gly Asn
    1010                1015                1020
His Gln Asn Ser Thr Val Arg Ala Asp Val Trp Glu Leu Gly Thr Pro
1025                1030                1035                1040
Glu Gly Gln Trp Val Pro Gln Ser Glu Pro Leu His Pro Ile Asn Lys
                1045                1050                1055
Ile Ser Ser Thr Glu Pro Cys Thr Gly Asp Arg Ser Val Phe Cys Gln
            1060                1065                1070
Met Glu Val Leu Asp Arg Tyr Cys Ser Ile Pro Gly Tyr His Arg Leu
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        1075                1080                1085
Cys Cys Val Ser Cys Ile Lys Lys Ala Ser Gly Pro Asn Pro Gly Pro
    1090                1095                1100
Asp Pro Gly Pro Thr Ser Leu Pro Pro Phe Ser Thr Pro Gly Ser Pro
1105                1110                1115                1120
Leu Pro Gly Pro Gln Asp Pro Ala Asp Ala Ala Glu Pro Pro Gly Lys
                1125                1130                1135
Pro Thr Gly Ser Glu Asp His Gln His Gly Arg Ala Thr Gln Leu Pro
            1140                1145                1150
Gly Ala Leu Asp Thr Ser Ser Pro Gly Thr Gln His Pro Phe Ala Pro
        1155                1160                1165
Glu Thr Pro Ile Pro Gly Ala Ser Trp Ser Ile Ser Pro Thr Thr Pro
    1170                1175                1180
Gly Gly Leu Pro Trp Gly Trp Thr Gln Thr Pro Thr Pro Val Pro Glu
1185                1190                1195                1200
Asp Lys Gly Gln Pro Gly Glu Asp Leu Arg His Pro Gly Thr Ser Leu
                1205                1210                1215
Pro Ala Ala Ser Pro Val Thr
            1220


<210> 177
<211> 971
<212> PRT
<213> 現代人

<220>
<223> 成熟ADAMTS14同功異型物2

<400> 177
His Ala Lys Pro Gly Ser Tyr Ser Ile Glu Val Leu Leu Val Val Asp
 1                5                  10                  15
Asp Ser Val Val Arg Phe His Gly Lys Glu His Val Gln Asn Tyr Val
            20                  25                  30
Leu Thr Leu Met Asn Ile Val Asp Glu Ile Tyr His Asp Glu Ser Leu
        35                  40                  45
Gly Val His Ile Asn Ile Ala Leu Val Arg Leu Ile Met Val Gly Tyr
    50                  55                  60
Arg Gln Ser Leu Ser Leu Ile Glu Arg Gly Asn Pro Ser Arg Ser Leu
65                  70                  75                  80
Glu Gln Val Cys Arg Trp Ala His Ser Gln Gln Arg Gln Asp Pro Ser
                85                  90                  95
His Ala Glu His His Asp His Val Val Phe Leu Thr Arg Gln Asp Phe
            100                 105                 110
Gly Pro Ser Gly Tyr Ala Pro Val Thr Gly Met Cys His Pro Leu Arg
        115                 120                 125
Ser Cys Ala Leu Asn His Glu Asp Gly Phe Ser Ser Ala Phe Val Ile
    130                 135                 140
Ala His Glu Thr Gly His Val Leu Gly Met Glu His Asp Gly Gln Gly
145                 150                 155                 160
Asn Gly Cys Ala Asp Glu Thr Ser Leu Gly Ser Val Met Ala Pro Leu
                165                 170                 175
Val Gln Ala Ala Phe His Arg Phe His Trp Ser Arg Cys Ser Lys Leu
            180                 185                 190
Glu Leu Ser Arg Tyr Leu Pro Ser Tyr Asp Cys Leu Leu Asp Asp Pro
        195                 200                 205
Phe Asp Pro Ala Trp Pro Gln Pro Pro Glu Leu Pro Gly Ile Asn Tyr
    210                 215                 220
Ser Met Asp Glu Gln Cys Arg Phe Asp Phe Gly Ser Gly Tyr Gln Thr
225                 230                 235                 240
Cys Leu Ala Phe Arg Thr Phe Glu Pro Cys Lys Gln Leu Trp Cys Ser
                245                 250                 255
His Pro Asp Asn Pro Tyr Phe Cys Lys Thr Lys Lys Gly Pro Pro Leu
            260                 265                 270
Asp Gly Thr Glu Cys Ala Pro Gly Lys Trp Cys Phe Lys Gly His Cys
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        275                 280                 285
Ile Trp Lys Ser Pro Glu Gln Thr Tyr Gly Gln Asp Gly Gly Trp Ser
    290                 295                 300
Ser Trp Thr Lys Phe Gly Ser Cys Ser Arg Ser Cys Gly Gly Gly Val
305                 310                 315                 320
Arg Ser Arg Ser Arg Ser Cys Asn Asn Pro Ser Pro Ala Tyr Gly Gly
                325                 330                 335
Arg Leu Cys Leu Gly Pro Met Phe Glu Tyr Gln Val Cys Asn Ser Glu
            340                 345                 350
Glu Cys Pro Gly Thr Tyr Glu Asp Phe Arg Ala Gln Gln Cys Ala Lys
        355                 360                 365
Arg Asn Ser Tyr Tyr Val His Gln Asn Ala Lys His Ser Trp Val Pro
    370                 375                 380
Tyr Glu Pro Asp Asp Asp Ala Gln Lys Cys Glu Leu Ile Cys Gln Ser
385                 390                 395                 400
Ala Asp Thr Gly Asp Val Val Phe Met Asn Gln Val Val His Asp Gly
                405                 410                 415
Thr Arg Cys Ser Tyr Arg Asp Pro Tyr Ser Val Cys Ala Arg Gly Glu
            420                 425                 430
Cys Val Pro Val Gly Cys Asp Lys Glu Val Gly Ser Met Lys Ala Asp
        435                 440                 445
Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser His Cys Arg Thr Val
    450                 455                 460
Lys Gly Thr Leu Gly Lys Ala Ser Lys Gln Ala Gly Ala Leu Lys Leu
465                 470                 475                 480
Val Gln Ile Pro Ala Gly Ala Arg His Ile Gln Ile Glu Ala Leu Glu
                485                 490                 495
Lys Ser Pro His Arg Ile Val Val Lys Asn Gln Val Thr Gly Ser Phe
            500                 505                 510
Ile Leu Asn Pro Lys Gly Lys Glu Ala Thr Ser Arg Thr Phe Thr Ala
        515                 520                 525
Met Gly Leu Glu Trp Glu Asp Ala Val Glu Asp Ala Lys Glu Ser Leu
    530                 535                 540
Lys Thr Ser Gly Pro Leu Pro Glu Ala Ile Ala Ile Leu Ala Leu Pro
545                 550                 555                 560
Pro Thr Glu Gly Gly Pro Arg Ser Ser Leu Ala Tyr Lys Tyr Val Ile
                565                 570                 575
His Glu Asp Leu Leu Pro Leu Ile Gly Ser Asn Asn Val Leu Leu Glu
            580                 585                 590
Glu Met Asp Thr Tyr Glu Trp Ala Leu Lys Ser Trp Ala Pro Cys Ser
        595                 600                 605
Lys Ala Cys Gly Gly Gly Ile Gln Phe Thr Lys Tyr Gly Cys Arg Arg
    610                 615                 620
Arg Arg Asp His His Met Val Gln Arg His Leu Cys Asp His Lys Lys
625                 630                 635                 640
Arg Pro Lys Pro Ile Arg Arg Arg Cys Asn Gln His Pro Cys Ser Gln
                645                 650                 655
Pro Val Trp Val Thr Glu Glu Trp Gly Ala Cys Ser Arg Ser Cys Gly
            660                 665                 670
Lys Leu Gly Val Gln Thr Arg Gly Ile Gln Cys Leu Leu Pro Leu Ser
        675                 680                 685
Asn Gly Thr His Lys Val Met Pro Ala Lys Ala Cys Ala Gly Asp Arg
    690                 695                 700
Pro Glu Ala Arg Arg Pro Cys Leu Arg Val Pro Cys Pro Ala Gln Trp
705                 710                 715                 720
Arg Leu Gly Ala Trp Ser Gln Cys Ser Ala Thr Cys Gly Glu Gly Ile
                725                 730                 735
Gln Gln Arg Gln Val Val Cys Arg Thr Asn Ala Asn Ser Leu Gly His
            740                 745                 750
Cys Glu Gly Asp Arg Pro Asp Thr Val Gln Val Cys Ser Leu Pro Ala
        755                 760                 765
Cys Gly Gly Asn His Gln Asn Ser Thr Val Arg Ala Asp Val Trp Glu
    770                 775                 780
Leu Gly Thr Pro Glu Gly Gln Trp Val Pro Gln Ser Glu Pro Leu His
785                 790                 795                 800
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Pro Ile Asn Lys Ile Ser Ser Thr Glu Pro Cys Thr Gly Asp Arg Ser
                805                 810                 815
Val Phe Cys Gln Met Glu Val Leu Asp Arg Tyr Cys Ser Ile Pro Gly
            820                 825                 830
Tyr His Arg Leu Cys Cys Val Ser Cys Ile Lys Lys Ala Ser Gly Pro
        835                 840                 845
Asn Pro Gly Pro Asp Pro Gly Pro Thr Ser Leu Pro Pro Phe Ser Thr
    850                 855                 860
Pro Gly Ser Pro Leu Pro Gly Pro Gln Asp Pro Ala Asp Ala Ala Glu
865                 870                 875                 880
Pro Pro Gly Lys Pro Thr Gly Ser Glu Asp His Gln His Gly Arg Ala
                885                 890                 895
Thr Gln Leu Pro Gly Ala Leu Asp Thr Ser Ser Pro Gly Thr Gln His
            900                 905                 910
Pro Phe Ala Pro Glu Thr Pro Ile Pro Gly Ala Ser Trp Ser Ile Ser
        915                 920                 925
Pro Thr Thr Pro Gly Gly Leu Pro Trp Gly Trp Thr Gln Thr Pro Thr
    930                 935                 940
Pro Val Pro Glu Asp Lys Gly Gln Pro Gly Glu Asp Leu Arg His Pro
945                 950                 955                 960
Gly Thr Ser Leu Pro Ala Ala Ser Pro Val Thr
                965                 970
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<210> 178
<211> 1904
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶C

<400> 178

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gtgcaattga gagcatagca gtggcagcca caccaattcc taaattgtag ggtatgcctt 1500
ccagtatttc ataatgatct gcatcagttg taaaggggaa ttggtatatt cacagactgt 1560
agactttcag cagcaatctc agaagcttac aaatagattt ccatgaagat atttgtcttc 1620
agaattaaaa ctgcccttaa ttttaatata cctttcaatc ggccactggc catttttttc 1680
taagtattca attaagtggg aattttctgg aagatggtca gctatgaagt aatagagttt 1740
gcttaatcat ttgtaattca aacatgctat atttttttaaa atcaatgtga aaacatagac 1800
ttatttttaa attgtaccaa tcacaagaaa ataatggcaa taattatcaa aacttttaaa 1860
atagatgctc atatttttaa aataaagttt taaaaataac tgca                  1904
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<210> 179
<211> 463
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶C前驅體

<400> 179

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Met Gly Ala Gly Pro Ser Leu Leu Leu Ala Ala Leu Leu Leu Leu Leu
 1               5                  10                  15
Ser Gly Asp Gly Ala Val Arg Cys Asp Thr Pro Ala Asn Cys Thr Tyr
            20                  25                  30
Leu Asp Leu Leu Gly Thr Trp Val Phe Gln Val Gly Ser Ser Gly Ser
        35                  40                  45
Gln Arg Asp Val Asn Cys Ser Val Met Gly Pro Gln Glu Lys Lys Val
    50                  55                  60
Val Val Tyr Leu Gln Lys Leu Asp Thr Ala Tyr Asp Asp Leu Gly Asn
65                  70                  75                  80
Ser Gly His Phe Thr Ile Ile Tyr Asn Gln Gly Phe Glu Ile Val Leu
                85                  90                  95
Asn Asp Tyr Lys Trp Phe Ala Phe Phe Lys Tyr Lys Glu Glu Gly Ser
            100                 105                 110
Lys Val Thr Thr Tyr Cys Asn Glu Thr Met Thr Gly Trp Val His Asp
        115                 120                 125
Val Leu Gly Arg Asn Trp Ala Cys Phe Thr Gly Lys Lys Val Gly Thr
    130                 135                 140
Ala Ser Glu Asn Val Tyr Val Asn Thr Ala His Leu Lys Asn Ser Gln
145                 150                 155                 160
Glu Lys Tyr Ser Asn Arg Leu Tyr Lys Tyr Asp His Asn Phe Val Lys
                165                 170                 175
Ala Ile Asn Ala Ile Gln Lys Ser Trp Thr Ala Thr Thr Tyr Met Glu
            180                 185                 190
Tyr Glu Thr Leu Thr Leu Gly Asp Met Ile Arg Arg Ser Gly Gly His
        195                 200                 205
Ser Arg Lys Ile Pro Arg Pro Lys Pro Ala Pro Leu Thr Ala Glu Ile
    210                 215                 220
Gln Gln Lys Ile Leu His Leu Pro Thr Ser Trp Asp Trp Arg Asn Val
225                 230                 235                 240
His Gly Ile Asn Phe Val Ser Pro Val Arg Asn Gln Ala Ser Cys Gly
                245                 250                 255
Ser Cys Tyr Ser Phe Ala Ser Met Gly Met Leu Glu Ala Arg Ile Arg
            260                 265                 270
Ile Leu Thr Asn Asn Ser Gln Thr Pro Ile Leu Ser Pro Gln Glu Val
        275                 280                 285
Val Ser Cys Ser Gln Tyr Ala Gln Gly Cys Glu Gly Gly Phe Pro Tyr
    290                 295                 300
Leu Ile Ala Gly Lys Tyr Ala Gln Asp Phe Gly Leu Val Glu Glu Ala
305                 310                 315                 320
Cys Phe Pro Tyr Thr Gly Thr Asp Ser Pro Cys Lys Met Lys Glu Asp
                325                 330                 335
Cys Phe Arg Tyr Tyr Ser Ser Glu Tyr His Tyr Val Gly Gly Phe Tyr
            340                 345                 350
Gly Gly Cys Asn Glu Ala Leu Met Lys Leu Glu Leu Val His His Gly
        355                 360                 365
Pro Met Ala Val Ala Phe Glu Val Tyr Asp Asp Phe Leu His Tyr Lys
    370                 375                 380
Lys Gly Ile Tyr His His Thr Gly Leu Arg Asp Pro Phe Asn Pro Phe
385                 390                 395                 400
Glu Leu Thr Asn His Ala Val Leu Leu Val Gly Tyr Gly Thr Asp Ser
                405                 410                 415
Ala Ser Gly Met Asp Tyr Trp Ile Val Lys Asn Ser Trp Gly Thr Gly
            420                 425                 430
Trp Gly Glu Asn Gly Tyr Phe Arg Ile Arg Arg Gly Thr Asp Glu Cys
```

```
        435                 440                 445
Ala Ile Glu Ser Ile Ala Val Ala Ala Thr Pro Ile Pro Lys Leu
    450                 455                 460


<210> 180
<211> 343
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶C

<220>
<223> 二肽基-肽酶排除域鏈1-110

<220>
<223> 二肽基-肽酶重鏈111-274

<220>
<223> 二肽基-肽酶輕鏈275-343

<400> 180
Asp Thr Pro Ala Asn Cys Thr Tyr Leu Asp Leu Leu Gly Thr Trp Val
 1               5                  10                  15

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

            180                 185                 190
Asp Phe Gly Leu Val Glu Glu Ala Cys Phe Pro Tyr Thr Gly Thr Asp
        195                 200                 205
Ser Pro Cys Lys Met Lys Glu Asp Cys Phe Arg Tyr Tyr Ser Ser Glu
    210                 215                 220
Tyr His Tyr Val Gly Gly Phe Tyr Gly Gly Cys Asn Glu Ala Leu Met
225                 230                 235                 240
Lys Leu Glu Leu Val His His Gly Pro Met Ala Val Ala Phe Glu Val
                245                 250                 255
Tyr Asp Asp Phe Leu His Tyr Lys Lys Gly Ile Tyr His His Thr Gly
            260                 265                 270
Leu Arg Asp Pro Phe Asn Pro Phe Glu Leu Thr Asn His Ala Val Leu
        275                 280                 285
Leu Val Gly Tyr Gly Thr Asp Ser Ala Ser Gly Met Asp Tyr Trp Ile
    290                 295                 300
Val Lys Asn Ser Trp Gly Thr Gly Trp Gly Glu Asn Gly Tyr Phe Arg
305                 310                 315                 320
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Ile Arg Arg Gly Thr Asp Glu Cys Ala Ile Glu Ser Ile Ala Val Ala
325 330 335
Ala Thr Pro Ile Pro Lys Leu
340

<210> 181
<211> 2032
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶F

<400> 181
ggaggactca ggccccgctg gccgcgggct cggtacccgg tgggtcggtg gagcgtctgt 60
tgggtccggg ccgccggctt cgccctcgcc atggcgccct ggctgcagct cctgtcgctg 120
ctggggctgc tcccgggcgc agtggccgcc cccgcccagc cccgagccgc cagctttcag 180
gcctgggggc cgccgtcccc ggagctgctg gcgcccaccc gcttcgcgct ggagatgttc 240
aaccgcggcc gggctgcggg gacgcgggcc gtgctgggcc ttgtgcgcgg ccgcgtccgc 300
cgggcgggtc aggggtcgct gtactccctg gaggccaccc tggaggagcc accctgcaac 360
gaccccatgg tgtgccggct ccccgtgtcc aagaaaaccc tgctctgcag cttccaagtc 420
ctggatgagc tcggaagaca cgtgctgctg cggaaggact gtggcccagt ggacaccaag 480
gttccaggtg ctggggagcc caagtcagcc ttcactcagg gctcagccat gatttcttct 540
ctgtcccaaa accatccaga caacagaaac gagactttca gctcagtcat ttccctgttg 600
aatgaggatc ccctgtccca ggacttgcct gtgaagatgg cttcaatctt caagaacttt 660
gtcattacct ataaccggac atatgagtca aaggaagaag cccggtggcg cctgtccgtc 720
tttgtcaata acatggtgcg agcacagaag atccaggccc tggaccgtgg cacagctcag 780
tatggagtca ccaagttcag tgatctcaca gaggaggagt tccgcactat ctacctgaat 840
actctcctga ggaaagagcc tggcaacaag atgaagcaag ccaagtctgt gggtgacctc 900
gccccacctg aatgggactg gaggagtaag ggggctgtca caaaagtcaa agaccagggc 960
atgtgtggct cctgctgggc cttctcagtc acaggcaatg tggagggcca gtggtttctc 1020
aaccagggga ccctgctctc cctctctgaa caggagctct tggactgtga caagatggac 1080
aaggcctgca tgggcggctt gccctccaat gcctactcgg ccataaagaa tttgggaggg 1140
ctggagacag aggatgacta cagctaccag ggtcacatgc agtcctgcaa cttctcagca 1200
gagaaggcca aggtctacat caatgactcc gtggagctga gccagaacga gcagaagctg 1260
gcagcctggc tggccaagag aggcccaatc tccgtggcca tcaatgcctt tggcatgcag 1320
ttttaccgcc acgggatctc ccgccctctc cggcccctct gcagcccttg gctcattgac 1380
catgcggtgt tgcttgtggg ctacggcaac cgctctgacg ttccctttg ggccatcaag 1440
aacagctggg gcactgactg gggtgagaag ggttactact acttgcatcg tgggtccggg 1500
gcctgtggcg tgaacaccat ggccagctcg gcggtggtgg actgaagagg ggcccccagc 1560
tcgggacctg gtgctgatca gagtggctgc tgccccagcc tgacatgtgt ccaggcccct 1620
ccccgggagg tacagctggc agagggaaag gcactgggta cctcagggtg agcagagggc 1680
actgggctgg ggcacagccc ctgcttccct gcaccccatt cccaccctga agttctgcac 1740
ctgcaccttt gttgaattgt ggtagcttag gaggatgtcg gggtgaaggg tggtatcttg 1800
gcagttgaag ctggggcaag aactctgggc ttgggtaatg agcaggaaga aaattttctg 1860
atcttaagcc cagctctgtt ctgcccccgc tttcctctgt ttgatactat aaattttctg 1920
gttcccttgg atttagggat agtgtccctc tccatgtcca ggaaacttgt aaccaccctt 1980
ttctaacagc aataaagagg tgtccttgtc ccgaaaaaaa aaaaaaaaaa aa 2032

<210> 182
<211> 484
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶F前驅體

<400> 182
Met Ala Pro Trp Leu Gln Leu Leu Ser Leu Leu Gly Leu Leu Pro Gly
1 5 10 15
Ala Val Ala Ala Pro Ala Gln Pro Arg Ala Ala Ser Phe Gln Ala Trp
20 25 30
Gly Pro Pro Ser Pro Glu Leu Leu Ala Pro Thr Arg Phe Ala Leu Glu
35 40 45

```
Met Phe Asn Arg Gly Arg Ala Ala Gly Thr Arg Ala Val Leu Gly Leu
    50                  55                  60
Val Arg Gly Arg Val Arg Arg Ala Gly Gln Gly Ser Leu Tyr Ser Leu
65                  70                  75                  80
Glu Ala Thr Leu Glu Glu Pro Pro Cys Asn Asp Pro Met Val Cys Arg
                85                  90                  95
Leu Pro Val Ser Lys Lys Thr Leu Leu Cys Ser Phe Gln Val Leu Asp
            100                 105                 110
Glu Leu Gly Arg His Val Leu Leu Arg Lys Asp Cys Gly Pro Val Asp
        115                 120                 125
Thr Lys Val Pro Gly Ala Gly Glu Pro Lys Ser Ala Phe Thr Gln Gly
    130                 135                 140
Ser Ala Met Ile Ser Ser Leu Ser Gln Asn His Pro Asp Asn Arg Asn
145                 150                 155                 160
Glu Thr Phe Ser Ser Val Ile Ser Leu Leu Asn Glu Asp Pro Leu Ser
                165                 170                 175
Gln Asp Leu Pro Val Lys Met Ala Ser Ile Phe Lys Asn Phe Val Ile
            180                 185                 190
Thr Tyr Asn Arg Thr Tyr Glu Ser Lys Glu Glu Ala Arg Trp Arg Leu
        195                 200                 205
Ser Val Phe Val Asn Asn Met Val Arg Ala Gln Lys Ile Gln Ala Leu
    210                 215                 220
Asp Arg Gly Thr Ala Gln Tyr Gly Val Thr Lys Phe Ser Asp Leu Thr
225                 230                 235                 240
Glu Glu Glu Phe Arg Thr Ile Tyr Leu Asn Thr Leu Leu Arg Lys Glu
                245                 250                 255
Pro Gly Asn Lys Met Lys Gln Ala Lys Ser Val Gly Asp Leu Ala Pro
            260                 265                 270
Pro Glu Trp Asp Trp Arg Ser Lys Gly Ala Val Thr Lys Val Lys Asp
        275                 280                 285
Gln Gly Met Cys Gly Ser Cys Trp Ala Phe Ser Val Thr Gly Asn Val
    290                 295                 300
Glu Gly Gln Trp Phe Leu Asn Gln Gly Thr Leu Leu Ser Leu Ser Glu
305                 310                 315                 320
Gln Glu Leu Leu Asp Cys Asp Lys Met Asp Lys Ala Cys Met Gly Gly
                325                 330                 335
Leu Pro Ser Asn Ala Tyr Ser Ala Ile Lys Asn Leu Gly Gly Leu Glu
            340                 345                 350
Thr Glu Asp Asp Tyr Ser Tyr Gln Gly His Met Gln Ser Cys Asn Phe
        355                 360                 365
Ser Ala Glu Lys Ala Lys Val Tyr Ile Asn Asp Ser Val Glu Leu Ser
    370                 375                 380
Gln Asn Glu Gln Lys Leu Ala Ala Trp Leu Ala Lys Arg Gly Pro Ile
385                 390                 395                 400
Ser Val Ala Ile Asn Ala Phe Gly Met Gln Phe Tyr Arg His Gly Ile
                405                 410                 415
Ser Arg Pro Leu Arg Pro Leu Cys Ser Pro Trp Leu Ile Asp His Ala
            420                 425                 430
Val Leu Leu Val Gly Tyr Gly Asn Arg Ser Asp Val Pro Phe Trp Ala
        435                 440                 445
Ile Lys Asn Ser Trp Gly Thr Asp Trp Gly Glu Lys Gly Tyr Tyr Tyr
    450                 455                 460
Leu His Arg Gly Ser Gly Ala Cys Gly Val Asn Thr Met Ala Ser Ser
465                 470                 475                 480
Ala Val Val Asp
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<210> 183
<211> 214
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶F

<400> 183

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Ala Pro Pro Glu Trp Asp Trp Arg Ser Lys Gly Ala Val Thr Lys Val
 1               5                  10                  15
Lys Asp Gln Gly Met Cys Gly Ser Cys Trp Ala Phe Ser Val Thr Gly
            20                  25                  30
Asn Val Glu Gly Gln Trp Phe Leu Asn Gln Gly Thr Leu Leu Ser Leu
        35                  40                  45
Ser Glu Gln Glu Leu Leu Asp Cys Asp Lys Met Asp Lys Ala Cys Met
    50                  55                  60
Gly Gly Leu Pro Ser Asn Ala Tyr Ser Ala Ile Lys Asn Leu Gly Gly
65                  70                  75                  80
Leu Glu Thr Glu Asp Asp Tyr Ser Tyr Gln Gly His Met Gln Ser Cys
                85                  90                  95
Asn Phe Ser Ala Glu Lys Ala Lys Val Tyr Ile Asn Asp Ser Val Glu
            100                 105                 110
Leu Ser Gln Asn Glu Gln Lys Leu Ala Ala Trp Leu Ala Lys Arg Gly
        115                 120                 125
Pro Ile Ser Val Ala Ile Asn Ala Phe Gly Met Gln Phe Tyr Arg His
    130                 135                 140
Gly Ile Ser Arg Pro Leu Arg Pro Leu Cys Ser Pro Trp Leu Ile Asp
145                 150                 155                 160
His Ala Val Leu Leu Val Gly Tyr Gly Asn Arg Ser Asp Val Pro Phe
                165                 170                 175
Trp Ala Ile Lys Asn Ser Trp Gly Thr Asp Trp Gly Glu Lys Gly Tyr
            180                 185                 190
Tyr Tyr Leu His Arg Gly Ser Gly Ala Cys Gly Val Asn Thr Met Ala
        195                 200                 205
Ser Ser Ala Val Val Asp
    210
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<210> 184
<211> 2943
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶O

<400> 184

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ccgaaagaga aaacaggccg cgcgggcggc agaggagccg ggcgccgcaa tggacgtgcg 60
ggcgctgccg tggctgccgt ggctgctgtg gctgctgtgc cggggcggcg gcgatgcgga 120
ctcccgcgcc cccttcaccc cgacctggcc gcggagccgc gagcgtgaag ccgccgcctt 180
ccgggaaagt cttaatagac atcgatactt gaattcttta tttcccagtg aaaactccac 240
cgccttctat ggaataaatc agttttccta tttgtttcct gaagagttta aagccattta 300
tttaagaagc aaaccttcca agtttcccag atactcagca gaagtacata tgtccatccc 360
caatgtgtct ttgccgttaa gatttgactg gagggacaag caggttgtga cacaagtgag 420
aaaccagcag atgtgtggag gatgctgggc cttcagcgtg gtgggggcag tggaatctgc 480
ttatgcaata aaggggaagc ccctggaaga cctaagtgtc cagcaggtca ttgactgttc 540
gtataataat tatggctgca atggaggctc tactctcaat gctttgaact ggttaaacaa 600
gatgcaagta aaactggtga aagattcaga atatcctttt aaagcacaaa atggtctgtg 660
ccattacttt tctggttcac attctggatt ttcaatcaaa ggttattctg catatgactt 720
cagtgaccaa gaagatgaaa tggcaaaagc acttcttacc tttggccctt tggtagtcat 780
agtagatgca gtgagctggc aagattatct gggaggcatt atacagcatc actgctctag 840
tggagaagca aatcatgcag ttctcataac tgggtttgat aaaacaggaa gcactccata 900
ttggattgtg cggaattcct ggggaagttc ttggggagta gatggttatg cccatgtcaa 960
aatgggaagt aatgtttgtg gtattgcaga ttccgtttct tctatatttg tgtgacatgt 1020
tgggcagatc aagagacagc tacaaaaatg aaggttttca taatgcaatg taacatagta 1080
cttcaaagta ttattcaact tcaagtttca gcaactacct acaaaagatt ctaaggccta 1140
gtagtattta aactaagttt cagaatgttc ccttcttgta gagagatgga caaccaaagt 1200
cagtgggaca aactccagca cagaagcctg cgaggaagcc tatggaatag tttcctgtcc 1260
tgagacgaaa ttcagattag gagatatttt aggcccctgc aactggggaa ggctactgtt 1320
tgtttttgtt tgcttattat ttatttgttt gtttattgtg agatatttca ggtgggatca 1380
aagaggtcat aagaatttat tttcttttgt ggggtgtaac tactagcttt agattacccc 1440
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tatacacaag aatggccaac ctaaaattat gtgtgtcttg tacagttagt tatattagca 1500
gccctctgag atggcgtatc tatcggaagg atttcaaaca ccaattgctt tacctgaaca 1560
aatggtgctt acccctttgaa cagcagagtg accacgtaga aggaaggaaa agggcaaaat 1620
cgcttcagtt aaactgaaat taaatgaaca ataaggcaac tatataagta acttctagta 1680
gcattgcctg agagacaaat tattgtttga taattttcat tgtgaatagg aatccaatag 1740
atcatattgc ttactttgtt ctttttatac tatagaataa tattttgttc tctagtatat 1800
caaaatacca aaatattatc tcatattttc tccctctttc tcttactctt taccaagttt 1860
tcctggtggc ttggcttccc tgactaaaga attaagtctc atttttactt tccatttcta 1920
ttttcttacc acttggttgg ctccctttgt ctctgtacct ttaccaacat taggatctca 1980
cctctttctt cctcccttaa ttcataagca ccactcctat caaagtccca tctcttaacc 2040
ctgggtatca aacaaactgt gagttttcca gaatctgttt cccagttttc ccctcagctt 2100
tcctggtctc ccatccgaac tgcttctttg tgcacctctt gttctttctc ttggctccca 2160
gtcttgattc ctgtgatcac tcttgcatca ctaattgcac aagtgatttc aggtgcaatt 2220
ctgattagcc tgcgtccaca cagtgatcga tgatcctatg tgcctagaaa ggacactgtg 2280
tgctgctcat gacctgcaac aggaaaaaag ccatttcttg ttagcagtgt aagaacctta 2340
gagcaaagga gttgaccttc tgattgaata taagcacaac catattaaat gaatcaatac 2400
aagaaaatta tttctgatac tatgtatgta catatttctt ctctaaaatg tatcattctt 2460
ttctaatgta tatgatctaa caaaaatgaa acatgaaatg cagtagcaac cactaaaaaa 2520
aaaaattcaa ggacatctaa ctttttctct cacttttgcc ctttgtttat ccttccctgt 2580
gattagataa acaaaataaa aaacaaaatg ctgtatttct cttcttacgc cagtcagaac 2640
caatccgaaa agaatgtgtg ttgactcagg tttggagtta tttcaggaag acagatattg 2700
acctttttaat tgataaatat tcttattatc ctggaatgcc agaaaagaac tatgtcctgc 2760
ttgtctagtt tgtattcgct gactttctat gtgatataga tgcatttgta atactctttt 2820
tcaagtgcta aaggatttct aaaatttcaa actgattaat atgtttctgc tgttctggat 2880
tttgatgaca tttacaataa aacaacctac atttgacttt ggtttaaaaa gaaaaaaaaa 2940
aaa 2943

<210> 185
<211> 321
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶O前驅體

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

```
225                 230                 235                 240
Leu Val Val Ile Val Asp Ala Val Ser Trp Gln Asp Tyr Leu Gly Gly
                245                 250                 255
Ile Ile Gln His His Cys Ser Ser Gly Glu Ala Asn His Ala Val Leu
            260                 265                 270
Ile Thr Gly Phe Asp Lys Thr Gly Ser Thr Pro Tyr Trp Ile Val Arg
        275                 280                 285
Asn Ser Trp Gly Ser Ser Trp Gly Val Asp Gly Tyr Ala His Val Lys
    290                 295                 300
Met Gly Ser Asn Val Cys Gly Ile Ala Asp Ser Val Ser Ser Ile Phe
305                 310                 315                 320
Val
```

<210> 186
<211> 214
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶O

<400> 186

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Leu Pro Leu Arg Phe Asp Trp Arg Asp Lys Gln Val Val Thr Gln Val
 1               5                  10                  15
Arg Asn Gln Gln Met Cys Gly Gly Cys Trp Ala Phe Ser Val Val Gly
            20                  25                  30
Ala Val Glu Ser Ala Tyr Ala Ile Lys Gly Lys Pro Leu Glu Asp Leu
        35                  40                  45
Ser Val Gln Gln Val Ile Asp Cys Ser Tyr Asn Asn Tyr Gly Cys Asn
    50                  55                  60
Gly Gly Ser Thr Leu Asn Ala Leu Asn Trp Leu Asn Lys Met Gln Val
65                  70                  75                  80
Lys Leu Val Lys Asp Ser Glu Tyr Pro Phe Lys Ala Gln Asn Gly Leu
                85                  90                  95
Cys His Tyr Phe Ser Gly Ser His Ser Gly Phe Ser Ile Lys Gly Tyr
            100                 105                 110
Ser Ala Tyr Asp Phe Ser Asp Gln Glu Asp Glu Met Ala Lys Ala Leu
        115                 120                 125
Leu Thr Phe Gly Pro Leu Val Val Ile Val Asp Ala Val Ser Trp Gln
    130                 135                 140
Asp Tyr Leu Gly Gly Ile Ile Gln His His Cys Ser Ser Gly Glu Ala
145                 150                 155                 160
Asn His Ala Val Leu Ile Thr Gly Phe Asp Lys Thr Gly Ser Thr Pro
                165                 170                 175
Tyr Trp Ile Val Arg Asn Ser Trp Gly Ser Ser Trp Gly Val Asp Gly
            180                 185                 190
Tyr Ala His Val Lys Met Gly Ser Asn Val Cys Gly Ile Ala Asp Ser
        195                 200                 205
Val Ser Ser Ile Phe Val
    210
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<210> 187
<211> 1496
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶V

<400> 187

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gctctaagcg cccggggccc cgcccagtgg ccggcacagc caatcgcagc gcgggaaggc 60
ggtgggggcg gggaaggccg cctggaaact taaatcccga ggcgggcgaa cctgcaccag 120
```

accgcggacg tctgtaatct cagaggcttg tttgctgagg gtgcctgcgc agctgcgacg 180
gctgctggtt ttgaaacatg aatctttcgc tcgtcctggc tgccttttgc ttgggaatag 240
cctccgctgt tccaaaattt gaccaaaatt tggatacaaa gtggtaccag tggaaggcaa 300
cacacagaag attatatggc gcgaatgaag aaggatggag gagagcagtg tgggaaaaga 360
atatgaaaat gattgaactg cacaatgggg aatacagcca agggaaacat ggcttcacaa 420
tggccatgaa tgcttttggt gacatgacca atgaagaatt caggcagatg atgggttgct 480
ttcgaaacca gaaattcagg aaggggaaag tgttccgtga gcctctgttt cttgatcttc 540
ccaaatctgt ggattggaga aagaaaggct acgtgacgcc agtgaagaat cagaaacagt 600
gtggttcttg ttgggctttt agtgcgactg gtgctcttga aggacagatg ttccggaaaa 660
ctgggaaact tgtctcactg agcgagcaga atctggtgga ctgttcgcgt cctcaaggca 720
atcagggctg caatggtggc ttcatggcta gggccttcca gtatgtcaag gagaacggag 780
gcctggactc tgaggaatcc tatccatatg tagcagtgga tgaaatctgt aagtacagac 840
ctgagaattc tgttgctaat gacactggct tcacagtggt cgcacctgga aaggagaagg 900
ccctgatgaa agcagtcgca actgtggggc ccatctccgt tgctatggat gcaggccatt 960
cgtccttcca gttctacaaa tcaggcattt attttgaacc agactgcagc agcaaaaacc 1020
tggatcatgg tgttctggtg gttggctacg gctttgaagg agcaaattcg aataacagca 1080
agtattggct cgtcaaaaac agctggggtc cagaatgggg ctcgaatggc tatgtaaaaa 1140
tagccaaaga caagaacaac cactgtggaa tcgccacagc agccagctac cccaatgtgt 1200
gagctgatgg atggtgagga ggaaggactt aaggacagca tgtctgggga aattttatct 1260
tgaaactgac caaacgctta ttgtgtaaga taaaccagtt gaatcattga ggatccaagt 1320
tgagatttta attctgtgac atttttacaa gggtaaaatg ttaccactac tttaattatt 1380
gttatacaca gctttatgat atcaaagact cattgcttaa ttctaagact tttgaatttt 1440
catttttaa aaagatgtac aaaacagttt gaaataaatt ttaattcgta tataaa 1496

<210> 188
<211> 334
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶V前驅體

<400> 188
Met Asn Leu Ser Leu Val Leu Ala Ala Phe Cys Leu Gly Ile Ala Ser
 1   5   10   15
Ala Val Pro Lys Phe Asp Gln Asn Leu Asp Thr Lys Trp Tyr Gln Trp
            20   25   30
Lys Ala Thr His Arg Arg Leu Tyr Gly Ala Asn Glu Glu Gly Trp Arg
        35   40   45
Arg Ala Val Trp Glu Lys Asn Met Lys Met Ile Glu Leu His Asn Gly
    50   55   60
Glu Tyr Ser Gln Gly Lys His Gly Phe Thr Met Ala Met Asn Ala Phe
65   70   75   80
Gly Asp Met Thr Asn Glu Glu Phe Arg Gln Met Met Gly Cys Phe Arg
                85   90   95
Asn Gln Lys Phe Arg Lys Gly Lys Val Phe Arg Glu Pro Leu Phe Leu
            100   105   110
Asp Leu Pro Lys Ser Val Asp Trp Arg Lys Lys Gly Tyr Val Thr Pro
        115   120   125
Val Lys Asn Gln Lys Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr
    130   135   140
Gly Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Lys Leu Val Ser
145   150   155   160
Leu Ser Glu Gln Asn Leu Val Asp Cys Ser Arg Pro Gln Gly Asn Gln
                165   170   175
Gly Cys Asn Gly Gly Phe Met Ala Arg Ala Phe Gln Tyr Val Lys Glu
            180   185   190
Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Val Ala Val Asp
        195   200   205
Glu Ile Cys Lys Tyr Arg Pro Glu Asn Ser Val Ala Asn Asp Thr Gly
    210   215   220
Phe Thr Val Val Ala Pro Gly Lys Glu Lys Ala Leu Met Lys Ala Val
225   230   235   240
Ala Thr Val Gly Pro Ile Ser Val Ala Met Asp Ala Gly His Ser Ser

```
                245                 250                 255
Phe Gln Phe Tyr Lys Ser Gly Ile Tyr Phe Glu Pro Asp Cys Ser Ser
            260                 265                 270
Lys Asn Leu Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Gly
        275                 280                 285
Ala Asn Ser Asn Asn Ser Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly
    290                 295                 300
Pro Glu Trp Gly Ser Asn Gly Tyr Val Lys Ile Ala Lys Asp Lys Asn
305                 310                 315                 320
Asn His Cys Gly Ile Ala Thr Ala Ala Ser Tyr Pro Asn Val
                325                 330
```

<210> 189
<211> 221
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶V

<400> 189

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

Asn Ser Asn Asn Ser Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Pro
            180                 185                 190
Glu Trp Gly Ser Asn Gly Tyr Val Lys Ile Ala Lys Asp Lys Asn Asn
        195                 200                 205
His Cys Gly Ile Ala Thr Ala Ala Ser Tyr Pro Asn Val
    210                 215                 220
```

<210> 190
<211> 2048
<212> DNA
<213> 現代人

<220>
<223> 豆莢蛋白

<400> 190

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gcacagtggc ccttaagcga ggagcggcgg cgcccgcagc aatcacagca gtgccgacgt 60
cgtgggtgtt tggtgtgagg ctgcgagccg ccgcgagttc tcacggtccc gccggcgcca 120
ccaccgcggt cactcaccgc cgccgccgcc accactgcca ccacggtcgc ctgccacagg 180
```

tgtctgcaat tgaactccaa ggtgcagaat ggtttggaaa gtagctgtat tcctcagtgt 240
ggccctgggc attggtgccg ttcctataga tgatcctgaa gatggaggca agcactgggt 300
ggtgatcgtg gcaggttcaa atggctggta taattatagg caccaggcag acgcgtgcca 360
tgcctaccag atcattcacc gcaatgggat tcctgacgaa cagatcgttg tgatgatgta 420
cgatgacatt gcttactctg aagacaatcc cactccagga attgtgatca acaggcccaa 480
tggcacagat gtctatcagg gagtcccgaa ggactacact ggagaggatg ttaccccaca 540
aaatttcctt gctgtgttga gaggcgatgc agaagcagtg aagggcatag gatccggcaa 600
agtcctgaag agtggccccc aggatcacgt gttcatttac ttcactgacc atggatctac 660
tggaatactg gtttttccca atgaagatct tcatgtaaag gacctgaatg agaccatcca 720
ttacatgtac aaacacaaaa tgtaccgaaa gatggtgttc tacattgaag cctgtgagtc 780
tgggtccatg atgaaccacc tgccggataa catcaatgtt tatgcaacta ctgctgccaa 840
ccccagagag tcgtcctacg cctgttacta tgatgagaag aggtccacgt acctggggga 900
ctggtacagc gtcaactgga tggaagattc ggacgtggaa gatctgacta aagagaccct 960
gcacaagcag taccacctgg taaaatcgca caccaacacc agccacgtca tgcagtatgg 1020
aaacaaaaca atctccacca tgaaagtgat gcagtttcag ggtatgaaac gcaaagccag 1080
ttctcccgtc cccctacctc cagtcacaca ccttgacctc acccccagcc ctgatgtgcc 1140
tctcaccatc atgaaaagga aactgatgaa caccaatgat ctggaggagt ccaggcagct 1200
cacggaggag atccagcggc atctggatgc caggcacctc attgagaagt cagtgcgtaa 1260
gatcgtctcc ttgctggcag cgtccgaggc tgaggtggag cagctcctgt ccgagagagc 1320
cccgctcacg gggcacagct gctacccaga ggccctgctg cacttccgga cccactgctt 1380
caactggcac tcccccacgt acgagtatgc gttgagacat ttgtacgtgc tggtcaacct 1440
ttgtgagaag ccgtatccgc ttcacaggat aaaattgtcc atggaccacg tgtgccttgg 1500
tcactactga agagctgcct cctggaagct tttccaagtg tgagcgcccc accgactgtg 1560
tgctgatcag agactggaga ggtggagtga gaagtctccg ctgctcgggc cctcctgggg 1620
agcccccgct ccagggctcg ctccaggacc ttcttcacaa gatgacttgc tcgctgttac 1680
ctgcttcccc agtcttttct gaaaaactac aaattagggt gggaaaagct ctgtattgag 1740
aagggtcata tttgctttct aggaggtttg ttgttttgcc tgttagtttt gaggagcagg 1800
aagctcatgg gggcttctgt agcccctctc aaaaggagtc tttattctga gaatttgaag 1860
ctgaaacctc tttaaatctt cagaatgatt ttattgaaga gggccgcaag ccccaaatgg 1920
aaaactgttt ttagaaaata tgatgatttt tgattgcttt tgtatttaat tctgcaggtg 1980
ttcaagtctt aaaaaataaa gatttataac agaacccaaa aaaaaaaaaa aaaaaaaaaa 2040
aaaaaaaa 2048

<210> 191
<211> 433
<212> PRT
<213> 現代人

<220>
<223> 豆莢蛋白前驅體

<400> 191
Met Val Trp Lys Val Ala Val Phe Leu Ser Val Ala Leu Gly Ile Gly
 1   5   10   15
Ala Val Pro Ile Asp Asp Pro Glu Asp Gly Gly Lys His Trp Val Val
            20   25   30
Ile Val Ala Gly Ser Asn Gly Trp Tyr Asn Tyr Arg His Gln Ala Asp
        35   40   45
Ala Cys His Ala Tyr Gln Ile Ile His Arg Asn Gly Ile Pro Asp Glu
    50   55   60
Gln Ile Val Val Met Met Tyr Asp Asp Ile Ala Tyr Ser Glu Asp Asn
65   70   75   80
Pro Thr Pro Gly Ile Val Ile Asn Arg Pro Asn Gly Thr Asp Val Tyr
                85   90   95
Gln Gly Val Pro Lys Asp Tyr Thr Gly Glu Asp Val Thr Pro Gln Asn
            100   105   110
Phe Leu Ala Val Leu Arg Gly Asp Ala Glu Ala Val Lys Gly Ile Gly
        115   120   125
Ser Gly Lys Val Leu Lys Ser Gly Pro Gln Asp His Val Phe Ile Tyr
    130   135   140
Phe Thr Asp His Gly Ser Thr Gly Ile Leu Val Phe Pro Asn Glu Asp
145   150   155   160
Leu His Val Lys Asp Leu Asn Glu Thr Ile His Tyr Met Tyr Lys His
                165   170   175
Lys Met Tyr Arg Lys Met Val Phe Tyr Ile Glu Ala Cys Glu Ser Gly

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

<210> 192
<211> 306
<212> PRT
<213> 現代人

<220>
<223> 成熟豆莢蛋白

<400> 192

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

    130                 135                 140
His Val Lys Asp Leu Asn Glu Thr Ile His Tyr Met Tyr Lys His Lys
145                 150                 155                 160
```

```
Met Tyr Arg Lys Met Val Phe Tyr Ile Glu Ala Cys Glu Ser Gly Ser
                165                 170                 175
Met Met Asn His Leu Pro Asp Asn Ile Asn Val Tyr Ala Thr Thr Ala
            180                 185                 190
Ala Asn Pro Arg Glu Ser Ser Tyr Ala Cys Tyr Tyr Asp Glu Lys Arg
        195                 200                 205
Ser Thr Tyr Leu Gly Asp Trp Tyr Ser Val Asn Trp Met Glu Asp Ser
    210                 215                 220
Asp Val Glu Asp Leu Thr Lys Glu Thr Leu His Lys Gln Tyr His Leu
225                 230                 235                 240
Val Lys Ser His Thr Asn Thr Ser His Val Met Gln Tyr Gly Asn Lys
                245                 250                 255
Thr Ile Ser Thr Met Lys Val Met Gln Phe Gln Gly Met Lys Arg Lys
            260                 265                 270
Ala Ser Ser Pro Val Pro Leu Pro Pro Val Thr His Leu Asp Leu Thr
        275                 280                 285
Pro Ser Pro Asp Val Pro Leu Thr Ile Met Lys Arg Lys Leu Met Asn
    290                 295                 300
Thr Asn
305
```

<210> 193
<211> 1501
<212> DNA
<213> 現代人

<220>
<223> 組織蛋白酶Z

<400> 193

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ggggtcggcc gggtgctagg ccggggccga ggccgaggcc ggggcgggat ccagagcggg 60
agccggcgcg ggatctggga ctcggagcgg gatccggagc gggacccagg agccggcgcg 120
gggccatggc gaggcgcggg ccagggtggc ggccgcttct gctgctcgtg ctgctggcgg 180
gcgcggcgca gggcggcctc tacttccgcc ggggacagac ctgctaccgg cctctgcggg 240
gggacgggct ggctccgctg gggcgcagca catacccccg gcctcatgag tacctgtccc 300
cagcggatct gcccaagagc tgggactggc gcaatgtgga tggtgtcaac tatgccagca 360
tcacccggaa ccagcacatc ccccaatact gcggctcctg ctgggcccac gccagcacca 420
gcgctatggc ggatcggatc aacatcaaga ggaagggagc gtggccctcc accctcctgt 480
ccgtgcagaa cgtcatcgac tgcggtaacg ctggctcctg tgaaggggt aatgacctgt 540
ccgtgtggga ctacgcccac cagcacggca tccctgacga gacctgcaac aactaccagg 600
ccaaggacca ggagtgtgac aagtttaacc aatgtgggac atgcaatgaa ttcaaagagt 660
gccacgccat ccggaactac accctctgga gggtgggaga ctacggctcc ctctctggga 720
gggagaagat gatggcagaa atctacgcaa atggtcccat cagctgtgga ataatggcaa 780
cagaaagact ggctaactac accggaggca tctatgccga ataccaggac accacatata 840
taaaccatgt cgtttccgtg gctgggtggg gcatcagtga tgggactgag tactggattg 900
tccggaattc atggggtgaa ccatggggcg agagaggctg gctgaggatc gtgaccagca 960
cctataagga tgggaagggc gccagataca accttgccat cgaggagcac tgtacatttg 1020
gggaccccat cgtttaaggc catgtcacta gaagcgcagt ttaagaaaag gcatggtgac 1080
ccatgaccag aggggatcct atggttatgt gtgccaggct ggctggcagg aactggggtg 1140
gctatcaata ttggatggcg aggacagcgt ggtactggct gcgagtgttc ctgagagttg 1200
aaagtgggat gacttatgac acttgcacag catggctctg cctcacaatg atgcagtcag 1260
ccacctggtg aagaagtgac ctgcaacaca ggaaacgatg ggacctcagt cttcttcagc 1320
agaggacttg atattttgta tttggcaact gtgggcaata atatggcatt taagaggtga 1380
aagagttcag acttatcacc attcttatgt cactttagaa tcaagggtgg gggagggagg 1440
gagggagttg gcagtttcaa atcgcccaag tgatgaataa agtatctggc tctgcacgag 1500
a                                                                  1501
```

<210> 194
<211> 303
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶Z前驅體

<400> 194
Met Ala Arg Arg Gly Pro Gly Trp Arg Pro Leu Leu Leu Leu Val Leu
 1   5   10   15
Leu Ala Gly Ala Ala Gln Gly Gly Leu Tyr Phe Arg Arg Gly Gln Thr
            20   25   30
Cys Tyr Arg Pro Leu Arg Gly Asp Gly Leu Ala Pro Leu Gly Arg Ser
        35   40   45
Thr Tyr Pro Arg Pro His Glu Tyr Leu Ser Pro Ala Asp Leu Pro Lys
    50   55   60
Ser Trp Asp Trp Arg Asn Val Asp Gly Val Asn Tyr Ala Ser Ile Thr
65   70   75   80
Arg Asn Gln His Ile Pro Gln Tyr Cys Gly Ser Cys Trp Ala His Ala
                85   90   95
Ser Thr Ser Ala Met Ala Asp Arg Ile Asn Ile Lys Arg Lys Gly Ala
            100   105   110
Trp Pro Ser Thr Leu Leu Ser Val Gln Asn Val Ile Asp Cys Gly Asn
        115   120   125
Ala Gly Ser Cys Glu Gly Gly Asn Asp Leu Ser Val Trp Asp Tyr Ala
    130   135   140
His Gln His Gly Ile Pro Asp Glu Thr Cys Asn Asn Tyr Gln Ala Lys
145   150   155   160
Asp Gln Glu Cys Asp Lys Phe Asn Gln Cys Gly Thr Cys Asn Glu Phe
                165   170   175
Lys Glu Cys His Ala Ile Arg Asn Tyr Thr Leu Trp Arg Val Gly Asp
            180   185   190
Tyr Gly Ser Leu Ser Gly Arg Glu Lys Met Met Ala Glu Ile Tyr Ala
        195   200   205
Asn Gly Pro Ile Ser Cys Gly Ile Met Ala Thr Glu Arg Leu Ala Asn
    210   215   220
Tyr Thr Gly Gly Ile Tyr Ala Glu Tyr Gln Asp Thr Thr Tyr Ile Asn
225   230   235   240
His Val Val Ser Val Ala Gly Trp Gly Ile Ser Asp Gly Thr Glu Tyr
                245   250   255
Trp Ile Val Arg Asn Ser Trp Gly Glu Pro Trp Gly Glu Arg Gly Trp
            260   265   270
Leu Arg Ile Val Thr Ser Thr Tyr Lys Asp Gly Lys Gly Ala Arg Tyr
        275   280   285
Asn Leu Ala Ile Glu Glu His Cys Thr Phe Gly Asp Pro Ile Val
    290   295   300

<210> 195
<211> 242
<212> PRT
<213> 現代人

<220>
<223> 成熟組織蛋白酶z

<400> 195
Leu Pro Lys Ser Trp Asp Trp Arg Asn Val Asp Gly Val Asn Tyr Ala
 1   5   10   15
Ser Ile Thr Arg Asn Gln His Ile Pro Gln Tyr Cys Gly Ser Cys Trp
            20   25   30
Ala His Ala Ser Thr Ser Ala Met Ala Asp Arg Ile Asn Ile Lys Arg
        35   40   45
Lys Gly Ala Trp Pro Ser Thr Leu Leu Ser Val Gln Asn Val Ile Asp
    50   55   60
Cys Gly Asn Ala Gly Ser Cys Glu Gly Gly Asn Asp Leu Ser Val Trp
65   70   75   80
Asp Tyr Ala His Gln His Gly Ile Pro Asp Glu Thr Cys Asn Asn Tyr
                85   90   95
Gln Ala Lys Asp Gln Glu Cys Asp Lys Phe Asn Gln Cys Gly Thr Cys

```
            100                 105                 110
Asn Glu Phe Lys Glu Cys His Ala Ile Arg Asn Tyr Thr Leu Trp Arg
        115                 120                 125
Val Gly Asp Tyr Gly Ser Leu Ser Gly Arg Glu Lys Met Met Ala Glu
    130                 135                 140
Ile Tyr Ala Asn Gly Pro Ile Ser Cys Gly Ile Met Ala Thr Glu Arg
145                 150                 155                 160
Leu Ala Asn Tyr Thr Gly Gly Ile Tyr Ala Glu Tyr Gln Asp Thr Thr
                165                 170                 175
Tyr Ile Asn His Val Val Ser Val Ala Gly Trp Gly Ile Ser Asp Gly
            180                 185                 190
Thr Glu Tyr Trp Ile Val Arg Asn Ser Trp Gly Glu Pro Trp Gly Glu
        195                 200                 205
Arg Gly Trp Leu Arg Ile Val Thr Ser Thr Tyr Lys Asp Gly Lys Gly
    210                 215                 220
Ala Arg Tyr Asn Leu Ala Ile Glu Glu His Cys Thr Phe Gly Asp Pro
225                 230                 235                 240
Ile Val
```

<210> 196
<211> 2654
<212> DNA
<213> 現代人

<220>
<223> 溶酶體酸性脂肪酶

<400> 196

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ttcccggtgg ctggctgctc tgattggctg aacaaatagt ccgagggtgg tgggcatccg 60
ccctcccgac aaggcagacc aggccccctg caggtcccct atccgcaccc cggcccctga 120
gagctggcac tgcgactcga gacagcggcc cggcaggaca gctccagaat gaaaatgcgg 180
ttcttggggt tggtggtctg tttggttctc tggaccctgc attctgaggg gtctggaggg 240
aaactgacag ctgtggatcc tgaaacaaac atgaatgtga gtgaaattat ctcttactgg 300
ggattcccta gtgaggaata cctagttgag acagaagatg gatatattct gtgccttaac 360
cgaattcctc atgggaggaa gaaccattct gacaaaggtc ccaaaccagt tgtcttcctg 420
caacatggct tgctggcaga ttctagtaac tgggtcacaa accttgccaa cagcagcctg 480
ggcttcattc ttgctgatgc tggttttgac gtgtggatgg gcaacagcag aggaaatacc 540
tggtctcgga aacataagac actctcagtt tctcaggatg aattctgggc tttcagttat 600
gatgagatgg caaaatatga cctaccagct tccattaact tcattctgaa taaaactggc 660
caagaacaag tgtattatgt gggtcattct caaggcacca ctataggttt tatagcattt 720
tcacagatcc ctgagctggc taaaaggatt aaaatgtttt ttgccctggg tcctgtggct 780
tccgtcgcct tctgtactag ccctatggcc aaattaggac gattaccaga tcatctcatt 840
aaggacttat ttggagacaa agaatttctt ccccagagtg cgtttttgaa gtggctgggt 900
acccacgttt gcactcatgt catactgaag gagctctgtg gaaatctctg ttttcttctg 960
tgtggattta atgagagaaa tttaaatatg tctagagtgg atgtatatac aacacattct 1020
cctgctggaa cttctgtgca aaacatgtta cactggagcc aggctgttaa attccaaaag 1080
tttcaagcct ttgactgggg aagcagtgcc aagaattatt ttcattacaa ccagagttat 1140
cctcccacat acaatgtgaa ggacatgctt gtgccgactg cagtctggag cgggggtcac 1200
gactggcttg cagatgtcta cgacgtcaat atcttactga ctcagatcac caacttggtg 1260
ttccatgaga gcattccgga atgggagcat cttgacttca tttggggcct ggatgcccct 1320
tggaggcttt ataataaaat tattaatcta atgaggaaat atcagtgaaa gctggacttg 1380
agctgtgtac caccaagtca atgattatgt catgtgaaaa tgtgtttgct tcatttctgt 1440
aaaacacttg tttttctttc ccaggtcttt tgtttttta tatccaagaa aatgataact 1500
ttgaagatgc ccagttcact ctagtttcaa ttagaaacat actagctatt ttttctttaa 1560
ttagggctgg aataggaagc cagtgtctca accatagtat tgtctcttta agtcttttaa 1620
atatcactga tgtgtaaaaa ggtcattata tccattctgt ttttaaaatt taaaatatat 1680
tgacttttg cccttcatag gacaaagtaa tatatgtgtt ggaattttaa aattgtgttg 1740
tcattggtaa atctgtcact gacttaagcg aggtataaaa gtacgcagtt ttcatgtcct 1800
tgccttaaag agctctctag tctaacggtc ttgtagttag agatctaaat gacattttat 1860
catgttttcc tgcagcaggt gcatagtcaa atccagaaat atcacagctg tgccagtaat 1920
aaggatgcta acaattaatt ttatcaaacc taactgtgac agctgtgatt tgacacgttt 1980
taattgctca ggttaaatga aatagttttc cggcgtcttc aaaaacaaat tgcactgata 2040
aaacaaaaac aaaagtatgt tttaaatgct ttgaagactg atacactcaa ccatctatat 2100
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tcatgagctc tcaatttcat ggcaggccat agttctactt atctgagaag caaatccctg 2160
tggagactat accactattt tttctgagat taatgtactc ttggagcccg ctactgtcgt 2220
tattgatcac atctgtgtga agccaaagcc ccgtggttgc ccatgagaag tgtccttgtt 2280
cattttcacc caaatgaagt gtgaacgtga tgttttcgga tgcaaactca gctcagggat 2340
tcattttgtg tcttagtttt atatgcatcc ttatttttaa tacacctgct tcacgtccct 2400
atgttgggaa gtccatattt gtctgctttt cttgcagcat catttcctta caatactgtc 2460
cggtggacaa aatgacaatt gatatgtttt tctgatataa ttactttagc tgcactaaca 2520
gtacaatgct tgttaatggt taatataggc agggcgaata ctactttgta acttttaaag 2580
tcttaaactt ttcaataaaa ttgagtgaga cttataggcc caaaaaaaaa aaaaaaaaaa 2640
aaaaaaaaaa aaaa 2654

<210> 197
<211> 399
<212> PRT
<213> 現代人

<220>
<223> 溶酶體酸性脂肪酶前驅體

<400> 197

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

```
Val Asn Ile Leu Leu Thr Gln Ile Thr Asn Leu Val Phe His Glu Ser
        355                 360                 365
Ile Pro Glu Trp Glu His Leu Asp Phe Ile Trp Gly Leu Asp Ala Pro
    370                 375                 380
Trp Arg Leu Tyr Asn Lys Ile Ile Asn Leu Met Arg Lys Tyr Gln
385                 390                 395
```

<210> 198
<211> 378
<212> PRT
<213> 現代人

<220>
<223> 溶酶體酸性脂肪酶成熟蛋白

<400> 198

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

370 375

<210> 199
<211> 1497
<212> DNA
<213> 現代人

<220>
<223> 胃脂肪酶

<400> 199
agatgatgcc cagatagtaa gtctttttgg taatgtaatc agtggatgag gaatctgacc 60
attgttgaag gttttgtata taagaagtca atacaacatt gaccaaaata ctaaccagcc 120
agagaaacag aatcctaact atttctgagg aaactgcagg tccaaaatgt ggctgctttt 180
aacaatggca agtttgatat ctgtactggg gactacacat ggtttgtttg gaaaattaca 240
tcctggaagc cctgaagtga ctatgaacat tagtcagatg attacttatt ggggataccc 300
aaatgaagaa tatgaagttg tgactgaaga tggttatatt cttgaagtca atagaattcc 360
ttatgggaag aaaaattcag ggaatacagg ccagagacct gttgtgtttt tgcagcatgg 420
tttgcttgca tcagccacaa actggatttc caacctgccg aacaacagcc ttgccttcat 480
tctggcagat gctggttatg atgtgtggct gggcaacagc agaggaaaca cctgggccag 540
aagaaacttg tactattcac cagattcagt tgaattctgg gctttcagct ttgatgaaat 600
ggctaaatat gaccttccag ccacaatcga cttcattgta aagaaaactg gacagaagca 660
gctacactat gttggccatt cccagggcac caccattggt tttattgcct tttccaccaa 720
tcccagcctg gctaaaagaa tcaaaacctt ctatgctcta gctcctgttg ccactgtgaa 780
gtatacaaaa agccttataa acaaacttag atttgttcct caatccctct tcaagtttat 840
atttggtgac aaaatattct acccacacaa cttctttgat caatttcttg ctactgaagt 900
gtgctcccgt gagatgctga atctcctttg cagcaatgcc ttatttataa tttgtggatt 960
tgacagtaag aactttaaca cgagtcgctt ggatgtgtat ctatcacata atccagcagg 1020
aacttctgtt caaaacatgt tccattggac ccaggctgtt aagtctggga aattccaagc 1080
ttatgactgg ggaagcccag ttcagaatag gatgcactat gatcagtccc aacctcccta 1140
ctacaatgtg acagccatga atgtaccaat tgcagtgtgg aacggtggca aggacctgtt 1200
ggctgacccc caagatgttg gccttttgct tccaaaactc cccaatctta tttaccacaa 1260
ggagattcct ttttacaatc acttggactt tatctgggca atggatgccc ctcaagaagt 1320
ttacaatgac attgtttcta tgatatcaga agataaaaag tagttctgga tttaaagaat 1380
tatccgtttg tttttccaaa atactttatt ctctcataca tagtattttc ataatgtttg 1440
acatgcagtg cttctttctg taattttgac tttagaaata tattggcatc aacaaac 1497

<210> 200
<211> 398
<212> PRT
<213> 現代人

<220>
<223> 胃脂肪酶前驅體

<400> 200
Met Trp Leu Leu Leu Thr Met Ala Ser Leu Ile Ser Val Leu Gly Thr
1 5 10 15
Thr His Gly Leu Phe Gly Lys Leu His Pro Gly Ser Pro Glu Val Thr
20 25 30
Met Asn Ile Ser Gln Met Ile Thr Tyr Trp Gly Tyr Pro Asn Glu Glu
35 40 45
Tyr Glu Val Val Thr Glu Asp Gly Tyr Ile Leu Glu Val Asn Arg Ile
50 55 60
Pro Tyr Gly Lys Lys Asn Ser Gly Asn Thr Gly Gln Arg Pro Val Val
65 70 75 80
Phe Leu Gln His Gly Leu Leu Ala Ser Ala Thr Asn Trp Ile Ser Asn
85 90 95
Leu Pro Asn Asn Ser Leu Ala Phe Ile Leu Ala Asp Ala Gly Tyr Asp
100 105 110
Val Trp Leu Gly Asn Ser Arg Gly Asn Thr Trp Ala Arg Arg Asn Leu
115 120 125
Tyr Tyr Ser Pro Asp Ser Val Glu Phe Trp Ala Phe Ser Phe Asp Glu
130 135 140

```
Met Ala Lys Tyr Asp Leu Pro Ala Thr Ile Asp Phe Ile Val Lys Lys
145                 150                 155                 160
Thr Gly Gln Lys Gln Leu His Tyr Val Gly His Ser Gln Gly Thr Thr
                165                 170                 175
Ile Gly Phe Ile Ala Phe Ser Thr Asn Pro Ser Leu Ala Lys Arg Ile
            180                 185                 190
Lys Thr Phe Tyr Ala Leu Ala Pro Val Ala Thr Val Lys Tyr Thr Lys
        195                 200                 205
Ser Leu Ile Asn Lys Leu Arg Phe Val Pro Gln Ser Leu Phe Lys Phe
    210                 215                 220
Ile Phe Gly Asp Lys Ile Phe Tyr Pro His Asn Phe Phe Asp Gln Phe

225                 230                 235                 240
Leu Ala Thr Glu Val Cys Ser Arg Glu Met Leu Asn Leu Leu Cys Ser
                245                 250                 255
Asn Ala Leu Phe Ile Ile Cys Gly Phe Asp Ser Lys Asn Phe Asn Thr
            260                 265                 270
Ser Arg Leu Asp Val Tyr Leu Ser His Asn Pro Ala Gly Thr Ser Val
        275                 280                 285
Gln Asn Met Phe His Trp Thr Gln Ala Val Lys Ser Gly Lys Phe Gln
    290                 295                 300
Ala Tyr Asp Trp Gly Ser Pro Val Gln Asn Arg Met His Tyr Asp Gln
305                 310                 315                 320
Ser Gln Pro Pro Tyr Tyr Asn Val Thr Ala Met Asn Val Pro Ile Ala
                325                 330                 335
Val Trp Asn Gly Gly Lys Asp Leu Leu Ala Asp Pro Gln Asp Val Gly
            340                 345                 350
Leu Leu Leu Pro Lys Leu Pro Asn Leu Ile Tyr His Lys Glu Ile Pro
        355                 360                 365
Phe Tyr Asn His Leu Asp Phe Ile Trp Ala Met Asp Ala Pro Gln Glu
    370                 375                 380
Val Tyr Asn Asp Ile Val Ser Met Ile Ser Glu Asp Lys Lys
385                 390                 395
```

<210> 201
<211> 379
<212> PRT
<213> 現代人

<220>
<221> 未確認
<222> (0)...(0)
<223> 胃脂肪酶成熟蛋白

<400> 201

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

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

<210> 202
<211> 2764
<212> DNA
<213> 現代人

<220>
<223> 溶酶體磷脂酶A2

<400> 202

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aagcgcgtcg ccaccgcccc cgcctaggcg agagcccaga gagctgaacc tgcatcccgg 60
acctgcggcg accgtcgtac accatgggcc tccacctccg cccctaccgt gtggggctgc 120
tcccggatgg cctcctgttc ctcttgctgc tgctaatgct gctcgcggac ccagcgctcc 180
cggccggacg tcaccccca gtggtgctgg tccctggtga tttgggtaac caactggaag 240
ccaagctgga caagccgaca gtggtgcact acctctgctc caagaagacc gaaagctact 300
tcacaatctg gctgaacctg gaactgctgc tgcctgtcat cattgactgc tggattgaca 360
atatcaggct ggtttacaac aaaacatcca gggccaccca gtttcctgat ggtgtggatg 420
tacgtgtccc tggctttggg aagaccttct cactggagtt cctggacccc agcaaaagca 480
gcgtgggttc ctatttccac accatggtgg agagccttgt gggctggggc tacacacggg 540
gtgaggatgt ccgaggggct ccctatgact ggcgccgagc cccaaatgaa aacgggccct 600
acttcctggc cctccgcgag atgatcgagg agatgtacca gctgtatggg ggccccgtgg 660
tgctggttgc ccacagtatg ggcaacatgt acacgctcta ctttctgcag cggcagccgc 720
aggcctggaa ggacaagtat atccgggcct tcgtgtcact gggtgcgccc tgggggggcg 780
tggccaagac cctgcgcgtc ctggcttcag gagacaacaa ccggatccca gtcatcgggc 840
ccctgaagat ccgggagcag cagcggtcag ctgtctccac cagctggctg ctgccctaca 900
actacacatg gtcacctgag aaggtgttcg tgcagacacc cacaatcaac tacacactgc 960
gggactaccg caagttcttc caggacatcg gctttgaaga tggctggctc atgcggcagg 1020
acacagaagg gctggtggaa gccacgatgc cacctggcgt gcagctgcac tgcctctatg 1080
gtactggcgt ccccacacca gactccttct actatgagag cttccctgac cgtgacccta 1140
aaatctgctt tggtgacggc gatggtactg tgaacttgaa gagtgccctg cagtgccagg 1200
cctggcagag ccgccaggag caccaagtgt tgctgcagga gctgccaggc agcgagcaca 1260
tcgagatgct ggccaacgcc accaccctgg cctatctgaa acgtgtgctc cttgggccct 1320
gactcctgtg ccacaggact cctgtggctc ggccgtggac ctgctgttgg cctctggggc 1380
tgtcatggcc cacgcgtttt gcaaagtttg tgactcacca ttcaaggccc cgagtcttgg 1440
actgtgaagc atctgccatg gggaagtgct gtttgttatc ctttctctgt ggcagtgaag 1500
```

```
aaggaagaaa tgagagtcta gactcaaggg acactggatg gcaagaatgc tgctgatggt 1560
ggaactgctg tgaccttagg actggctcca cagggtggac tggctgggcc ctggtcccag 1620
tccctgcctg gggccatgtg tccccctat tcctgtgggc ttttcatact tgcctactgg 1680
gccctggccc cgcagccttc ctatgaggga tgttactggg ctgtggtcct gtacccagag 1740

gtcccaggga tcggctcctg gcccctcggg tgacccttcc cacacaccag ccacagatag 1800
gcctgccact ggtcatgggt agctagagct gctggcttcc ctgtggctta gctggtggcc 1860
agcctgactg gcttcctggg cgagcctagt agctcctgca ggcaggggca gtttgttgcg 1920
ttcttcgtgg ttcccaggcc ctgggacatc tcactccact cctacctccc ttaccaccag 1980
gagcattcaa gctctggatt gggcagcaga tgtgccccca gtcccgcagg ctgtgttcca 2040
ggggccctga tttcctcgga tgtgctattg gccccaggac tgaagctgcc tcccttcacc 2100
ctgggactgt ggttccaagg atgagagcag gggttggagc catggccttc tgggaaccta 2160
tggagaaagg gaatccaagg aagcagccaa ggctgctcgc agcttccctg agctgcacct 2220
cttgctaacc ccaccatcac actgccaccc tgccctaggg tctcactagt accaagtggg 2280
tcagcacagg gctgaggatg gggctcctat ccaccctggc cagcacccag cttagtgctg 2340
ggactagccc agaaacttga atgggaccct gagagagcca ggggtcccct gaggcccccc 2400
taggggcttt ctgtctgccc cagggtgctc catggatctc cctgtggcag caggcatgga 2460
gagtcagggc tgccttcatg gcagtaggct ctaagtgggt gactggccac aggccgagaa 2520
aagggtacag cctctaggtg gggttcccaa agacgccttc acgctggact gagctgctct 2580
cccacagggt ttctgtgcag ctggattttc tctgttgcat acatgcctgg catctgtctc 2640
cccttgttcc tgagtggccc cacatggggc tctgagcagg ctgtatctgg attctggcaa 2700
taaaagtact ctggatgctg taaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2760
aaaa                                                              2764
```

<210> 203
<211> 412
<212> PRT
<213> 現代人

<220>
<223> 溶酶體磷脂酶A2前驅體

<400> 203

```
Met Gly Leu His Leu Arg Pro Tyr Arg Val Gly Leu Leu Pro Asp Gly
 1               5                  10                  15
Leu Leu Phe Leu Leu Leu Leu Leu Met Leu Leu Ala Asp Pro Ala Leu
            20                  25                  30
Pro Ala Gly Arg His Pro Pro Val Val Leu Val Pro Gly Asp Leu Gly
        35                  40                  45
Asn Gln Leu Glu Ala Lys Leu Asp Lys Pro Thr Val Val His Tyr Leu
    50                  55                  60
Cys Ser Lys Lys Thr Glu Ser Tyr Phe Thr Ile Trp Leu Asn Leu Glu
65                  70                  75                  80
Leu Leu Leu Pro Val Ile Ile Asp Cys Trp Ile Asp Asn Ile Arg Leu
                85                  90                  95
Val Tyr Asn Lys Thr Ser Arg Ala Thr Gln Phe Pro Asp Gly Val Asp
            100                 105                 110
Val Arg Val Pro Gly Phe Gly Lys Thr Phe Ser Leu Glu Phe Leu Asp
        115                 120                 125
Pro Ser Lys Ser Ser Val Gly Ser Tyr Phe His Thr Met Val Glu Ser
    130                 135                 140
Leu Val Gly Trp Gly Tyr Thr Arg Gly Glu Asp Val Arg Gly Ala Pro
145                 150                 155                 160
Tyr Asp Trp Arg Arg Ala Pro Asn Glu Asn Gly Pro Tyr Phe Leu Ala
                165                 170                 175
Leu Arg Glu Met Ile Glu Glu Met Tyr Gln Leu Tyr Gly Gly Pro Val
            180                 185                 190
Val Leu Val Ala His Ser Met Gly Asn Met Tyr Thr Leu Tyr Phe Leu
        195                 200                 205
Gln Arg Gln Pro Gln Ala Trp Lys Asp Lys Tyr Ile Arg Ala Phe Val
    210                 215                 220
Ser Leu Gly Ala Pro Trp Gly Gly Val Ala Lys Thr Leu Arg Val Leu
225                 230                 235                 240
Ala Ser Gly Asp Asn Asn Arg Ile Pro Val Ile Gly Pro Leu Lys Ile
                245                 250                 255
```

```
Arg Glu Gln Gln Arg Ser Ala Val Ser Thr Ser Trp Leu Leu Pro Tyr
            260                 265                 270
Asn Tyr Thr Trp Ser Pro Glu Lys Val Phe Val Gln Thr Pro Thr Ile
        275                 280                 285
Asn Tyr Thr Leu Arg Asp Tyr Arg Lys Phe Phe Gln Asp Ile Gly Phe
    290                 295                 300
Glu Asp Gly Trp Leu Met Arg Gln Asp Thr Glu Gly Leu Val Glu Ala
305                 310                 315                 320
Thr Met Pro Pro Gly Val Gln Leu His Cys Leu Tyr Gly Thr Gly Val
                325                 330                 335
Pro Thr Pro Asp Ser Phe Tyr Tyr Glu Ser Phe Pro Asp Arg Asp Pro
            340                 345                 350
Lys Ile Cys Phe Gly Asp Gly Asp Gly Thr Val Asn Leu Lys Ser Ala
        355                 360                 365
Leu Gln Cys Gln Ala Trp Gln Ser Arg Gln Glu His Gln Val Leu Leu
    370                 375                 380
Gln Glu Leu Pro Gly Ser Glu His Ile Glu Met Leu Ala Asn Ala Thr
385                 390                 395                 400
Thr Leu Ala Tyr Leu Lys Arg Val Leu Leu Gly Pro
                405                 410
```

<210> 204
<211> 379
<212> PRT
<213> 現代人

<220>
<223> 溶酶體磷脂酶A2成熟蛋白

<400> 204

```
Ala Gly Arg His Pro Pro Val Val Leu Val Pro Gly Asp Leu Gly Asn
 1               5                  10                  15
Gln Leu Glu Ala Lys Leu Asp Lys Pro Thr Val Val His Tyr Leu Cys
            20                  25                  30
Ser Lys Lys Thr Glu Ser Tyr Phe Thr Ile Trp Leu Asn Leu Glu Leu
        35                  40                  45
Leu Leu Pro Val Ile Ile Asp Cys Trp Ile Asp Asn Ile Arg Leu Val
    50                  55                  60
Tyr Asn Lys Thr Ser Arg Ala Thr Gln Phe Pro Asp Gly Val Asp Val
65                  70                  75                  80
Arg Val Pro Gly Phe Gly Lys Thr Phe Ser Leu Glu Phe Leu Asp Pro
                85                  90                  95
Ser Lys Ser Ser Val Gly Ser Tyr Phe His Thr Met Val Glu Ser Leu
            100                 105                 110
Val Gly Trp Gly Tyr Thr Arg Gly Glu Asp Val Arg Gly Ala Pro Tyr
        115                 120                 125
Asp Trp Arg Arg Ala Pro Asn Glu Asn Gly Pro Tyr Phe Leu Ala Leu
    130                 135                 140
Arg Glu Met Ile Glu Glu Met Tyr Gln Leu Tyr Gly Gly Pro Val Val
145                 150                 155                 160
Leu Val Ala His Ser Met Gly Asn Met Tyr Thr Leu Tyr Phe Leu Gln
                165                 170                 175
Arg Gln Pro Gln Ala Trp Lys Asp Lys Tyr Ile Arg Ala Phe Val Ser
            180                 185                 190
Leu Gly Ala Pro Trp Gly Gly Val Ala Lys Thr Leu Arg Val Leu Ala
        195                 200                 205
Ser Gly Asp Asn Asn Arg Ile Pro Val Ile Gly Pro Leu Lys Ile Arg
    210                 215                 220
Glu Gln Gln Arg Ser Ala Val Ser Thr Ser Trp Leu Leu Pro Tyr Asn
225                 230                 235                 240
Tyr Thr Trp Ser Pro Glu Lys Val Phe Val Gln Thr Pro Thr Ile Asn
                245                 250                 255

Tyr Thr Leu Arg Asp Tyr Arg Lys Phe Phe Gln Asp Ile Gly Phe Glu
```

```
            260                 265                 270
Asp Gly Trp Leu Met Arg Gln Asp Thr Glu Gly Leu Val Glu Ala Thr
        275                 280                 285
Met Pro Pro Gly Val Gln Leu His Cys Leu Tyr Gly Thr Gly Val Pro
    290                 295                 300
Thr Pro Asp Ser Phe Tyr Tyr Glu Ser Phe Pro Asp Arg Asp Pro Lys
305                 310                 315                 320
Ile Cys Phe Gly Asp Gly Asp Gly Thr Val Asn Leu Lys Ser Ala Leu
                325                 330                 335
Gln Cys Gln Ala Trp Gln Ser Arg Gln Glu His Gln Val Leu Leu Gln
            340                 345                 350
Glu Leu Pro Gly Ser Glu His Ile Glu Met Leu Ala Asn Ala Thr Thr
        355                 360                 365

Leu Ala Tyr Leu Lys Arg Val Leu Leu Gly Pro
    370                 375
```

<210> 205
<211> 2428
<212> DNA
<213> 現代人

<220>
<223> 膽汁鹽活化脂肪酶

<400> 205

```
accttctgta tcagttaagt gtcaagatgg aaggaacagc agtctcaaga taatgcaaag 60
agtttattca tccagaggct gatgctcacc atggggcgcc tgcaactggt tgtgttgggc 120
ctcacctgct gctgggcagt ggcgagtgcc gcgaagctgg gcgccgtgta cacagaaggt 180
gggttcgtgg aaggcgtcaa taagaagctc ggcctcctgg gtgactctgt ggacatcttc 240
aagggcatcc ccttcgcagc tcccaccaag gccctggaaa atcctcagcc acatcctggc 300
tggcaaggga ccctgaaggc caagaacttc aagaagagat gcctgcaggc caccatcacc 360
caggacagca cctacgggga tgaagactgc ctgtacctca acatttgggt gccccagggc 420
aggaagcaag tctcccggga cctgcccgtt atgatctgga tctatggagg cgccttcctc 480
atggggtccg gccatggggc caacttcctc aacaactacc tgtatgacgg cgaggagatc 540
gccacacgcg gaaacgtcat cgtggtcacc ttcaactacc gtgtcggccc ccttgggttc 600
ctcagcactg gggacgccaa tctgccaggt aactatggcc ttcgggatca gcacatggcc 660
attgcttggg tgaagaggaa tatcgcggcc ttcgggggggg accccaacaa catcacgctc 720
ttcggggagt ctgctggagg tgccagcgtc tctctgcaga ccctctcccc ctacaacaag 780
ggcctcatcc ggcgagccat cagccagagc ggcgtggccc tgagtccctg ggtcatccag 840
aaaaacccac tcttctgggc caaaaaggtg gctgagaagg tgggttgccc tgtgggtgat 900
gccgccagga tggcccagtg tctgaaggtt actgatcccc gagccctgac gctggcctat 960
aaggtgccgc tggcaggcct ggagtacccc atgctgcact atgtgggctt cgtccctgtc 1020
attgatggag acttcatccc cgctgacccg atcaacctgt acgccaacgc cgccgacatc 1080
gactatatag caggcaccaa caacatggac ggccacatct tcgccagcat cgacatgcct 1140
gccatcaaca agggcaacaa gaaagtcacg gaggaggact tctacaagct ggtcagtgag 1200
ttcacaatca ccaaggggct cagaggcgcc aagacgacct ttgatgtcta caccgagtcc 1260
tgggcccagg acccatccca ggagaataag aagaagactg tggtggactt tgagaccgat 1320
gtcctcttcc tggtgcccac cgagattgcc ctagcccagc acagagccaa tgccaagagt 1380
gccaagacct acgcctacct gttttcccat ccctctcgga tgcccgtcta ccccaaatgg 1440
gtgggggccg accatgcaga tgacattcag tacgttttcg ggaagccctt cgccaccccc 1500
acgggctacc ggccccaaga caggacagtc tctaaggcca tgatcgccta ctggaccaac 1560
tttgccaaaa caggggaccc caacatgggc gactcggctg tgcccacaca ctgggaaccc 1620
tacactacgg aaaacagcgg ctacctggag atcaccaaga agatgggcag cagctccatg 1680
aagcggagcc tgagaaccaa cttcctgcgc tactggaccc tcacctatct ggcgctgccc 1740
acagtgaccg accaggaggc cacccctgtg ccccccacag gggactccga ggccactccc 1800
gtgccccccа cgggtgactc cgagaccgcc cccgtgccgc ccacgggtga ctccggggcc 1860
ccccccgtgc cgcccacggg tgactccggg gccccccccg tgccgcccac gggtgactcc 1920
ggggcccccc ccgtgccgcc cacgggtgac tccggggccc cccccgtgcc gcccacgggt 1980
gactccgggg ccccccccgt gccgcccacg ggtgactccg gggccccccc cgtgccgccc 2040
acgggtgact ccggcgcccc ccccgtgccg cccacgggtg acgccgggcc ccccccccgtg 2100
ccgcccacgg gtgactccgg cgccccccccc gtgccgccca cgggtgactc cggggccccc 2160
cccgtgaccc ccacgggtga ctccgagacc gcccccgtgc cgcccacggg tgactccggg 2220
gccccccctg tgcccccccac gggtgactct gaggctgccc ctgtgccccc cacagatgac 2280
```

tccaaggaag ctcagatgcc tgcagtcatt aggttttagc gtcccatgag ccttggtatc 2340
aagaggccac aagagtggga ccccaggggc tcccctccca tcttgagctc ttcctgaata 2400
aagcctcata cccctaaaaa aaaaaaaa 2428

<210> 206
<211> 745
<212> PRT
<213> 現代人

<220>
<223> 膽汁鹽活化脂肪酶前驅體

<400> 206

```
Met Leu Thr Met Gly Arg Leu Gln Leu Val Val Leu Gly Leu Thr Cys
 1               5                  10                  15
Cys Trp Ala Val Ala Ser Ala Ala Lys Leu Gly Ala Val Tyr Thr Glu
            20                  25                  30
Gly Gly Phe Val Glu Gly Val Asn Lys Lys Leu Gly Leu Leu Gly Asp
        35                  40                  45
Ser Val Asp Ile Phe Lys Gly Ile Pro Phe Ala Ala Pro Thr Lys Ala
    50                  55                  60
Leu Glu Asn Pro Gln Pro His Pro Gly Trp Gln Gly Thr Leu Lys Ala
65                  70                  75                  80
Lys Asn Phe Lys Lys Arg Cys Leu Gln Ala Thr Ile Thr Gln Asp Ser
                85                  90                  95
Thr Tyr Gly Asp Glu Asp Cys Leu Tyr Leu Asn Ile Trp Val Pro Gln
            100                 105                 110
Gly Arg Lys Gln Val Ser Arg Asp Leu Pro Val Met Ile Trp Ile Tyr
        115                 120                 125
Gly Gly Ala Phe Leu Met Gly Ser Gly His Gly Ala Asn Phe Leu Asn
    130                 135                 140
Asn Tyr Leu Tyr Asp Gly Glu Glu Ile Ala Thr Arg Gly Asn Val Ile
145                 150                 155                 160
Val Val Thr Phe Asn Tyr Arg Val Gly Pro Leu Gly Phe Leu Ser Thr
                165                 170                 175
Gly Asp Ala Asn Leu Pro Gly Asn Tyr Gly Leu Arg Asp Gln His Met
            180                 185                 190
Ala Ile Ala Trp Val Lys Arg Asn Ile Ala Ala Phe Gly Gly Asp Pro
        195                 200                 205
Asn Asn Ile Thr Leu Phe Gly Glu Ser Ala Gly Gly Ala Ser Val Ser
    210                 215                 220
Leu Gln Thr Leu Ser Pro Tyr Asn Lys Gly Leu Ile Arg Arg Ala Ile
225                 230                 235                 240
Ser Gln Ser Gly Val Ala Leu Ser Pro Trp Val Ile Gln Lys Asn Pro
                245                 250                 255
Leu Phe Trp Ala Lys Lys Val Ala Glu Lys Val Gly Cys Pro Val Gly
            260                 265                 270
Asp Ala Ala Arg Met Ala Gln Cys Leu Lys Val Thr Asp Pro Arg Ala
        275                 280                 285
Leu Thr Leu Ala Tyr Lys Val Pro Leu Ala Gly Leu Glu Tyr Pro Met
    290                 295                 300
Leu His Tyr Val Gly Phe Val Pro Val Ile Asp Gly Asp Phe Ile Pro
305                 310                 315                 320
Ala Asp Pro Ile Asn Leu Tyr Ala Asn Ala Ala Asp Ile Asp Tyr Ile
                325                 330                 335
Ala Gly Thr Asn Asn Met Asp Gly His Ile Phe Ala Ser Ile Asp Met
            340                 345                 350
Pro Ala Ile Asn Lys Gly Asn Lys Lys Val Thr Glu Glu Asp Phe Tyr
        355                 360                 365
Lys Leu Val Ser Glu Phe Thr Ile Thr Lys Gly Leu Arg Gly Ala Lys
    370                 375                 380
Thr Thr Phe Asp Val Tyr Thr Glu Ser Trp Ala Gln Asp Pro Ser Gln
385                 390                 395                 400
Glu Asn Lys Lys Lys Thr Val Val Asp Phe Glu Thr Asp Val Leu Phe
                405                 410                 415
```

```
Leu Val Pro Thr Glu Ile Ala Leu Ala Gln His Arg Ala Asn Ala Lys
            420                 425                 430
Ser Ala Lys Thr Tyr Ala Tyr Leu Phe Ser His Pro Ser Arg Met Pro
        435                 440                 445
Val Tyr Pro Lys Trp Val Gly Ala Asp His Ala Asp Asp Ile Gln Tyr
    450                 455                 460
Val Phe Gly Lys Pro Phe Ala Thr Pro Thr Gly Tyr Arg Pro Gln Asp
465                 470                 475                 480
Arg Thr Val Ser Lys Ala Met Ile Ala Tyr Trp Thr Asn Phe Ala Lys
                485                 490                 495
Thr Gly Asp Pro Asn Met Gly Asp Ser Ala Val Pro Thr His Trp Glu
            500                 505                 510
Pro Tyr Thr Thr Glu Asn Ser Gly Tyr Leu Glu Ile Thr Lys Lys Met
        515                 520                 525
Gly Ser Ser Ser Met Lys Arg Ser Leu Arg Thr Asn Phe Leu Arg Tyr
    530                 535                 540
Trp Thr Leu Thr Tyr Leu Ala Leu Pro Thr Val Thr Asp Gln Glu Ala
545                 550                 555                 560
Thr Pro Val Pro Pro Thr Gly Asp Ser Glu Ala Thr Pro Val Pro Pro
                565                 570                 575
Thr Gly Asp Ser Glu Thr Ala Pro Val Pro Pro Thr Gly Asp Ser Gly
            580                 585                 590
Ala Pro Pro Val Pro Pro Thr Gly Asp Ser Gly Ala Pro Pro Val Pro
        595                 600                 605
Pro Thr Gly Asp Ser Gly Ala Pro Pro Val Pro Pro Thr Gly Asp Ser
    610                 615                 620
Gly Ala Pro Pro Val Pro Pro Thr Gly Asp Ser Gly Ala Pro Pro Val
625                 630                 635                 640
Pro Pro Thr Gly Asp Ser Gly Ala Pro Pro Val Pro Pro Thr Gly Asp
                645                 650                 655
Ser Gly Ala Pro Pro Val Pro Pro Thr Gly Asp Ala Gly Pro Pro Pro
            660                 665                 670
Val Pro Pro Thr Gly Asp Ser Gly Ala Pro Pro Val Pro Pro Thr Gly
        675                 680                 685
Asp Ser Gly Ala Pro Pro Val Thr Pro Thr Gly Asp Ser Glu Thr Ala
    690                 695                 700
Pro Val Pro Pro Thr Gly Asp Ser Gly Ala Pro Pro Val Pro Pro Thr
705                 710                 715                 720
Gly Asp Ser Glu Ala Ala Pro Val Pro Pro Thr Asp Asp Ser Lys Glu
                725                 730                 735
Ala Gln Met Pro Ala Val Ile Arg Phe
            740                 745
```

<210> 207
<211> 722
<212> PRT
<213> 現代人

<220>
<223> 膽汁鹽活化脂肪酶成熟蛋白

<400> 207

```
Ala Lys Leu Gly Ala Val Tyr Thr Glu Gly Gly Phe Val Glu Gly Val
 1                5                  10                  15
Asn Lys Lys Leu Gly Leu Leu Gly Asp Ser Val Asp Ile Phe Lys Gly
            20                  25                  30
Ile Pro Phe Ala Ala Pro Thr Lys Ala Leu Glu Asn Pro Gln Pro His
        35                  40                  45
Pro Gly Trp Gln Gly Thr Leu Lys Ala Lys Asn Phe Lys Lys Arg Cys
    50                  55                  60
Leu Gln Ala Thr Ile Thr Gln Asp Ser Thr Tyr Gly Asp Glu Asp Cys
65                  70                  75                  80
Leu Tyr Leu Asn Ile Trp Val Pro Gln Gly Arg Lys Gln Val Ser Arg
                85                  90                  95
```

```
Asp Leu Pro Val Met Ile Trp Ile Tyr Gly Gly Ala Phe Leu Met Gly
            100                 105                 110
Ser Gly His Gly Ala Asn Phe Leu Asn Asn Tyr Leu Tyr Asp Gly Glu
        115                 120                 125
Glu Ile Ala Thr Arg Gly Asn Val Ile Val Val Thr Phe Asn Tyr Arg
    130                 135                 140
Val Gly Pro Leu Gly Phe Leu Ser Thr Gly Asp Ala Asn Leu Pro Gly
145                 150                 155                 160
Asn Tyr Gly Leu Arg Asp Gln His Met Ala Ile Ala Trp Val Lys Arg
                165                 170                 175
Asn Ile Ala Ala Phe Gly Gly Asp Pro Asn Asn Ile Thr Leu Phe Gly
            180                 185                 190
Glu Ser Ala Gly Gly Ala Ser Val Ser Leu Gln Thr Leu Ser Pro Tyr
        195                 200                 205
Asn Lys Gly Leu Ile Arg Arg Ala Ile Ser Gln Ser Gly Val Ala Leu
    210                 215                 220
Ser Pro Trp Val Ile Gln Lys Asn Pro Leu Phe Trp Ala Lys Lys Val
225                 230                 235                 240
Ala Glu Lys Val Gly Cys Pro Val Gly Asp Ala Ala Arg Met Ala Gln
                245                 250                 255
Cys Leu Lys Val Thr Asp Pro Arg Ala Leu Thr Leu Ala Tyr Lys Val
            260                 265                 270
Pro Leu Ala Gly Leu Glu Tyr Pro Met Leu His Tyr Val Gly Phe Val
        275                 280                 285
Pro Val Ile Asp Gly Asp Phe Ile Pro Ala Asp Pro Ile Asn Leu Tyr
    290                 295                 300
Ala Asn Ala Ala Asp Ile Asp Tyr Ile Ala Gly Thr Asn Asn Met Asp
305                 310                 315                 320
Gly His Ile Phe Ala Ser Ile Asp Met Pro Ala Ile Asn Lys Gly Asn
                325                 330                 335
Lys Lys Val Thr Glu Glu Asp Phe Tyr Lys Leu Val Ser Glu Phe Thr
            340                 345                 350
Ile Thr Lys Gly Leu Arg Gly Ala Lys Thr Thr Phe Asp Val Tyr Thr
        355                 360                 365
Glu Ser Trp Ala Gln Asp Pro Ser Gln Glu Asn Lys Lys Lys Thr Val
    370                 375                 380
Val Asp Phe Glu Thr Asp Val Leu Phe Leu Val Pro Thr Glu Ile Ala
385                 390                 395                 400
Leu Ala Gln His Arg Ala Asn Ala Lys Ser Ala Lys Thr Tyr Ala Tyr
                405                 410                 415
Leu Phe Ser His Pro Ser Arg Met Pro Val Tyr Pro Lys Trp Val Gly
            420                 425                 430
Ala Asp His Ala Asp Asp Ile Gln Tyr Val Phe Gly Lys Pro Phe Ala
        435                 440                 445
Thr Pro Thr Gly Tyr Arg Pro Gln Asp Arg Thr Val Ser Lys Ala Met
    450                 455                 460
Ile Ala Tyr Trp Thr Asn Phe Ala Lys Thr Gly Asp Pro Asn Met Gly
465                 470                 475                 480
Asp Ser Ala Val Pro Thr His Trp Glu Pro Tyr Thr Thr Glu Asn Ser
                485                 490                 495
Gly Tyr Leu Glu Ile Thr Lys Lys Met Gly Ser Ser Ser Met Lys Arg
            500                 505                 510
Ser Leu Arg Thr Asn Phe Leu Arg Tyr Trp Thr Leu Thr Tyr Leu Ala
        515                 520                 525
Leu Pro Thr Val Thr Asp Gln Glu Ala Thr Pro Val Pro Pro Thr Gly
    530                 535                 540
Asp Ser Glu Ala Thr Pro Val Pro Pro Thr Gly Asp Ser Glu Thr Ala
545                 550                 555                 560
Pro Val Pro Pro Thr Gly Asp Ser Gly Ala Pro Pro Val Pro Pro Thr
                565                 570                 575
Gly Asp Ser Gly Ala Pro Pro Val Pro Pro Thr Gly Asp Ser Gly Ala
            580                 585                 590
Pro Pro Val Pro Pro Thr Gly Asp Ser Gly Ala Pro Pro Val Pro Pro
        595                 600                 605
Thr Gly Asp Ser Gly Ala Pro Pro Val Pro Pro Thr Gly Asp Ser Gly
```

610 615 620
Ala Pro Pro Val Pro Pro Thr Gly Asp Ser Gly Ala Pro Pro Val Pro
625 630 635 640
Pro Thr Gly Asp Ala Gly Pro Pro Pro Val Pro Pro Thr Gly Asp Ser
645 650 655
Gly Ala Pro Pro Val Pro Pro Thr Gly Asp Ser Gly Ala Pro Pro Val
660 665 670
Thr Pro Thr Gly Asp Ser Glu Thr Ala Pro Val Pro Pro Thr Gly Asp
675 680 685
Ser Gly Ala Pro Pro Val Pro Pro Thr Gly Asp Ser Glu Ala Ala Pro
690 695 700
Val Pro Pro Thr Asp Asp Ser Lys Glu Ala Gln Met Pro Ala Val Ile
705 710 715 720
Arg Phe

<210> 208
<211> 334
<212> PRT
<213> 西藏黃牛（Bos taurus）

<220>
<223> 組織蛋白酶L前驅體

<400> 208
Met Asn Pro Ser Phe Phe Leu Thr Val Leu Cys Leu Gly Val Ala Ser
1 5 10 15
Ala Ala Pro Lys Leu Asp Pro Asn Leu Asp Ala His Trp His Gln Trp
20 25 30
Lys Ala Thr His Arg Arg Leu Tyr Gly Met Asn Glu Glu Glu Trp Arg
35 40 45
Arg Ala Val Trp Glu Lys Asn Lys Lys Ile Ile Asp Leu His Asn Gln
50 55 60
Glu Tyr Ser Glu Gly Lys His Gly Phe Arg Met Ala Met Asn Ala Phe
65 70 75 80
Gly Asp Met Thr Asn Glu Glu Phe Arg Gln Val Met Asn Gly Phe Gln

85 90 95
Asn Gln Lys His Lys Lys Gly Lys Leu Phe His Glu Pro Leu Leu Val
100 105 110
Asp Val Pro Lys Ser Val Asp Trp Thr Lys Lys Gly Tyr Val Thr Pro
115 120 125
Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr
130 135 140
Gly Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Lys Leu Val Ser
145 150 155 160
Leu Ser Glu Gln Asn Leu Val Asp Cys Ser Arg Ala Gln Gly Asn Gln
165 170 175
Gly Cys Asn Gly Gly Leu Met Asp Asn Ala Phe Gln Tyr Ile Lys Asp
180 185 190
Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Leu Ala Thr Asp
195 200 205
Thr Asn Ser Cys Asn Tyr Lys Pro Glu Cys Ser Ala Ala Asn Asp Thr
210 215 220
Gly Phe Val Asp Ile Pro Gln Arg Glu Lys Ala Leu Met Lys Ala Val
225 230 235 240
Ala Thr Val Gly Pro Ile Ser Val Ala Ile Asp Ala Gly His Thr Ser
245 250 255
Phe Gln Phe Tyr Lys Ser Gly Ile Tyr Tyr Asp Pro Asp Cys Ser Ser
260 265 270
Lys Asp Leu Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Gly
275 280 285
Thr Asp Ser Asn Asn Asn Lys Phe Trp Ile Val Lys Asn Ser Trp Gly
290 295 300

```
Pro Glu Trp Gly Trp Asn Gly Tyr Val Lys Met Ala Lys Asp Gln Asn
305                 310                 315                 320
Asn His Cys Gly Ile Ala Thr Ala Ala Ser Tyr Pro Thr Val
                325                 330
```

<210> 209
<211> 217
<212> PRT
<213> 西藏黃牛（Bos taurus）

<220>
<223> 成熟組織蛋白酶L

<400> 209

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

<210> 210
<211> 333
<212> PRT
<213> 狗（Canis familiaris）

<220>
<223> 組織蛋白酶L前驅體

<400> 210

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

```
                85                  90                  95
Asn Gln Lys His Lys Lys Gly Lys Met Phe Gln Glu Pro Leu Phe Ala
            100                 105                 110
Glu Ile Pro Lys Ser Val Asp Trp Arg Glu Lys Gly Tyr Val Thr Pro
        115                 120                 125
Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr
    130                 135                 140
Gly Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Lys Leu Val Ser
145                 150                 155                 160
Leu Ser Glu Gln Asn Leu Val Asp Cys Ser Arg Ala Gln Gly Asn Glu
                165                 170                 175
Gly Cys Asn Gly Gly Leu Met Asp Asn Ala Phe Arg Tyr Val Lys Asp
            180                 185                 190
Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Leu Gly Arg Asp
        195                 200                 205
Thr Glu Thr Cys Asn Tyr Lys Pro Glu Cys Ser Ala Ala Asn Asp Thr
    210                 215                 220
Gly Phe Val Asp Leu Pro Gln Arg Glu Lys Ala Leu Met Lys Ala Val
225                 230                 235                 240
Ala Thr Leu Gly Pro Ile Ser Val Ala Ile Asp Ala Gly His Gln Ser
                245                 250                 255
Phe Gln Phe Tyr Lys Ser Gly Ile Tyr Phe Asp Pro Asp Cys Ser Ser
            260                 265                 270
Lys Asp Leu Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Gly
        275                 280                 285
Thr Asp Ser Asn Asn Lys Phe Trp Ile Val Lys Asn Ser Trp Gly Pro
    290                 295                 300
Glu Trp Gly Trp Asn Gly Tyr Val Lys Met Ala Lys Asp Gln Asn Asn
305                 310                 315                 320
His Cys Gly Ile Ala Thr Ala Ala Ser Tyr Pro Thr Val
                325                 330
```

<210> 211
<211> 216
<212> PRT
<213> 狗（Canis familiaris）

<220>
<223> 成熟組織蛋白酶L

<400> 211

```
Val Asp Trp Arg Glu Lys Gly Tyr Val Thr Pro Val Lys Asn Gln Gly

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

```
Lys Phe Trp Ile Val Lys Asn Ser Trp Gly Pro Glu Trp Gly Trp Asn
            180                 185                 190
Gly Tyr Val Lys Met Ala Lys Asp Gln Asn Asn His Cys Gly Ile Ala
        195                 200                 205
Thr Ala Ala Ser Tyr Pro Thr Val
    210                 215
```

<210> 212
<211> 333
<212> PRT
<213> 非洲綠猴（Cercopithecus aethiops）

<220>
<223> 組織蛋白酶L前驅體

<400> 212

```
Met Asn Pro Thr Phe Ile Leu Ala Ala Leu Cys Leu Gly Ile Ala Ser
 1               5                  10                  15
Ala Thr Leu Thr Phe Asn His Ser Leu Glu Ala Gln Trp Thr Lys Trp
            20                  25                  30
Lys Ala Met His Asn Arg Leu Tyr Gly Met Asn Glu Glu Gly Trp Arg
        35                  40                  45
Arg Ala Val Trp Glu Lys Asn Met Lys Met Ile Glu Leu His Asn Gln
    50                  55                  60
Glu Tyr Ser Gln Gly Lys His Ser Phe Thr Met Ala Met Asn Thr Phe
65                  70                  75                  80
Gly Asp Met Thr Ser Glu Glu Phe Arg Gln Val Met Asn Gly Phe Gln
                85                  90                  95
Asn Arg Lys Pro Arg Lys Gly Lys Val Phe Gln Glu Pro Leu Phe Tyr
            100                 105                 110
Glu Ala Pro Arg Ser Val Asp Trp Arg Glu Lys Gly Tyr Val Thr Pro
        115                 120                 125
Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr
    130                 135                 140
Gly Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Lys Leu Val Ser
145                 150                 155                 160
Leu Ser Glu Gln Asn Leu Val Asp Cys Ser Gly Pro Gln Gly Asn Glu
                165                 170                 175
Gly Cys Asn Gly Gly Leu Met Asp Tyr Ala Phe Gln Tyr Val Ala Asp
            180                 185                 190
Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Glu Ala Thr Glu
        195                 200                 205
Glu Ser Cys Lys Tyr Asn Pro Glu Tyr Ser Val Ala Asn Asp Thr Gly
    210                 215                 220
Phe Val Asp Ile Pro Lys Gln Glu Lys Ala Leu Met Lys Ala Val Ala
225                 230                 235                 240
Thr Val Gly Pro Ile Ser Val Ala Ile Asp Ala Gly His Glu Ser Phe
                245                 250                 255
Met Phe Tyr Lys Glu Gly Ile Tyr Phe Glu Pro Asp Cys Ser Ser Glu

            260                 265                 270
Asp Met Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Ser Thr
        275                 280                 285
Glu Ser Asp Asn Ser Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Glu
    290                 295                 300
Glu Trp Gly Met Gly Gly Tyr Ile Lys Met Ala Lys Asp Arg Arg Asn
305                 310                 315                 320
His Cys Gly Ile Ala Ser Ala Ala Ser Tyr Pro Thr Val

                325                 330
```

<210> 213
<211> 220

<212> PRT
<213> 非洲綠猴（Cercopithecus aethiops）

<220>
<223> 成熟組織蛋白酶L

<400> 213
Ala Pro Arg Ser Val Asp Trp Arg Glu Lys Gly Tyr Val Thr Pro Val
 1   5   10   15
Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr Gly
            20   25   30
Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Lys Leu Val Ser Leu
        35   40   45
Ser Glu Gln Asn Leu Val Asp Cys Ser Gly Pro Gln Gly Asn Glu Gly
    50   55   60
Cys Asn Gly Gly Leu Met Asp Tyr Ala Phe Gln Tyr Val Ala Asp Asn
65   70   75   80
Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Glu Ala Thr Glu Glu
                85   90   95
Ser Cys Lys Tyr Asn Pro Glu Tyr Ser Val Ala Asn Asp Thr Gly Phe
            100   105   110
Val Asp Ile Pro Lys Gln Glu Lys Ala Leu Met Lys Ala Val Ala Thr
        115   120   125
Val Gly Pro Ile Ser Val Ala Ile Asp Ala Gly His Glu Ser Phe Met
    130   135   140
Phe Tyr Lys Glu Gly Ile Tyr Phe Glu Pro Asp Cys Ser Ser Glu Asp
145   150   155   160
Met Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Ser Thr Glu
                165   170   175
Ser Asp Asn Ser Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Glu Glu
            180   185   190
Trp Gly Met Gly Gly Tyr Ile Lys Met Ala Lys Asp Arg Arg Asn His
        195   200   205
Cys Gly Ile Ala Ser Ala Ala Ser Tyr Pro Thr Val
    210   215   220

<210> 214
<211> 218
<212> PRT
<213> 家雞（Gallus gallus）

<220>
<223> 組織蛋白酶L前蛋白

<400> 214
Ala Pro Arg Ser Val Asp Trp Arg Glu Lys Gly Tyr Val Thr Pro Val
 1   5   10   15
Lys Asp Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Thr Thr Gly
            20   25   30
Ala Leu Glu Gly Gln His Phe Arg Thr Lys Gly Lys Leu Val Ser Leu
        35   40   45
Ser Glu Gln Asn Leu Val Asp Cys Ser Arg Pro Glu Gly Asn Gln Gly
    50   55   60
Cys Asn Gly Gly Leu Met Asp Gln Ala Phe Gln Tyr Val Gln Asp Asn
65   70   75   80
Gly Gly Ile Asp Ser Glu Glu Ser Tyr Pro Tyr Thr Ala Lys Asp Asp
                85   90   95
Glu Asp Cys Arg Tyr Lys Ala Glu Tyr Asn Ala Ala Asn Asp Thr Gly
            100   105   110
Phe Val Asp Ile Pro Gln Gly His Glu Arg Ala Leu Met Lys Ala Val
        115   120   125
Ala Ser Val Gly Pro Val Ser Val Ala Ile Asp Ala Gly His Ser Ser
    130   135   140
Phe Gln Phe Tyr Gln Ser Gly Ile Tyr Tyr Glu Pro Asp Cys Ser Ser

```
145                 150                 155                 160
Glu Asp Leu Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Gly
                165                 170                 175
Gly Lys Lys Tyr Trp Ile Val Lys Asn Ser Trp Gly Glu Lys Trp Gly
            180                 185                 190
Asp Lys Gly Tyr Ile Tyr Met Ala Lys Asp Arg Lys Asn His Cys Gly
        195                 200                 205
Ile Ala Thr Ala Ala Ser Tyr Pro Leu Val
    210                 215
```

<210> 215
<211> 334
<212> PRT
<213> 小家鼠

<220>
<223> 組織蛋白酶L前驅體

```
<400> 215
Met Asn Leu Leu Leu Leu Leu Ala Val Leu Cys Leu Gly Thr Ala Leu
 1               5                  10                  15
Ala Thr Pro Lys Phe Asp Gln Thr Phe Ser Ala Glu Trp His Gln Trp
            20                  25                  30
Lys Ser Thr His Arg Arg Leu Tyr Gly Thr Asn Glu Glu Glu Trp Arg
        35                  40                  45
Arg Ala Ile Trp Glu Lys Asn Met Arg Met Ile Gln Leu His Asn Gly
    50                  55                  60
Glu Tyr Ser Asn Gly Gln His Gly Phe Ser Met Glu Met Asn Ala Phe
65                  70                  75                  80
Gly Asp Met Thr Asn Glu Glu Phe Arg Gln Val Val Asn Gly Tyr Arg
                85                  90                  95
His Gln Lys His Lys Lys Gly Arg Leu Phe Gln Glu Pro Leu Met Leu
            100                 105                 110
Lys Ile Pro Lys Ser Val Asp Trp Arg Glu Lys Gly Cys Val Thr Pro
        115                 120                 125
Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Ser
    130                 135                 140
Gly Cys Leu Glu Gly Gln Met Phe Leu Lys Thr Gly Lys Leu Ile Ser
145                 150                 155                 160
Leu Ser Glu Gln Asn Leu Val Asp Cys Ser His Ala Gln Gly Asn Gln
                165                 170                 175
Gly Cys Asn Gly Gly Leu Met Asp Phe Ala Phe Gln Tyr Ile Lys Glu
            180                 185                 190
Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Glu Ala Lys Asp
        195                 200                 205
Gly Ser Cys Lys Tyr Arg Ala Glu Phe Ala Val Ala Asn Asp Thr Gly
    210                 215                 220
Phe Val Asp Ile Pro Gln Gln Glu Lys Ala Leu Met Lys Ala Val Ala
225                 230                 235                 240
Thr Val Gly Pro Ile Ser Val Ala Met Asp Ala Ser His Pro Ser Leu
                245                 250                 255
Gln Phe Tyr Ser Ser Gly Ile Tyr Tyr Glu Pro Asn Cys Ser Ser Lys
            260                 265                 270
Asn Leu Asp His Gly Val Leu Leu Val Gly Tyr Gly Tyr Glu Gly Thr
        275                 280                 285
Asp Ser Asn Lys Asn Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Ser
    290                 295                 300
Glu Trp Gly Met Glu Gly Tyr Ile Lys Ile Ala Lys Asp Arg Asp Asn
305                 310                 315                 320
His Cys Gly Leu Ala Thr Ala Ala Ser Tyr Pro Val Val Asn
                325                 330
```

<210> 216

<211> 221
<212> PRT
<213> 小家鼠

<220>
<223> 成熟組織蛋白酶L

<400> 216
Ile Pro Lys Ser Val Asp Trp Arg Glu Lys Gly Cys Val Thr Pro Val
 1   5   10   15
Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Ser Gly
            20   25   30
Cys Leu Glu Gly Gln Met Phe Leu Lys Thr Gly Lys Leu Ile Ser Leu
        35   40   45
Ser Glu Gln Asn Leu Val Asp Cys Ser His Ala Gln Gly Asn Gln Gly
    50   55   60
Cys Asn Gly Gly Leu Met Asp Phe Ala Phe Gln Tyr Ile Lys Glu Asn
65   70   75   80
Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Glu Ala Lys Asp Gly
                85   90   95
Ser Cys Lys Tyr Arg Ala Glu Phe Ala Val Ala Asn Asp Thr Gly Phe
            100   105   110
Val Asp Ile Pro Gln Gln Glu Lys Ala Leu Met Lys Ala Val Ala Thr
        115   120   125
Val Gly Pro Ile Ser Val Ala Met Asp Ala Ser His Pro Ser Leu Gln
    130   135   140
Phe Tyr Ser Ser Gly Ile Tyr Tyr Glu Pro Asn Cys Ser Ser Lys Asn
145   150   155   160
Leu Asp His Gly Val Leu Leu Val Gly Tyr Gly Tyr Glu Gly Thr Asp
                165   170   175
Ser Asn Lys Asn Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Ser Glu
            180   185   190
Trp Gly Met Glu Gly Tyr Ile Lys Ile Ala Lys Asp Arg Asp Asn His
        195   200   205
Cys Gly Leu Ala Thr Ala Ala Ser Tyr Pro Val Val Asn
    210   215   220

<210> 217
<211> 314
<212> PRT
<213> 纖毛蟲（Paramecium tetraurelia）

<220>
<223> 組織蛋白酶L前驅體

<400> 217
Met Met Leu Leu Gly Ala Ser Leu Tyr Leu Asn Asn Thr Gln Glu Val
 1   5   10   15
Ser Asp Glu Ile Asp Thr Ala Asn Leu Tyr Ala Asn Trp Lys Met Lys
            20   25   30
Tyr Asn Arg Arg Tyr Thr Asn Gln Arg Asp Glu Met Tyr Arg Tyr Lys
        35   40   45
Val Phe Thr Asp Asn Leu Asn Tyr Ile Arg Ala Phe Tyr Glu Ser Pro
    50   55   60
Glu Glu Ala Thr Phe Thr Leu Glu Leu Asn Gln Phe Ala Asp Met Ser
65   70   75   80
Gln Gln Glu Phe Ala Gln Thr Tyr Leu Ser Leu Lys Val Pro Arg Thr
                85   90   95
Ala Lys Leu Asn Ala Ala Asn Ser Asn Phe Gln Tyr Lys Gly Ala Glu
            100   105   110
Val Asp Trp Thr Asp Asn Lys Lys Val Lys Tyr Pro Ala Val Lys Asn
        115   120   125
Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Ser Ala Val Gly Ala Leu
    130   135   140

```
Glu Ile Asn Thr Asp Ile Glu Leu Asn Arg Lys Tyr Glu Leu Ser Glu
145                 150                 155                 160
Gln Asp Leu Val Asp Cys Ser Gly Pro Tyr Asp Asn Asp Gly Cys Asn
                165                 170                 175
Gly Gly Trp Met Asp Ser Ala Phe Glu Tyr Val Ala Asp Asn Gly Leu
            180                 185                 190
Ala Glu Ala Lys Asp Tyr Pro Tyr Thr Ala Lys Asp Gly Thr Cys Lys
        195                 200                 205
Thr Ser Val Lys Arg Pro Tyr Thr His Val Gln Gly Phe Lys Asp Ile
    210                 215                 220
Asp Ser Cys Asp Glu Leu Ala Gln Thr Ile Gln Glu Arg Thr Val Ala
225                 230                 235                 240
Val Ala Val Asp Ala Asn Pro Trp Gln Phe Tyr Arg Ser Gly Val Leu
                245                 250                 255
Ser Lys Cys Thr Lys Asn Leu Asn His Gly Val Val Leu Val Gly Val
            260                 265                 270
Gln Ala Asp Gly Ala Trp Lys Ile Arg Asn Ser Trp Gly Ser Ser Trp
        275                 280                 285
Gly Glu Ala Gly His Ile Arg Leu Ala Gly Gly Asp Thr Cys Gly Ile
    290                 295                 300
Cys Ala Ala Pro Ser Phe Pro Ile Leu Gly
305                 310
```

<210> 218
<211> 205
<212> PRT
<213> 纖毛蟲（Paramecium tetraurelia）

<220>
<223> 成熟組織蛋白酶L

```
<400> 218
Gly Ala Glu Val Asp Trp Thr Asp Asn Lys Lys Val Lys Tyr Pro Ala
 1               5                  10                  15
Val Lys Asn Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Ser Ala Val
            20                  25                  30
Gly Ala Leu Glu Ile Asn Thr Asp Ile Glu Leu Asn Arg Lys Tyr Glu
        35                  40                  45
Leu Ser Glu Gln Asp Leu Val Asp Cys Ser Gly Pro Tyr Asp Asn Asp
    50                  55                  60
Gly Cys Asn Gly Gly Trp Met Asp Ser Ala Phe Glu Tyr Val Ala Asp
65                  70                  75                  80
Asn Gly Leu Ala Glu Ala Lys Asp Tyr Pro Tyr Thr Ala Lys Asp Gly
                85                  90                  95
Thr Cys Lys Thr Ser Val Lys Arg Pro Tyr Thr His Val Gln Gly Phe
            100                 105                 110
Lys Asp Ile Asp Ser Cys Asp Glu Leu Ala Gln Thr Ile Gln Glu Arg
        115                 120                 125
Thr Val Ala Val Ala Val Asp Ala Asn Pro Trp Gln Phe Tyr Arg Ser
    130                 135                 140
Gly Val Leu Ser Lys Cys Thr Lys Asn Leu Asn His Gly Val Val Leu
145                 150                 155                 160
Val Gly Val Gln Ala Asp Gly Ala Trp Lys Ile Arg Asn Ser Trp Gly
                165                 170                 175
Ser Ser Trp Gly Glu Ala Gly His Ile Arg Leu Ala Gly Gly Asp Thr
            180                 185                 190
Cys Gly Ile Cys Ala Ala Pro Ser Phe Pro Ile Leu Gly
        195                 200                 205
```

<210> 219
<211> 334
<212> PRT
<213> 豬（Sus scrof）

<220>
<223> 組織蛋白酶L前驅體

<400> 219
Met Lys Pro Ser Leu Phe Leu Thr Ala Leu Cys Leu Gly Ile Ala Ser
 1   5   10   15
Ala Ala Pro Lys Leu Asp Gln Asn Leu Asp Ala Asp Trp Tyr Lys Trp
            20   25   30
Lys Ala Thr His Gly Arg Leu Tyr Gly Met Asn Glu Glu Gly Trp Arg
        35   40   45
Arg Ala Val Trp Glu Lys Asn Met Lys Met Ile Glu Leu His Asn Gln
    50   55   60
Glu Tyr Ser Gln Gly Lys His Gly Phe Ser Met Ala Met Asn Ala Phe
65   70   75   80
Gly Asp Met Thr Asn Glu Glu Phe Arg Gln Val Met Asn Gly Phe Gln
                85   90   95
Asn Gln Lys His Lys Lys Gly Lys Val Phe His Glu Ser Leu Val Leu
            100   105   110
Glu Val Pro Lys Ser Val Asp Trp Arg Glu Lys Gly Tyr Val Thr Ala
        115   120   125
Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr
    130   135   140
Gly Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Lys Leu Val Ser
145   150   155   160
Leu Ser Glu Gln Asn Leu Val Asp Cys Ser Arg Pro Gln Gly Asn Gln
                165   170   175
Gly Cys Asn Gly Gly Leu Met Asp Asn Ala Phe Gln Tyr Val Lys Asp
            180   185   190
Asn Gly Gly Leu Asp Thr Glu Glu Ser Tyr Pro Tyr Leu Gly Arg Glu
        195   200   205
Thr Asn Ser Cys Thr Tyr Lys Pro Glu Cys Ser Ala Ala Asn Asp Thr
    210   215   220
Gly Phe Val Asp Ile Pro Gln Arg Glu Lys Ala Leu Met Lys Ala Val
225   230   235   240
Ala Thr Val Gly Pro Ile Ser Val Ala Ile Asp Ala Gly His Ser Ser
                245   250   255
Phe Gln Phe Tyr Lys Ser Gly Ile Tyr Tyr Asp Pro Asp Cys Ser Ser
            260   265   270
Lys Asp Leu Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Gly
        275   280   285
Thr Asp Ser Asn Ser Ser Lys Phe Trp Ile Val Lys Asn Ser Trp Gly
    290   295   300
Pro Glu Trp Gly Trp Asn Gly Tyr Val Lys Met Ala Lys Asp Gln Asn
305   310   315   320
Asn His Cys Gly Ile Ser Thr Ala Ala Ser Tyr Pro Thr Val
                325   330

<210> 220
<211> 217
<212> PRT
<213> 豬（Sus scrof）

<220>
<223> 成熟組織蛋白酶L

<400> 220
Val Asp Trp Arg Glu Lys Gly Tyr Val Thr Ala Val Lys Asn Gln Gly
 1   5   10   15
Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr Gly Ala Leu Glu Gly
            20   25   30
Gln Met Phe Arg Lys Thr Gly Lys Leu Val Ser Leu Ser Glu Gln Asn
        35   40   45

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

<210> 221
<211> 334
<212> PRT
<213> 大鼠（Rattus norvegicus）

<220>
<223> 組織蛋白酶L前驅體

<400> 221

```
Met Thr Pro Leu Leu Leu Leu Ala Val Leu Cys Leu Gly Thr Ala Leu
 1                  5                  10                  15
Ala Thr Pro Lys Phe Asp Gln Thr Phe Asn Ala Gln Trp His Gln Trp
            20                  25                  30
Lys Ser Thr His Arg Arg Leu Tyr Gly Thr Asn Glu Glu Glu Trp Arg
        35                  40                  45
Arg Ala Val Trp Glu Lys Asn Met Arg Met Ile Gln Leu His Asn Gly
    50                  55                  60
Glu Tyr Ser Asn Gly Lys His Gly Phe Thr Met Glu Met Asn Ala Phe
65                  70                  75                  80
Gly Asp Met Thr Asn Glu Glu Phe Arg Gln Ile Val Asn Gly Tyr Arg
                85                  90                  95
His Gln Lys His Lys Lys Gly Arg Leu Phe Gln Glu Pro Leu Met Leu
            100                 105                 110
Gln Ile Pro Lys Thr Val Asp Trp Arg Glu Lys Gly Cys Val Thr Pro
        115                 120                 125
Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Ser
    130                 135                 140
Gly Cys Leu Glu Gly Gln Met Phe Leu Lys Thr Gly Lys Leu Ile Ser
145                 150                 155                 160
Leu Ser Glu Gln Asn Leu Val Asp Cys Ser His Asp Gln Gly Asn Gln
                165                 170                 175
Gly Cys Asn Gly Gly Leu Met Asp Phe Ala Phe Gln Tyr Ile Lys Glu
            180                 185                 190
Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Glu Ala Lys Asp
        195                 200                 205
Gly Ser Cys Lys Tyr Arg Ala Glu Tyr Ala Val Ala Asn Asp Thr Gly
    210                 215                 220
Phe Val Asp Ile Pro Gln Gln Glu Lys Ala Leu Met Lys Ala Val Ala
225                 230                 235                 240
Thr Val Gly Pro Ile Ser Val Ala Met Asp Ala Ser His Pro Ser Leu
                245                 250                 255
```

```
Gln Phe Tyr Ser Ser Gly Ile Tyr Tyr Glu Pro Asn Cys Ser Ser Lys
            260                 265                 270
Asp Leu Asp His Gly Val Leu Val Val Gly Tyr Gly Tyr Glu Gly Thr
        275                 280                 285
Asp Ser Asn Lys Asp Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Lys
    290                 295                 300
Glu Trp Gly Met Asp Gly Tyr Ile Lys Ile Ala Lys Asp Arg Asn Asn
305                 310                 315                 320
His Cys Gly Leu Ala Thr Ala Ala Ser Tyr Pro Ile Val Asn
                325                 330
```

<210> 222
<211> 221
<212> PRT
<213> 大鼠 (Rattus norvegicus)

<220>
<223> 成熟組織蛋白酶L

```
<400> 222
Ile Pro Lys Thr Val Asp Trp Arg Glu Lys Gly Cys Val Thr Pro Val
 1               5                  10                  15
Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Ser Gly
            20                  25                  30
Cys Leu Glu Gly Gln Met Phe Leu Lys Thr Gly Lys Leu Ile Ser Leu
        35                  40                  45
Ser Glu Gln Asn Leu Val Asp Cys Ser His Asp Gln Gly Asn Gln Gly
    50                  55                  60
Cys Asn Gly Gly Leu Met Asp Phe Ala Phe Gln Tyr Ile Lys Glu Asn
65                  70                  75                  80
Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Glu Ala Lys Asp Gly
                85                  90                  95
Ser Cys Lys Tyr Arg Ala Glu Tyr Ala Val Ala Asn Asp Thr Gly Phe
            100                 105                 110
Val Asp Ile Pro Gln Gln Glu Lys Ala Leu Met Lys Ala Val Ala Thr
        115                 120                 125
Val Gly Pro Ile Ser Val Ala Met Asp Ala Ser His Pro Ser Leu Gln
    130                 135                 140
Phe Tyr Ser Ser Gly Ile Tyr Tyr Glu Pro Asn Cys Ser Ser Lys Asp
145                 150                 155                 160
Leu Asp His Gly Val Leu Val Val Gly Tyr Gly Tyr Glu Gly Thr Asp
                165                 170                 175
Ser Asn Lys Asp Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Lys Glu
            180                 185                 190
Trp Gly Met Asp Gly Tyr Ile Lys Ile Ala Lys Asp Arg Asn Asn His
        195                 200                 205
Cys Gly Leu Ala Thr Ala Ala Ser Tyr Pro Ile Val Asn
    210                 215                 220
```

<210> 223
<211> 217
<212> PRT
<213> 綿羊 (Ovis aries)

<220>
<223> 成熟組織蛋白酶L

```
<400> 223
Val Pro Lys Ser Val Asp Trp Thr Lys Lys Gly Tyr Val Thr Pro Val
 1               5                  10                  15
Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr Gly
            20                  25                  30
Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Lys Leu Val Ser Leu
```

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

<210> 224
<211> 6630
<212> DNA
<213> 人造序列

<220>
<223> 具有PH20及DHFR之HZ24（Gen1/Gen2）

<400> 224

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cgccccgttg acgcaaatgg gcggtaggcg tgtacggtgg gaggtctata taagcagagc 720
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<211> 482
<212> PRT
<213> 現代人

<220>
<223> 前驅體可溶性rHuPH20

<400> 225

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

```
Arg Ile Val Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu
305                 310                 315                 320
Leu Val Tyr Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile
                325                 330                 335
Val Ile Trp Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu
            340                 345                 350
Leu Leu Asp Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn
        355                 360                 365
Val Thr Leu Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln
    370                 375                 380
Gly Val Cys Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu
385                 390                 395                 400
Asn Pro Asp Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr
                405                 410                 415
Val Arg Gly Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys
            420                 425                 430
Phe Tyr Cys Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp
        435                 440                 445
Val Lys Asp Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys
    450                 455                 460
Ile Asp Ala Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile
465                 470                 475                 480
Phe Tyr
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<210> 226
<211> 447
<212> PRT
<213> 現代人

<220>
<223> 可溶性rHuPH20 1-447

<400> 226

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Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1                5                  10                  15
Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
            20                  25                  30
Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
        35                  40                  45
Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
    50                  55                  60
Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
65                  70                  75                  80
Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
                85                  90                  95
Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
            100                 105                 110
Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
        115                 120                 125
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
    130                 135                 140
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
145                 150                 155                 160
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
                165                 170                 175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
            180                 185                 190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
        195                 200                 205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
    210                 215                 220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225                 230                 235                 240
```

```
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
                245                 250                 255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
            260                 265                 270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
        275                 280                 285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
    290                 295                 300
Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu Leu Leu Asp
305                 310                 315                 320
Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
                325                 330                 335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
            340                 345                 350
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
        355                 360                 365
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
    370                 375                 380
Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385                 390                 395                 400
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
                405                 410                 415
Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
            420                 425                 430
Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr
        435                 440                 445
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<210> 227
<211> 446
<212> PRT
<213> 現代人

<220>
<223> 可溶性rHuPH20 1-446

<400> 227

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

Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
            180                 185                 190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
        195                 200                 205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
```

```
    210                 215                 220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225                 230                 235                 240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
                245                 250                 255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
            260                 265                 270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
        275                 280                 285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
    290                 295                 300
Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu Leu Leu Asp
305                 310                 315                 320
Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
                325                 330                 335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
            340                 345                 350
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
        355                 360                 365
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
    370                 375                 380
Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385                 390                 395                 400
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
                405                 410                 415
Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
            420                 425                 430
Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe
        435                 440                 445
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<210> 228
<211> 445
<212> PRT
<213> 現代人

<220>
<223> 可溶性rHuPH20 1-445

<400> 228

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

```
        195                 200                 205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
    210                 215                 220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225                 230                 235                 240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile

                245                 250                 255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
            260                 265                 270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
        275                 280                 285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
    290                 295                 300
Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu Leu Leu Asp
305                 310                 315                 320
Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
                325                 330                 335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
            340                 345                 350
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
        355                 360                 365
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
    370                 375                 380
Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385                 390                 395                 400
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
                405                 410                 415
Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
            420                 425                 430
Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile
        435                 440                 445
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<210> 229
<211> 444
<212> PRT
<213> 現代人

<220>
<223> 可溶性rHuPH20 1-444

<400> 229

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

```
                165                 170                 175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
            180                 185                 190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
        195                 200                 205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
    210                 215                 220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225                 230                 235                 240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
                245                 250                 255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
            260                 265                 270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
        275                 280                 285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
    290                 295                 300
Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu Leu Leu Asp
305                 310                 315                 320
Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
                325                 330                 335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
            340                 345                 350
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
        355                 360                 365
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
    370                 375                 380
Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385                 390                 395                 400
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
                405                 410                 415
Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
            420                 425                 430
Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln
        435                 440
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<220>
<223> 可溶性rHuPH20 1-443

<400> 230

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

```
145                 150                 155                 160
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
                165                 170                 175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
            180                 185                 190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
        195                 200                 205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
    210                 215                 220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225                 230                 235                 240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
                245                 250                 255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
            260                 265                 270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
        275                 280                 285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
    290                 295                 300
Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu Leu Leu Asp
305                 310                 315                 320
Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
                325                 330                 335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
            340                 345                 350
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
        355                 360                 365
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
    370                 375                 380
Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385                 390                 395                 400
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
                405                 410                 415
Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
            420                 425                 430
Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro
        435                 440
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<223> 可溶性rHuPH20 1-442

<400> 231

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

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

<210> 232
<211> 509
<212> PRT
<213> 現代人

<220>
<223> 前驅體PH20

<400> 232
Met Gly Val Leu Lys Phe Lys His Ile Phe Phe Arg Ser Phe Val Lys
1 5 10 15
Ser Ser Gly Val Ser Gln Ile Val Phe Thr Phe Leu Leu Ile Pro Cys
20 25 30
Cys Leu Thr Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro
35 40 45
Phe Leu Trp Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe
50 55 60
Asp Glu Pro Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg
65 70 75 80
Ile Asn Ala Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu
85 90 95
Gly Tyr Tyr Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly
100 105 110
Gly Ile Pro Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys

```
        115                 120                 125
Lys Asp Ile Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val
    130                 135                 140
Ile Asp Trp Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro
145                 150                 155                 160
Lys Asp Val Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn
                165                 170                 175
Val Gln Leu Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe
            180                 185                 190
Glu Lys Ala Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys
        195                 200                 205
Leu Leu Arg Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys
    210                 215                 220
Tyr Asn His His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn
225                 230                 235                 240
Val Glu Ile Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser
                245                 250                 255
Thr Ala Leu Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val
            260                 265                 270
Ala Ala Thr Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val
        275                 280                 285
Ser Lys Ile Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr
    290                 295                 300
Arg Ile Val Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu
305                 310                 315                 320
Leu Val Tyr Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile
                325                 330                 335
Val Ile Trp Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu
            340                 345                 350
Leu Leu Asp Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn
        355                 360                 365
Val Thr Leu Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln
    370                 375                 380
Gly Val Cys Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu
385                 390                 395                 400
Asn Pro Asp Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr
                405                 410                 415
Val Arg Gly Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys
            420                 425                 430
Phe Tyr Cys Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp
        435                 440                 445
Val Lys Asp Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys
    450                 455                 460
Ile Asp Ala Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile
465                 470                 475                 480
Phe Tyr Asn Ala Ser Pro Ser Thr Leu Ser Ala Thr Met Phe Ile Val
                485                 490                 495
Ser Ile Leu Phe Leu Ile Ile Ser Ser Val Ala Ser Leu
            500                 505
```

<210> 233
<211> 474
<212> PRT
<213> 現代人

<220>
<223> 成熟PH20

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<400> 233
Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1                  5                  10                  15
Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
            20                  25                  30
Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
```

```
        35                  40                  45
Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
    50                  55                  60
Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro

65                  70                  75                  80
Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
                85                  90                  95
Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
            100                 105                 110
Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
        115                 120                 125
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
    130                 135                 140
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
145                 150                 155                 160
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
                165                 170                 175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
            180                 185                 190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
        195                 200                 205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
    210                 215                 220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225                 230                 235                 240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
                245                 250                 255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
            260                 265                 270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
        275                 280                 285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
    290                 295                 300
Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu Leu Leu Asp
305                 310                 315                 320
Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
                325                 330                 335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
            340                 345                 350
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
        355                 360                 365
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
    370                 375                 380
Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385                 390                 395                 400
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
                405                 410                 415
Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
            420                 425                 430
Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
        435                 440                 445
Ala Ser Pro Ser Thr Leu Ser Ala Thr Met Phe Ile Val Ser Ile Leu
    450                 455                 460
Phe Leu Ile Ile Ser Ser Val Ala Ser Leu
465                 470
```

<210> 234
<211> 333
<212> PRT
<213> 現代人

<220>
<223> 組織蛋白酶L對偶基因變異體

<220>
<221> 變異體
<222> 56
<223> M 或 V

<220>

<221> 變異體
<222> 268
<223> D 或 N

<400> 234

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

His Cys Gly Ile Ala Ser Ala Ala Ser Tyr Pro Thr Val
                325                 330
```

<210> 235
<211> 5
<212> PRT
<213> 人造序列

<220>
<223> 6 x His標籤

<400> 235
His His His His His
1 5

<210> 236
<211> 8
<212> PRT
<213> 人造序列

<220>
<223> Flag標籤

<400> 236
Asp Tyr Lys Asp Asp Asp Asp Lys
1 5

<210> 237
<211> 450
<212> PRT
<213> 西藏黃牛（Bos taurus）

<220>
<223> 玻尿酸酶

<400> 237
Met Arg Pro Phe Ser Leu Glu Val Ser Leu His Leu Pro Trp Ala Met
1 5 10 15
Ala Ala His Leu Leu Pro Val Cys Thr Leu Phe Leu Asn Leu Leu Ser
20 25 30
Met Thr Gln Gly Ser Arg Asp Pro Val Val Pro Asn Gln Pro Phe Thr
35 40 45
Thr Ile Trp Asn Ala Asn Thr Glu Trp Cys Met Lys Lys His Gly Val
50 55 60
Asp Val Asp Ile Ser Ile Phe Asp Val Val Thr Asn Pro Gly Gln Thr
65 70 75 80
Phe Arg Gly Pro Asn Met Thr Ile Phe Tyr Ser Ser Gln Leu Gly Thr
85 90 95
Tyr Pro Tyr Tyr Thr Ser Ala Gly Glu Pro Val Phe Gly Gly Leu Pro
100 105 110
Gln Asn Ala Ser Leu Asn Ala His Leu Ala Arg Thr Phe Gln Asp Ile
115 120 125
Leu Ala Ala Met Pro Glu Pro Arg Phe Ser Gly Leu Ala Val Ile Asp
130 135 140
Trp Glu Ala Trp Arg Pro Arg Trp Ala Phe Asn Trp Asp Thr Lys Asp
145 150 155 160
Ile Tyr Arg Gln Arg Ser Arg Ala Leu Val Gln Lys Gln His Pro Asp
165 170 175
Trp Leu Ala Pro Arg Val Glu Ala Ala Ala Gln Asp Gln Phe Glu Gly
180 185 190
Ala Ala Glu Glu Trp Met Ala Gly Thr Leu Lys Leu Gly Gln Ala Leu
195 200 205
Arg Pro Gln Gly Leu Trp Gly Phe Tyr Asn Phe Pro Glu Cys Tyr Asn
210 215 220
Tyr Asp Phe Lys Ser Pro Asn Tyr Thr Gly Arg Cys Pro Leu Asn Ile
225 230 235 240
Cys Ala Gln Asn Asp Gln Leu Gly Trp Leu Trp Gly Gln Ser Arg Ala
245 250 255
Leu Tyr Pro Ser Ile Tyr Leu Pro Ala Ala Leu Glu Gly Thr Lys Lys
260 265 270
Thr Gln Met Phe Val Gln His Arg Val Ala Glu Ala Phe Arg Val Ala
275 280 285
Ala Gly Ala Gly Asp Pro Lys Leu Pro Val Leu Pro Tyr Met Gln Leu

```
    290                 295                 300
Phe Tyr Asp Met Thr Asn His Phe Leu Pro Ala Glu Glu Leu Glu His
305                 310                 315                 320
Ser Leu Gly Glu Ser Ala Ala Gln Gly Ala Ala Gly Val Val Leu Trp
                325                 330                 335
Val Ser Trp Leu Ser Thr Ser Thr Lys Glu Ser Cys Gln Ala Ile Lys
            340                 345                 350
Glu Tyr Val Asp Thr Thr Leu Gly Pro Ser Ile Leu Asn Val Thr Ser
        355                 360                 365
Gly Ala Arg Leu Cys Ser Gln Val Leu Cys Ser Gly His Gly Arg Cys
    370                 375                 380
Ala Arg Arg Pro Ser Tyr Pro Lys Ala Arg Leu Ile Leu Asn Ser Thr
385                 390                 395                 400
Ser Phe Ser Ile Lys Pro Thr Pro Gly Gly Gly Pro Leu Thr Leu Gln
                405                 410                 415
Gly Ala Leu Ser Leu Glu Asp Arg Leu Arg Met Ala Val Glu Phe Glu
            420                 425                 430
Cys Arg Cys Tyr Arg Gly Trp Arg Gly Thr Arg Cys Glu Gln Trp Gly
        435                 440                 445
Met Trp
    450
```

<210> 238
<211> 331
<212> PRT
<213> 黃胡蜂（Vespula vulgaris）

<220>
<223> 玻尿酸酶A

```
<400> 238
Ser Glu Arg Pro Lys Arg Val Phe Asn Ile Tyr Trp Asn Val Pro Thr
 1                5                  10                  15
Phe Met Cys His Gln Tyr Asp Leu Tyr Phe Asp Glu Val Thr Asn Phe
            20                  25                  30
Asn Ile Lys Arg Asn Ser Lys Asp Asp Phe Gln Gly Asp Lys Ile Ala
        35                  40                  45
Ile Phe Tyr Asp Pro Gly Glu Phe Pro Ala Leu Leu Ser Leu Lys Asp
    50                  55                  60
Gly Lys Tyr Lys Lys Arg Asn Gly Gly Val Pro Gln Glu Gly Asn Ile
65                  70                  75                  80
Thr Ile His Leu Gln Lys Phe Ile Glu Asn Leu Asp Lys Ile Tyr Pro
                85                  90                  95
Asn Arg Asn Phe Ser Gly Ile Gly Val Ile Asp Phe Glu Arg Trp Arg
            100                 105                 110
Pro Ile Phe Arg Gln Asn Trp Gly Asn Met Lys Ile His Lys Asn Phe
        115                 120                 125
Ser Ile Asp Leu Val Arg Asn Glu His Pro Thr Trp Asn Lys Lys Met
    130                 135                 140
Ile Glu Leu Glu Ala Ser Lys Arg Phe Glu Lys Tyr Ala Arg Phe Phe
145                 150                 155                 160
Met Glu Glu Thr Leu Lys Leu Ala Lys Lys Thr Arg Lys Gln Ala Asp
                165                 170                 175
Trp Gly Tyr Tyr Gly Tyr Pro Tyr Cys Phe Asn Met Ser Pro Asn Asn
            180                 185                 190
Leu Val Pro Glu Cys Asp Val Thr Ala Met His Glu Asn Asp Lys Met
        195                 200                 205
Ser Trp Leu Phe Asn Asn Gln Asn Val Leu Leu Pro Ser Val Tyr Val
    210                 215                 220
Arg Gln Glu Leu Thr Pro Asp Gln Arg Ile Gly Leu Val Gln Gly Arg
225                 230                 235                 240
Val Lys Glu Ala Val Arg Ile Ser Asn Asn Leu Lys His Ser Pro Lys
                245                 250                 255
Val Leu Ser Tyr Trp Trp Tyr Val Tyr Gln Asp Glu Thr Asn Thr Phe
```

```
            260                 265                 270
Leu Thr Glu Thr Asp Val Lys Lys Thr Phe Gln Glu Ile Val Ile Asn
        275                 280                 285
Gly Gly Asp Gly Ile Ile Ile Trp Gly Ser Ser Ser Asp Val Asn Ser
    290                 295                 300
Leu Ser Lys Cys Lys Arg Leu Gln Asp Tyr Leu Leu Thr Val Leu Gly
305                 310                 315                 320
Pro Ile Ala Ile Asn Val Thr Glu Ala Val Asn
                325                 330
```

<210> 239
<211> 340
<212> PRT
<213> 黃胡蜂（Vespula vulgaris）

<220>
<223> 玻尿酸酶B

<400> 239

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

<210> 240
<211> 382
<212> PRT
<213> 蜜蜂 (Apis mellifer)

<220>
<223> 玻尿酸酶

<400> 240

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

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

<210> 241
<211> 331
<212> PRT
<213> 白麵長黃胡蜂 (Dolichovespula maculata)

<220>
<223> 玻尿酸酶

<400> 241
Ser Glu Arg Pro Lys Arg Val Phe Asn Ile Tyr Trp Asn Val Pro Thr
 1   5   10   15
Phe Met Cys His Gln Tyr Gly Leu Tyr Phe Asp Glu Val Thr Asn Phe
            20   25   30
Asn Ile Lys His Asn Ser Lys Asp Asp Phe Gln Gly Asp Lys Ile Ser
        35   40   45
Ile Phe Tyr Asp Pro Gly Glu Phe Pro Ala Leu Leu Pro Leu Lys Glu
    50   55   60
Gly Asn Tyr Lys Ile Arg Asn Gly Gly Val Pro Gln Glu Gly Asn Ile
65   70   75   80
Thr Ile His Leu Gln Arg Phe Ile Glu Asn Leu Asp Lys Thr Tyr Pro
                85   90   95
Asn Arg Asn Phe Asn Gly Ile Gly Val Ile Asp Phe Glu Arg Trp Arg
            100   105   110
Pro Ile Phe Arg Gln Asn Trp Gly Asn Met Met Ile His Lys Lys Phe
        115   120   125
Ser Ile Asp Leu Val Arg Asn Glu His Pro Phe Trp Asp Lys Lys Met
    130   135   140
Ile Glu Leu Glu Ala Ser Lys Arg Phe Glu Lys Tyr Ala Arg Leu Phe
145   150   155   160
Met Glu Glu Thr Leu Lys Leu Ala Lys Lys Thr Arg Lys Gln Ala Asp
                165   170   175
Trp Gly Tyr Tyr Gly Tyr Pro Tyr Cys Phe Asn Met Ser Pro Asn Asn
            180   185   190
Leu Val Pro Asp Cys Asp Ala Thr Ala Met Leu Glu Asn Asp Lys Met
        195   200   205
Ser Trp Leu Phe Asn Asn Gln Asn Val Leu Leu Pro Ser Val Tyr Ile
    210   215   220
Arg His Glu Leu Thr Pro Asp Gln Arg Val Gly Leu Val Gln Gly Arg
225   230   235   240
Val Lys Glu Ala Val Arg Ile Ser Asn Asn Leu Lys His Ser Pro Lys
                245   250   255
Val Leu Ser Tyr Trp Trp Tyr Val Tyr Gln Asp Asp Thr Asn Thr Phe
            260   265   270
Leu Thr Glu Thr Asp Val Lys Lys Thr Phe Gln Glu Ile Ala Ile Asn
        275   280   285
Gly Gly Asp Gly Ile Ile Ile Trp Gly Ser Ser Ser Asp Val Asn Ser
    290   295   300
Leu Ser Lys Cys Lys Arg Leu Arg Glu Tyr Leu Leu Thr Val Leu Gly
305   310   315   320
Pro Ile Thr Val Asn Val Thr Glu Thr Val Asn
                325   330

<210> 242
<211> 367
<212> PRT
<213> 馬蜂 (Polistes annularis)

<220>
<223> 玻尿酸酶

<400> 242
Tyr Val Ser Leu Ser Pro Asp Ser Val Phe Asn Ile Ile Thr Asp Asp
 1   5   10   15
Ile Ser His Gln Ile Leu Ser Arg Ser Asn Cys Glu Arg Ser Lys Arg
            20   25   30
Pro Lys Arg Val Phe Ser Ile Tyr Trp Asn Val Pro Thr Phe Met Cys
        35   40   45
His Gln Tyr Gly Met Asn Phe Asp Glu Val Thr Asp Phe Asn Ile Lys

```
    50                  55                  60
His Asn Ser Lys Asp Asn Phe Arg Gly Glu Thr Ile Ser Ile Tyr Tyr
65                  70                  75                  80
Asp Pro Gly Lys Phe Pro Ala Leu Met Pro Leu Lys Asn Gly Asn Tyr
                85                  90                  95
Glu Glu Arg Asn Gly Gly Val Pro Gln Arg Gly Asn Ile Thr Ile His
            100                 105                 110
Leu Gln Gln Phe Asn Glu Asp Leu Asp Lys Met Thr Pro Asp Lys Asn
        115                 120                 125
Phe Gly Gly Ile Gly Val Ile Asp Phe Glu Arg Trp Lys Pro Ile Phe
    130                 135                 140
Arg Gln Asn Trp Gly Asn Thr Glu Ile His Lys Lys Tyr Ser Ile Glu
145                 150                 155                 160
Leu Val Arg Lys Glu His Pro Lys Trp Ser Glu Ser Met Ile Glu Ala
                165                 170                 175
Glu Ala Thr Lys Lys Phe Glu Lys Tyr Ala Arg Tyr Phe Met Glu Glu
            180                 185                 190
Thr Leu Lys Leu Ala Lys Lys Thr Arg Lys Arg Ala Lys Trp Gly Tyr
        195                 200                 205
Tyr Gly Phe Pro Tyr Cys Tyr Asn Val Thr Pro Asn Asn Pro Gly Pro
    210                 215                 220
Asp Cys Asp Ala Lys Ala Thr Ile Glu Asn Asp Arg Leu Ser Trp Met
225                 230                 235                 240
Tyr Asn Asn Gln Glu Ile Leu Phe Pro Ser Val Tyr Val Arg His Glu
                245                 250                 255
Gln Lys Pro Glu Glu Arg Val Tyr Leu Val Gln Gly Arg Ile Lys Glu
            260                 265                 270

Ala Val Arg Ile Ser Asn Asn Leu Glu His Ser Pro Ser Val Leu Ala
        275                 280                 285
Tyr Trp Trp Tyr Val Tyr Gln Asp Lys Met Asp Ile Tyr Leu Ser Glu
    290                 295                 300
Thr Asp Val Glu Lys Thr Phe Gln Glu Ile Val Thr Asn Gly Gly Asp
305                 310                 315                 320
Gly Ile Ile Ile Trp Gly Ser Ser Ser Asp Val Asn Ser Leu Ser Lys
                325                 330                 335
Cys Lys Arg Leu Arg Glu Tyr Leu Leu Asn Thr Leu Gly Pro Phe Ala
            340                 345                 350
Val Asn Val Thr Glu Thr Val Asn Gly Arg Ser Ser Leu Asn Phe
        355                 360                 365


<210> 243
<211> 462
<212> PRT
<213> 小家鼠

<220>
<223> 玻尿酸酶

<400> 243
Met Leu Gly Leu Thr Gln His Ala Gln Lys Val Trp Arg Met Lys Pro
 1               5                  10                  15
Phe Ser Pro Glu Val Ser Pro Gly Ser Ser Pro Ala Thr Ala Gly His
            20                  25                  30
Leu Leu Arg Ile Ser Thr Leu Phe Leu Thr Leu Leu Glu Leu Ala Gln
        35                  40                  45
Val Cys Arg Gly Ser Val Val Ser Asn Arg Pro Phe Ile Thr Val Trp
    50                  55                  60
Asn Gly Asp Thr His Trp Cys Leu Thr Glu Tyr Gly Val Asp Val Asp
65                  70                  75                  80
Val Ser Val Phe Asp Val Val Ala Asn Lys Glu Gln Ser Phe Gln Gly
                85                  90                  95
Ser Asn Met Thr Ile Phe Tyr Arg Glu Glu Leu Gly Thr Tyr Pro Tyr
            100                 105                 110
```

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

<210> 244
<211> 473
<212> PRT
<213> 小家鼠

<220>
<223> 玻尿酸酶2

<400> 244

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

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

            180                 185                 190
Tyr Val Lys Ala Val Arg Pro Gln His Leu Trp Gly Phe Tyr Leu Phe
        195                 200                 205
Pro Asp Cys Tyr Asn His Asp Tyr Val Gln Asn Trp Glu Ser Tyr Thr
    210                 215                 220
Gly Arg Cys Pro Asp Val Glu Val Ala Arg Asn Asp Gln Leu Ala Trp
225                 230                 235                 240
Leu Trp Ala Glu Ser Thr Ala Leu Phe Pro Ser Val Tyr Leu Asp Glu
                245                 250                 255
Thr Leu Ala Ser Ser Val His Ser Arg Asn Phe Val Ser Phe Arg Val
            260                 265                 270
Arg Glu Ala Leu Arg Val Ala His Thr His His Ala Asn His Ala Leu
        275                 280                 285
Pro Val Tyr Val Phe Thr Arg Pro Thr Tyr Thr Arg Gly Leu Thr Gly
    290                 295                 300
Leu Ser Gln Val Asp Leu Ile Ser Thr Ile Gly Glu Ser Ala Ala Leu
305                 310                 315                 320
Gly Ser Ala Gly Val Ile Phe Trp Gly Asp Ser Glu Asp Ala Ser Ser
                325                 330                 335
Met Glu Thr Cys Gln Tyr Leu Lys Asn Tyr Leu Thr Gln Leu Leu Val
            340                 345                 350
Pro Tyr Ile Val Asn Val Ser Trp Ala Thr Gln Tyr Cys Ser Trp Thr
        355                 360                 365
Gln Cys His Gly His Gly Arg Cys Val Arg Arg Asn Pro Ser Ala Asn
    370                 375                 380
Thr Phe Leu His Leu Asn Ala Ser Ser Phe Arg Leu Val Pro Gly His
385                 390                 395                 400
Thr Pro Ser Glu Pro Gln Leu Arg Pro Glu Gly Gln Leu Ser Glu Ala
                405                 410                 415
Asp Leu Asn Tyr Leu Gln Lys His Phe Arg Cys Gln Cys Tyr Leu Gly
            420                 425                 430
Trp Gly Gly Glu Gln Cys Gln Arg Asn Tyr Lys Gly Ala Ala Gly Asn
        435                 440                 445
Ala Ser Arg Ala Trp Ala Gly Ser His Leu Thr Ser Leu Leu Gly Leu
    450                 455                 460
Val Ala Val Ala Leu Thr Trp Thr Leu
465                 470
```

<210> 245
<211> 412
<212> PRT
<213> 小家鼠

<220>
<223> 玻尿酸酶3

<400> 245

```
Met Ile Met His Leu Gly Leu Met Met Val Val Gly Leu Thr Leu Cys
 1               5                  10                  15
Leu Met His Gly Gln Ala Leu Leu Gln Val Pro Glu His Pro Phe Ser
```

```
            20                  25                  30
Val Val Trp Asn Val Pro Ser Ala Arg Cys Lys Ala His Phe Gly Val
        35                  40                  45
His Leu Pro Leu Asp Ala Leu Gly Ile Val Ala Asn His Gly Gln His
    50                  55                  60
Phe His Gly Gln Asn Ile Ser Ile Phe Tyr Lys Asn Gln Phe Gly Leu
65                  70                  75                  80
Tyr Pro Tyr Phe Gly Pro Arg Gly Thr Ala His Asn Gly Gly Ile Pro
                85                  90                  95
Gln Ala Val Ser Leu Asp His His Leu Ala Arg Ala Ala His Gln Ile
            100                 105                 110
Leu His Ser Leu Gly Ser Ser Phe Ala Gly Leu Ala Val Leu Asp Trp
        115                 120                 125
Glu Glu Trp Tyr Pro Leu Trp Ala Gly Asn Trp Gly Pro His Arg Gln

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

<210> 246
<211> 435
<212> PRT
<213> 豬（Sus scrof）

<220>
<223> 玻尿酸酶

<400> 246

```
Met Ala Ala His Leu Leu Pro Ile Cys Thr Leu Phe Leu Asn Leu Leu
 1               5                  10                  15
Ser Val Ala Gln Gly Ser Arg Asp Pro Val Val Leu Asn Arg Pro Phe
            20                  25                  30
```

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

<210> 247
<211> 419
<212> PRT
<213> 豬（Sus scrof）

<220>
<223> 玻尿酸酶3

<400> 247

```
Met Thr Met Gln Leu Gly Leu Ala Leu Val Leu Gly Val Ala Met Cys
 1               5                  10                  15
```

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

<210> 248
<211> 449
<212> PRT
<213> 大鼠（Rattus norvegicus）

<220>
<223> 玻尿酸酶1

<400> 248

```
Met Lys Pro Phe Ser Pro Glu Val Ser Pro Asp Pro Cys Pro Ala Thr
 1               5                  10                  15
```

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

Ile Tyr Gln Gln Arg Ser Met Glu Leu Val Arg Ala Glu His Pro Asp
                165                 170                 175

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

<210> 249
<211> 473
<212> PRT
<213> 大鼠 (Rattus norvegicus)

<220>
<223> 玻尿酸酶2

<400> 249

```
Met Arg Ala Gly Leu Gly Pro Ile Ile Thr Leu Ala Leu Val Leu Glu
 1               5                  10                  15
Val Ala Trp Ala Ser Glu Leu Lys Pro Thr Ala Pro Pro Ile Phe Thr
            20                  25                  30
Gly Arg Pro Phe Val Val Ala Trp Asn Val Pro Thr Gln Glu Cys Ala
        35                  40                  45
Pro Arg His Lys Val Pro Leu Asp Leu Arg Ala Phe Asp Val Glu Ala
    50                  55                  60
Thr Pro Asn Glu Gly Phe Phe Asn Gln Asn Ile Thr Thr Phe Tyr Tyr
65                  70                  75                  80
Asp Arg Leu Gly Leu Tyr Pro Arg Phe Asp Ala Ala Gly Met Ser Val
                85                  90                  95
His Gly Gly Val Pro Gln Asn Gly Ser Leu Cys Ala His Leu Pro Met
            100                 105                 110
Leu Lys Glu Ala Val Glu Arg Tyr Ile Gln Thr Gln Glu Pro Ala Gly
        115                 120                 125
Leu Ala Val Ile Asp Trp Glu Glu Trp Arg Pro Val Trp Val Arg Asn
    130                 135                 140
Trp Gln Glu Lys Asp Val Tyr Arg Gln Ser Ser Arg Gln Leu Val Ala
145                 150                 155                 160
Ser Arg His Pro Asp Trp Pro Ser Asp Arg Ile Val Lys Gln Ala Gln
                165                 170                 175
Tyr Glu Phe Glu Phe Ala Ala Arg Gln Phe Met Leu Asn Thr Leu Arg
            180                 185                 190
Tyr Val Lys Ala Val Arg Pro Gln His Leu Trp Gly Phe Tyr Leu Phe
        195                 200                 205
Pro Asp Cys Tyr Asn His Asp Tyr Val Gln Asn Trp Asp Ser Tyr Thr
    210                 215                 220
Gly Arg Cys Pro Asp Val Glu Val Ala Gln Asn Asp Gln Leu Ala Trp
225                 230                 235                 240
Leu Trp Ala Glu Asn Thr Ala Leu Phe Pro Ser Val Tyr Leu Asp Lys
                245                 250                 255
Thr Leu Ala Ser Ser Lys His Ser Arg Asn Phe Val Ser Phe Arg Val
            260                 265                 270
Gln Glu Ala Leu Arg Val Ala His Thr His His Ala Asn His Ala Leu
        275                 280                 285
Pro Val Tyr Val Phe Thr Arg Pro Thr Tyr Thr Arg Arg Leu Thr Glu
    290                 295                 300
Leu Asn Gln Met Asp Leu Ile Ser Thr Ile Gly Glu Ser Ala Ala Leu
305                 310                 315                 320
Gly Ser Ala Gly Val Ile Phe Trp Gly Asp Ser Val Tyr Ala Ser Ser
                325                 330                 335
Met Glu Asn Cys Gln Asn Leu Lys Lys Tyr Leu Thr Gln Thr Leu Val
            340                 345                 350
Pro Tyr Ile Val Asn Val Ser Trp Ala Thr Gln Tyr Cys Ser Trp Thr
        355                 360                 365
Gln Cys His Gly His Gly Arg Cys Val Arg Arg Asn Pro Ser Ala Ser
    370                 375                 380
Thr Phe Leu His Leu Ser Pro Ser Ser Phe Arg Leu Val Pro Gly Arg
385                 390                 395                 400
Thr Pro Ser Glu Pro Gln Leu Arg Pro Glu Gly Glu Leu Ser Glu Asp
                405                 410                 415
Asp Leu Ser Tyr Leu Gln Met His Phe Arg Cys His Cys Tyr Leu Gly
            420                 425                 430
Trp Gly Gly Glu Gln Cys Gln Trp Asn His Lys Arg Ala Ala Gly Asp
        435                 440                 445
Ala Ser Arg Ala Trp Ala Gly Ala His Leu Ala Ser Leu Leu Gly Leu
    450                 455                 460
Val Ala Met Thr Leu Thr Trp Thr Leu
465                 470
```

<210> 250
<211> 412
<212> PRT
<213> 大鼠 (Rattus norvegicus)

<220>
<223> 玻尿酸酶3

<400> 250

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

Asp Asp Asn Leu Gly Ala Trp Lys Ser Phe Arg Cys Arg Cys Tyr Leu
385                 390                 395                 400
Gly Trp Ser Gly Pro Thr Cys Leu Glu Pro Lys Pro
                405                 410
```

<210> 251
<211> 545
<212> PRT
<213> 歐洲野兔（Oryctolagus cuniculus）

<220>
<223> PH20

<400> 251

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

Tyr Asn His His Tyr Asp Lys Pro Asn Leu Tyr Lys Gly Ser Cys Phe
225                 230                 235                 240
Asp Ile Glu Lys Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Lys Glu
                245                 250                 255
Ser Thr Ala Leu Phe Pro Ser Val Tyr Leu Thr Ser Arg Ala Arg Ser
            260                 265                 270
Ala Thr Ala Leu Ser Lys Leu Tyr Val Val Arg Asn Arg Val His Glu
        275                 280                 285
Ala Ile Arg Val Ser Lys Ile Pro Asp Asp Lys Ser Pro Leu Pro Asn
    290                 295                 300
Phe Val Tyr Thr Arg Leu Val Phe Thr Asp Gln Ile Phe Gln Phe Leu
305                 310                 315                 320
Ser His His Asp Leu Val Tyr Thr Ile Gly Glu Ile Val Ala Leu Gly
                325                 330                 335
Ala Ser Gly Ile Val Val Trp Gly Ser Gln Ser Leu Ala Arg Ser Met
            340                 345                 350
Lys Ser Cys Leu His Leu Asp Asn Tyr Met Lys Thr Ile Leu Asn Pro
        355                 360                 365
Tyr Leu Ile Asn Val Thr Leu Ala Ala Lys Met Cys Asn Gln Val Leu
    370                 375                 380
Cys Gln Glu Gln Gly Val Cys Thr Arg Lys Asn Trp Asn Pro Asn Asp
385                 390                 395                 400
Tyr Leu His Leu Asn Pro Gly Asn Phe Ala Ile Gln Leu Gly Ser Asn
                405                 410                 415
Gly Thr Tyr Lys Val Asp Gly Lys Pro Thr Leu Thr Asp Leu Glu Gln
            420                 425                 430
```

```
Phe Ser Lys Asn Phe Gln Cys Ser Cys Tyr Thr Asn Leu Asn Cys Lys
        435                 440                 445
Glu Arg Thr Asp Met Asn Asn Val Arg Thr Val Asn Val Cys Ala Val
    450                 455                 460
Glu Asn Val Cys Ile Asp Thr Asn Val Gly Pro Gln Ala Val Thr Tyr
465                 470                 475                 480
Ala Pro Lys Glu Lys Lys Asp Val Ala His Ile Leu Ser Asn Thr Thr
                485                 490                 495
Ser Ile Asn Ser Ser Thr Thr Met Ser Leu Pro Phe Pro Arg Lys His
            500                 505                 510
Val Ser Gly Cys Leu Leu Val Leu Cys Met Tyr Ser Gln Tyr Leu Asn
        515                 520                 525
Ile Cys Tyr Arg Leu Val Ala Ile Gly Ile Gln His Gly Tyr Tyr Leu
    530                 535                 540
Lys
545
```

<210> 252
<211> 476
<212> PRT
<213> 綿羊 (Ovis aries)

<220>
<223> 玻尿酸酶2

```
<400> 252
Met Trp Thr Gly Leu Gly Pro Ala Val Thr Leu Ala Leu Val Leu Val
 1               5                  10                  15
Val Ala Trp Ala Thr Glu Leu Lys Pro Thr Ala Pro Pro Ile Phe Thr
            20                  25                  30
Gly Arg Pro Phe Val Val Ala Trp Asp Val Pro Thr Gln Asp Cys Gly
        35                  40                  45
Pro Arg His Lys Met Pro Leu Asp Pro Lys Asp Met Lys Ala Phe Asp
    50                  55                  60
Val Gln Ala Ser Pro Asn Glu Gly Phe Val Asn Gln Asn Ile Thr Ile
65                  70                  75                  80
Phe Tyr Arg Asp Arg Leu Gly Met Tyr Pro His Phe Asn Ser Val Gly
                85                  90                  95
Arg Ser Val His Gly Gly Val Pro Gln Asn Gly Ser Leu Trp Val His
            100                 105                 110
Leu Glu Met Leu Lys Gly His Val Glu His Tyr Ile Arg Thr Gln Glu
        115                 120                 125
Pro Ala Gly Leu Ala Val Ile Asp Trp Glu Asp Trp Arg Pro Val Trp
    130                 135                 140
Val Arg Asn Trp Gln Asp Lys Asp Val Tyr Arg Arg Leu Ser Arg Gln
145                 150                 155                 160
Leu Val Ala Ser His His Pro Asp Trp Pro Pro Glu Arg Ile Val Lys
                165                 170                 175
Glu Ala Gln Tyr Glu Phe Glu Phe Ala Ala Arg Gln Phe Met Leu Glu
            180                 185                 190
Thr Leu Arg Phe Val Lys Ala Phe Arg Pro Arg His Leu Trp Gly Phe
        195                 200                 205
Tyr Leu Phe Pro Asp Cys Tyr Asn His Asp Tyr Val Gln Asn Trp Glu
    210                 215                 220
Thr Tyr Thr Gly Arg Cys Pro Asp Val Glu Val Ser Arg Asn Asp Gln
225                 230                 235                 240
Leu Ser Trp Leu Trp Ala Glu Ser Thr Ala Leu Phe Pro Ser Val Tyr
                245                 250                 255
Leu Glu Glu Thr Leu Ala Ser Ser Thr His Gly Arg Asn Phe Val Ser
            260                 265                 270
Phe Arg Val Gln Glu Ala Leu Arg Val Ala Asp Val His His Ala Asn
        275                 280                 285
His Ala Leu Pro Val Tyr Val Phe Thr Arg Pro Thr Tyr Ser Arg Gly
    290                 295                 300
```

```
Leu Thr Gly Leu Ser Glu Met Asp Leu Ile Ser Thr Ile Gly Glu Ser
305                 310                 315                 320
Ala Ala Leu Gly Ala Ala Gly Val Ile Leu Trp Gly Asp Ala Gly Phe
                325                 330                 335
Thr Thr Ser Asn Glu Thr Cys Arg Arg Leu Lys Asp Tyr Leu Thr Arg
            340                 345                 350
Ser Leu Val Pro Tyr Val Val Asn Val Ser Trp Ala Ala Gln Tyr Cys
        355                 360                 365
Ser Trp Ala Gln Cys His Gly His Gly Arg Cys Val Arg Arg Asp Pro
    370                 375                 380
Asn Ala His Thr Phe Leu His Leu Ser Ala Ser Ser Phe Arg Leu Val
385                 390                 395                 400
Pro Ser His Ala Pro Asp Glu Pro Arg Leu Arg Pro Glu Gly Glu Leu
                405                 410                 415
Ser Trp Ala Asp Arg Asn His Leu Gln Thr His Phe Arg Cys Gln Cys
            420                 425                 430
Tyr Leu Gly Trp Gly Gly Glu Gln Cys Gln Trp Asp Arg Arg Arg Ala
        435                 440                 445

Ala Gly Gly Ala Ser Gly Ala Trp Ala Gly Ser His Leu Thr Gly Leu
    450                 455                 460
Leu Ala Val Ala Val Leu Ala Phe Thr Trp Thr Ser
465                 470                 475


<210> 253
<211> 414
<212> PRT
<213>猩猩（Pongo pygmaeus）

<220>
<223> 玻尿酸酶3

<400> 253
Met Thr Thr Arg Leu Gly Pro Ala Leu Val Leu Gly Val Ala Leu Cys
 1               5                  10                  15
Leu Gly Cys Gly Gln Pro Leu Pro Gln Val Pro Glu Arg Pro Phe Ser
            20                  25                  30
Val Leu Trp Asn Val Pro Ser Ala His Cys Lys Ser Arg Phe Gly Val
        35                  40                  45
His Leu Pro Leu Asn Ala Leu Gly Ile Ile Ala Asn Arg Gly Gln His
    50                  55                  60
Phe His Gly Gln Asn Met Thr Ile Phe Tyr Lys Asn Gln Leu Gly Leu
65                  70                  75                  80
Tyr Pro Tyr Phe Gly Pro Lys Gly Thr Ala His Asn Gly Gly Ile Pro
                85                  90                  95
Gln Ala Leu Pro Leu Asp Arg His Leu Ala Leu Ala Ala Tyr Gln Ile
            100                 105                 110
His His Ser Leu Arg Pro Gly Phe Ala Gly Pro Ala Val Leu Asp Trp
        115                 120                 125
Glu Glu Trp Cys Pro Leu Trp Ala Gly Asn Trp Gly Arg Arg Arg Ala
    130                 135                 140
Tyr Gln Ala Ala Ser Trp Ala Trp Ala Gln Gln Val Phe Pro Asp Leu
145                 150                 155                 160
Asp Pro Gln Glu Gln Leu Tyr Lys Ala Tyr Thr Gly Phe Glu Gln Ala
                165                 170                 175
Ala Arg Ala Leu Met Glu Asp Thr Leu Arg Val Ala Gln Ala Leu Arg
            180                 185                 190
Pro His Gly Leu Trp Gly Phe Tyr His Tyr Pro Ala Cys Gly Asn Gly
        195                 200                 205
Trp His Ser Met Ala Ser Asn Tyr Thr Gly Arg Cys His Ala Ala Thr
    210                 215                 220
Leu Ala Arg Asn Thr Gln Leu His Trp Leu Trp Ala Ala Ser Ser Ala
225                 230                 235                 240
Leu Phe Pro Ser Ile Tyr Leu Pro Pro Arg Leu Pro Pro Ala His His
```

```
                245                 250                 255
Gln Ala Phe Val Arg His Arg Leu Glu Glu Ala Phe Arg Val Ala Leu
            260                 265                 270
Val Gly His Leu Pro Val Leu Ala Tyr Val Arg Leu Thr His Arg Arg
        275                 280                 285
Ser Gly Arg Phe Leu Ser Gln Asp Asp Leu Val Gln Thr Ile Gly Val
    290                 295                 300
Ser Ala Ala Leu Gly Ala Ala Gly Val Val Leu Trp Gly Asp Leu Ser
305                 310                 315                 320

Leu Ser Ser Ser Glu Glu Glu Cys Trp His Leu His Asp Tyr Leu Val
                325                 330                 335
Asp Thr Leu Gly Pro Tyr Gly Ile Asn Val Thr Arg Ala Ala Met Ala
            340                 345                 350
Cys Ser His Gln Arg Cys His Gly His Gly Arg Cys Ala Arg Arg Asp
        355                 360                 365
Pro Gly Gln Met Glu Ala Phe Leu His Leu Trp Pro Asp Gly Ser Leu
    370                 375                 380
Gly Asp Trp Lys Ser Phe Ser Cys His Cys Tyr Trp Gly Trp Ala Gly
385                 390                 395                 400
Pro Thr Cys Gln Glu Pro Arg Leu Gly Pro Lys Glu Ala Val
                405                 410
```

<210> 254
<211> 510
<212> PRT
<213> 食蟹猴（Macaca fascicularis）

<220>
<223> PH20

<400> 254

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

Ile Asp Trp Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro
145                 150                 155                 160
Lys Asp Val Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn
                165                 170                 175
Val Gln Leu Ser Leu Pro Gln Ala Thr Asp Lys Ala Lys Gln Glu Phe
            180                 185                 190
Glu Lys Ala Gly Lys Asp Phe Met Leu Glu Thr Ile Lys Leu Gly Arg
        195                 200                 205
Ser Leu Arg Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys
    210                 215                 220
Tyr Asn His His Tyr Arg Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asp
225                 230                 235                 240
Val Glu Ile Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser
```

```
                245                 250                 255
Thr Ala Leu Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Val Val
            260                 265                 270
Val Ala Thr Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val
        275                 280                 285
Ser Lys Ile Pro Asp Ala Lys Asn Pro Leu Pro Val Phe Val Tyr Ala
    290                 295                 300
Arg Leu Val Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Arg Glu Glu
305                 310                 315                 320
Leu Val Ser Thr Leu Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile
                325                 330                 335
Val Ile Trp Gly Ser Leu Ser Ile Thr Arg Ser Met Lys Ser Cys Leu
            340                 345                 350
Leu Leu Asp Thr Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn
        355                 360                 365
Val Thr Leu Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln
    370                 375                 380
Gly Val Cys Ile Arg Lys Asp Trp Asn Ser Ser Asp Tyr Leu His Leu
385                 390                 395                 400
Asn Pro Asp Asn Phe Asp Ile Arg Leu Glu Lys Gly Gly Lys Phe Thr

                405                 410                 415
Val His Gly Lys Pro Thr Val Glu Asp Leu Glu Glu Phe Ser Glu Lys
            420                 425                 430
Phe Tyr Cys Ser Cys Tyr Thr Asn Leu Ser Cys Lys Glu Lys Ala Asp
        435                 440                 445
Val Lys Asp Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys
    450                 455                 460
Ile Asp Ala Ser Leu Lys Pro Pro Val Glu Thr Glu Gly Ser Pro Pro
465                 470                 475                 480
Ile Phe Tyr Asn Thr Ser Ser Ser Thr Val Ser Thr Thr Met Phe Ile

                485                 490                 495
Val Asn Ile Leu Phe Leu Ile Ile Ser Ser Val Ala Ser Leu
            500                 505                 510


<210> 255
<211> 529
<212> PRT
<213>豚鼠 (Cavia porcellus)

<220>
<223> PH20

<400> 255
Met Gly Ala Phe Thr Phe Lys His Ser Phe Phe Gly Ser Phe Val Glu
 1               5                  10                  15
Cys Ser Gly Val Leu Gln Thr Val Phe Ile Phe Leu Leu Ile Pro Cys
            20                  25                  30
Cys Leu Ala Asp Lys Arg Ala Pro Pro Leu Ile Pro Asn Val Pro Leu
        35                  40                  45
Leu Trp Val Trp Asn Ala Pro Thr Glu Phe Cys Ile Gly Gly Thr Asn
    50                  55                  60
Gln Pro Leu Asp Met Ser Phe Phe Ser Ile Val Gly Thr Pro Arg Lys
65                  70                  75                  80
Asn Ile Thr Gly Gln Ser Ile Thr Leu Tyr Tyr Val Asp Arg Leu Gly
                85                  90                  95
Tyr Tyr Pro Tyr Ile Asp Pro His Thr Gly Ala Ile Val His Gly Gly
            100                 105                 110
Leu Pro Gln Leu Met Asn Leu Gln Gln His Leu Arg Lys Ser Arg Gln
        115                 120                 125
Asp Ile Leu Phe Tyr Met Pro Thr Asp Ser Val Gly Leu Ala Val Ile
    130                 135                 140
Asp Trp Glu Glu Trp Arg Pro Thr Trp Thr Arg Asn Trp Arg Pro Lys
```

```
145                 150                 155                 160
Asp Ile Tyr Arg Asn Lys Ser Ile Glu Leu Val Lys Ser Gln His Pro
                165                 170                 175
Gln Tyr Asn His Ser Tyr Ala Val Ala Val Ala Lys Arg Asp Phe Glu
            180                 185                 190
Arg Thr Gly Lys Ala Phe Met Leu Glu Thr Leu Lys Leu Gly Lys Ser
        195                 200                 205
Leu Arg Pro Ser Ser Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr
    210                 215                 220
Asn Thr His Phe Thr Lys Pro Asn Tyr Asp Gly His Cys Pro Pro Ile
225                 230                 235                 240
Glu Leu Gln Arg Asn Asn Asp Leu Gln Trp Leu Trp Asn Asp Ser Thr
                245                 250                 255
Ala Leu Tyr Pro Ser Val Tyr Leu Thr Ser Arg Val Arg Ser Ser Gln
            260                 265                 270
Asn Gly Ala Leu Tyr Val Arg Asn Arg Val His Glu Ser Ile Arg Val
        275                 280                 285
Ser Lys Leu Met Asp Asp Lys Asn Pro Leu Pro Ile Tyr Val Tyr Ile
    290                 295                 300
Arg Leu Val Phe Thr Asp Gln Thr Thr Thr Phe Leu Glu Leu Asp Asp
305                 310                 315                 320
Leu Val His Ser Val Gly Glu Ile Val Pro Leu Gly Val Ser Gly Ile
                325                 330                 335
Ile Ile Trp Gly Ser Leu Ser Leu Thr Arg Ser Leu Val Ser Cys Ile
            340                 345                 350
Gly Leu Glu Asn Tyr Met Lys Gly Thr Leu Leu Pro Tyr Leu Ile Asn
        355                 360                 365
Val Thr Leu Ala Ala Lys Met Cys Gly Gln Val Leu Cys Lys Asn Gln
    370                 375                 380
Gly Ile Cys Thr Arg Lys Asp Trp Asn Thr Asn Thr Tyr Leu His Leu
385                 390                 395                 400
Asn Ala Thr Asn Phe Asp Ile Glu Leu Gln Gln Asn Gly Lys Phe Val
                405                 410                 415
Val His Gly Lys Pro Ser Leu Glu Asp Leu Gln Glu Phe Ser Lys Asn
            420                 425                 430
Phe His Cys Ser Cys Tyr Thr Asn Val Ala Cys Lys Asp Arg Leu Asp
        435                 440                 445
Val His Asn Val Arg Ser Val Asn Val Cys Thr Ala Asn Asn Ile Cys
    450                 455                 460
Ile Asp Ala Val Leu Asn Phe Pro Ser Leu Asp Asp Asp Asp Glu Pro
465                 470                 475                 480
Pro Ile Thr Asp Asp Thr Ser Gln Asn Gln Asp Ser Ile Ser Asp Ile
                485                 490                 495
Thr Ser Ser Ala Pro Pro Ser Ser His Ile Leu Pro Lys Asp Leu Ser
            500                 505                 510
Trp Cys Leu Phe Leu Leu Ser Ile Phe Ser Gln His Trp Lys Tyr Leu
        515                 520                 525
Leu
```

<210> 256
<211> 512
<212> PRT
<213> 大鼠 (Rattus norvegicus)

<220>
<223> PH20

<400> 256

```
Met Gly Glu Leu Gln Phe Lys Trp Leu Phe Trp Arg Ser Phe Ala Glu
 1               5                  10                  15
Ser Gly Gly Thr Phe Gln Thr Val Leu Ile Phe Leu Phe Ile Pro Tyr
            20                  25                  30
Ser Leu Thr Val Asp Tyr Arg Ala Thr Pro Val Leu Ser Asp Thr Thr
```

```
        35                  40                  45
Phe Val Trp Val Trp Asn Val Pro Thr Glu Ala Cys Val Glu Asn Val
    50                  55                  60

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

                405                 410                 415
Val Leu Gly Lys Pro Glu Val Lys Asp Leu Glu Tyr Phe Ser Glu His
            420                 425                 430
Phe Lys Cys Ser Cys Phe Ser Lys Met Thr Cys Glu Glu Thr Ser Asp
        435                 440                 445
Met Arg Ser Ile Gln Asp Val Asn Val Cys Met Gly Asp Asn Val Cys
    450                 455                 460
Ile Lys Ala Thr Leu Gly Pro Asn Ser Ala Phe His Leu Leu Pro Gly
465                 470                 475                 480
Lys Gly Leu Leu Leu Met Thr Thr Leu Ala His Ile Leu His His Leu
                485                 490                 495
Pro His Asp Ile Phe Val Phe Pro Trp Lys Met Leu Val Ser Thr Pro
            500                 505                 510
```

<210> 257
<211> 512

<212> PRT
<213> 小家鼠

<220>
<223> PH20

<400> 257

```
Met Gly Glu Leu Arg Phe Lys His Leu Phe Trp Gly Ser Phe Val Glu
 1               5                  10                  15
Ser Gly Gly Thr Phe Gln Thr Val Leu Ile Phe Leu Leu Ile Pro Cys
            20                  25                  30
Ser Leu Thr Val Asp Tyr Arg Ala Ala Pro Ile Leu Ser Asn Thr Thr
        35                  40                  45
Phe Leu Trp Ile Trp Asn Val Pro Thr Glu Arg Cys Val Gly Asn Val
    50                  55                  60
Asn Asp Pro Ile Asp Leu Ser Phe Phe Ser Leu Ile Gly Ser Pro Arg
65                  70                  75                  80
Lys Thr Ala Thr Gly Gln Pro Val Thr Leu Phe Tyr Val Asp Arg Leu
                85                  90                  95
Gly Leu Tyr Pro His Ile Asp Ala Asn Gln Ala Glu His Tyr Gly Gly
            100                 105                 110
Ile Pro Gln Arg Gly Asp Tyr Gln Ala His Leu Arg Lys Ala Lys Thr
        115                 120                 125
Asp Ile Glu His Tyr Ile Pro Asp Asp Lys Leu Gly Leu Ala Ile Ile
    130                 135                 140
Asp Trp Glu Glu Trp Arg Pro Thr Trp Leu Arg Asn Trp Lys Pro Lys
145                 150                 155                 160
Asp Asn Tyr Arg Asn Lys Ser Ile Glu Leu Val Gln Ser Thr Asn Pro
                165                 170                 175
Gly Leu Ser Ile Thr Glu Ala Thr Gln Lys Ala Ile Gln Gln Phe Glu
            180                 185                 190
Glu Ala Gly Arg Lys Phe Met Glu Gly Thr Leu His Leu Gly Lys Phe
        195                 200                 205
Leu Arg Pro Asn Gln Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr
    210                 215                 220
Asn Asn Lys Phe Gln Asp Pro Lys Tyr Asp Gly Gln Cys Pro Ala Val
225                 230                 235                 240
Glu Lys Lys Arg Asn Asp Asn Leu Lys Trp Leu Trp Lys Ala Ser Thr
                245                 250                 255
Gly Leu Tyr Pro Ser Val Tyr Leu Lys Lys Asp Leu Lys Ser Asn Arg
            260                 265                 270
Gln Ala Thr Leu Tyr Val Arg Tyr Arg Val Val Glu Ala Ile Arg Val
        275                 280                 285
Ser Lys Val Gly Asn Ala Ser Asp Pro Val Pro Ile Phe Val Tyr Ile
    290                 295                 300
Arg Leu Val Phe Thr Asp Arg Thr Ser Glu Tyr Leu Leu Glu Asp Asp
305                 310                 315                 320
Leu Val Asn Thr Ile Gly Glu Ile Val Ala Leu Gly Thr Ser Gly Ile
                325                 330                 335
Ile Ile Trp Asp Ala Met Ser Leu Ala Gln Arg Ala Ala Gly Cys Pro
            340                 345                 350
Ile Leu His Lys Tyr Met Gln Thr Thr Leu Asn Pro Tyr Ile Val Asn
        355                 360                 365
Val Thr Leu Ala Ala Lys Met Cys Ser Gln Thr Leu Cys Asn Glu Lys
    370                 375                 380
Gly Met Cys Ser Arg Arg Lys Glu Ser Ser Asp Val Tyr Leu His Leu
385                 390                 395                 400
Asn Pro Ser His Phe Asp Ile Met Leu Thr Glu Thr Gly Lys Tyr Glu
                405                 410                 415
Val Leu Gly Asn Pro Arg Val Gly Asp Leu Glu Tyr Phe Ser Glu His
            420                 425                 430
Phe Lys Cys Ser Cys Phe Ser Arg Met Thr Cys Lys Glu Thr Ser Asp
        435                 440                 445
Val Lys Asn Val Gln Asp Val Asn Val Cys Val Gly Asp Asn Val Cys
    450                 455                 460
```

```
Ile Lys Ala Lys Val Glu Pro Asn Pro Ala Phe Tyr Leu Leu Pro Gly
465                 470                 475                 480
Lys Ser Leu Leu Phe Met Thr Thr Leu Gly His Val Leu Tyr His Leu
                485                 490                 495
Pro Gln Asp Ile Phe Val Phe Pro Arg Lys Thr Leu Val Ser Thr Pro
            500                 505                 510
```

<210> 258
<211> 807
<212> PRT
<213> 金黃色葡萄球菌（Staphylococcus aureus）

<220>
<223> 玻尿酸酶

<400> 258

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

```
Asp Ala Met Asp Asp Ser Thr Lys Ala Lys Tyr Lys Lys Ile Val Lys
385                 390                 395                 400
Ser Ser Val Glu Ser Asp Ser Ser Tyr Lys Gln Asn Asp Tyr Leu Asn
                405                 410                 415
Ser Tyr Ser Asp Ile Asp Lys Met Lys Ser Leu Met Thr Asp Asn Ser
            420                 425                 430
Ile Ser Lys Asn Gly Leu Thr Gln Gln Leu Lys Ile Tyr Asn Asp Met
        435                 440                 445
Asp Arg Val Thr Tyr His Asn Lys Asp Leu Asp Phe Ala Phe Gly Leu
    450                 455                 460
Ser Met Thr Ser Lys Asn Val Ala Arg Tyr Glu Ser Ile Asn Gly Glu
465                 470                 475                 480
Asn Leu Lys Gly Trp His Thr Gly Ala Gly Met Ser Tyr Leu Tyr Asn
                485                 490                 495
Ser Asp Val Lys His Tyr His Asp Asn Phe Trp Val Thr Ala Asp Met
            500                 505                 510
Lys Arg Leu Ser Gly Thr Thr Thr Leu Asp Asn Glu Ile Leu Lys Asp
        515                 520                 525
Thr Asp Asp Lys Lys Ser Ser Lys Thr Phe Val Gly Gly Thr Lys Val
    530                 535                 540
Asp Asp Gln His Ala Ser Ile Gly Met Asp Phe Glu Asn Gln Asp Lys
545                 550                 555                 560
Thr Leu Thr Ala Lys Lys Ser Tyr Phe Ile Leu Asn Asp Lys Ile Val
                565                 570                 575
Phe Leu Gly Thr Gly Ile Lys Ser Thr Asp Ser Ser Lys Asn Pro Val
            580                 585                 590
Thr Thr Ile Glu Asn Arg Lys Ala Asn Gly Tyr Thr Leu Tyr Thr Asp
        595                 600                 605
Asp Lys Gln Thr Thr Asn Ser Asp Asn Gln Glu Asn Asn Ser Val Phe
    610                 615                 620
Leu Glu Ser Thr Asp Thr Lys Lys Asn Ile Gly Tyr His Phe Leu Asn
625                 630                 635                 640
Lys Pro Lys Ile Thr Val Lys Lys Glu Ser His Thr Gly Lys Trp Lys
                645                 650                 655
Glu Ile Asn Lys Ser Gln Lys Asp Thr Gln Lys Thr Asp Glu Tyr Tyr
            660                 665                 670
Glu Val Thr Gln Lys His Ser Asn Ser Asp Asn Lys Tyr Gly Tyr Val
        675                 680                 685
Leu Tyr Pro Gly Leu Ser Lys Asp Val Phe Lys Thr Lys Lys Asp Glu
    690                 695                 700
Val Thr Val Val Lys Gln Glu Asp Asp Phe His Val Val Lys Asp Asn
705                 710                 715                 720
Glu Ser Val Trp Ala Gly Val Asn Tyr Ser Asn Ser Thr Gln Thr Phe
                725                 730                 735
Asp Ile Asn Asn Thr Lys Val Glu Val Lys Ala Lys Gly Met Phe Ile
            740                 745                 750
Leu Lys Lys Lys Asp Asp Asn Thr Tyr Glu Cys Ser Phe Tyr Asn Pro
        755                 760                 765
Glu Ser Thr Asn Ser Ala Ser Asp Ile Glu Ser Lys Ile Ser Met Thr
    770                 775                 780

Gly Tyr Ser Ile Thr Asn Lys Asn Thr Ser Thr Ser Asn Glu Ser Gly
785                 790                 795                 800
Val His Phe Glu Leu Thr Lys
                805
```

<210> 259
<211> 371
<212> PRT
<213> 化膿鏈球菌噬菌體（Streptococcus pyogenes bacteriophage） H4489A

<220>
<223> 玻尿酸酶

<400> 259
Met Thr Glu Asn Ile Pro Leu Arg Val Gln Phe Lys Arg Met Ser Ala
 1   5   10   15
Asp Glu Trp Ala Arg Ser Asp Val Ile Leu Leu Glu Gly Glu Ile Gly
            20   25   30
Phe Glu Thr Asp Thr Gly Phe Ala Lys Phe Gly Asp Gly Gln Asn Thr
        35   40   45
Phe Ser Lys Leu Lys Tyr Leu Thr Gly Pro Lys Gly Pro Lys Gly Asp
    50   55   60
Thr Gly Leu Gln Gly Lys Thr Gly Gly Thr Gly Pro Arg Gly Pro Ala
65   70   75   80
Gly Lys Pro Gly Thr Thr Asp Tyr Asp Gln Leu Gln Asn Lys Pro Asp
                85   90   95
Leu Gly Ala Phe Ala Gln Lys Glu Glu Thr Asn Ser Lys Ile Thr Lys
            100   105   110
Leu Glu Ser Ser Lys Ala Asp Lys Ser Ala Val Tyr Ser Lys Ala Glu
        115   120   125
Ser Lys Ile Glu Leu Asp Lys Lys Leu Ser Leu Thr Gly Gly Ile Val
    130   135   140
Thr Gly Gln Leu Gln Phe Lys Pro Asn Lys Ser Gly Ile Lys Pro Ser
145   150   155   160
Ser Ser Val Gly Gly Ala Ile Asn Ile Asp Met Ser Lys Ser Glu Gly
                165   170   175
Ala Ala Met Val Met Tyr Thr Asn Lys Asp Thr Thr Asp Gly Pro Leu
            180   185   190
Met Ile Leu Arg Ser Asp Lys Asp Thr Phe Asp Gln Ser Ala Gln Phe
        195   200   205
Val Asp Tyr Ser Gly Lys Thr Asn Ala Val Asn Ile Val Met Arg Gln
    210   215   220
Pro Ser Ala Pro Asn Phe Ser Ser Ala Leu Asn Ile Thr Ser Ala Asn
225   230   235   240
Glu Gly Gly Ser Ala Met Gln Ile Arg Gly Val Glu Lys Ala Leu Gly
                245   250   255
Thr Leu Lys Ile Thr His Glu Asn Pro Asn Val Glu Ala Lys Tyr Asp
            260   265   270
Glu Asn Ala Ala Ala Leu Ser Ile Asp Ile Val Lys Lys Gln Lys Gly
        275   280   285
Gly Lys Gly Thr Ala Ala Gln Gly Ile Tyr Ile Asn Ser Thr Ser Gly
    290   295   300
Thr Ala Gly Lys Met Leu Arg Ile Arg Asn Lys Asn Glu Asp Lys Phe
305   310   315   320
Tyr Val Gly Pro Asp Gly Gly Phe His Ser Gly Ala Asn Ser Thr Val
                325   330   335
Ala Gly Asn Leu Thr Val Lys Asp Pro Thr Ser Gly Lys His Ala Ala
            340   345   350
Thr Lys Asp Tyr Val Asp Glu Lys Ile Ala Glu Leu Lys Lys Leu Ile
        355   360   365
Leu Lys Lys
    370

<210> 260
<211> 1628
<212> PRT
<213> 荚膜梭菌（Clostridium perfringens）

<220>
<223> 玻尿酸酶

<400> 260
Met Asn Lys Asn Ile Arg Lys Ile Ile Thr Ser Thr Val Leu Ala Ala
 1   5   10   15
Met Thr Ile Ser Val Leu Pro Ser Asn Leu Val Val Phe Ala Thr Asp
            20   25   30
Gly Ile Thr Glu Asn Phe Tyr Glu Ile Tyr Pro Lys Pro Gln Glu Ile

```
         35                  40                  45
Ser Tyr Ser Gly Gly Glu Phe Gln Ile Ser Asp Glu Ile Asn Ile Val
     50                  55                  60
Tyr Asp Asp Gly Ile Asp Thr Tyr Thr Lys Lys Arg Val Asp Glu Val
65                  70                  75                  80
Leu Glu Ala Ser Asn Leu Glu Ala Thr Val Ser Asn Glu Ile Val Pro
                85                  90                  95
Gly Lys Thr Asn Phe Leu Val Gly Ile Asn Glu Ser Gly Gly Val Val
            100                 105                 110
Asp Asn Tyr Phe Asn Lys Asn Ile Pro His Asp Glu Ser Phe Phe Asp
        115                 120                 125
Glu Lys Met Asp Ala Asn Ile Val Ser Val Lys Asp Gly Val Ile Gly
    130                 135                 140
Val Ile Gly Glu Asp Thr Asp Ser Ala Phe Tyr Gly Val Thr Thr Leu
145                 150                 155                 160
Lys His Val Phe Asn Gln Leu Glu Glu Gly Asn Lys Ile Gln Ser Phe
                165                 170                 175
Arg Ala Asp Asp Tyr Ala Glu Val Ala His Arg Gly Phe Ile Glu Gly
            180                 185                 190
Tyr Tyr Gly Asn Pro Trp Ser Asn Glu Asp Arg Ala Glu Leu Met Lys
        195                 200                 205
Phe Gly Gly Asp Tyr Lys Leu Asn Gln Tyr Val Phe Ala Pro Lys Asp
    210                 215                 220
Asp Pro Tyr His Asn Ser Lys Trp Arg Asp Leu Tyr Pro Glu Glu Lys
225                 230                 235                 240
Leu Ser Glu Ile Lys Lys Leu Ala Gln Val Gly Asn Glu Thr Lys Asn
                245                 250                 255
Arg Tyr Val Tyr Ala Leu His Pro Phe Met Asn Asn Pro Val Arg Phe
            260                 265                 270
Asp Thr Glu Glu Asn Tyr Gln Asn Asp Leu Gly Val Ile Lys Ala Lys
        275                 280                 285
Phe Thr Gln Leu Leu Glu Asn Asp Val Arg Gln Phe Ala Ile Leu Ala
    290                 295                 300
Asp Asp Ala Ser Ala Pro Ala Gln Gly Ala Ser Met Tyr Val Lys Leu
305                 310                 315                 320
Leu Thr Asp Leu Thr Arg Trp Leu Glu Glu Gln Gln Ser Thr Tyr Pro
                325                 330                 335
Asp Leu Lys Thr Asp Leu Met Phe Cys Pro Ser Asp Tyr Tyr Gly Asn
            340                 345                 350
Gly Ser Ser Ala Gln Leu Lys Glu Leu Asn Lys Ala Glu Asp Asn Val
        355                 360                 365
Ser Ile Val Met Thr Gly Gly Arg Ile Trp Gly Glu Val Asp Glu Asn
    370                 375                 380
Phe Ala Asn Asn Phe Met Asn Asn Ile Ser Thr Glu Gly His Pro Gly
385                 390                 395                 400
Arg Ala Pro Phe Phe Trp Ile Asn Trp Pro Cys Ser Asp Asn Ser Lys
                405                 410                 415
Gln His Leu Ile Met Gly Gly Asn Asp Thr Phe Leu His Pro Gly Val
            420                 425                 430
Asp Pro Ser Lys Ile Asp Gly Ile Val Leu Asn Pro Met Gln Gln Ala
        435                 440                 445
Glu Ala Asn Lys Ser Ala Leu Phe Ala Ile Ala Asp Tyr Ala Trp Asn
    450                 455                 460
Ile Trp Asp Asn Lys Glu Glu Ala Asp Glu Asn Trp Asn Asp Ser Phe
465                 470                 475                 480
Lys Tyr Met Asp His Gly Thr Ala Glu Glu Thr Asn Ser Ser Leu Ala
                485                 490                 495
Leu Arg Glu Ile Ser Lys His Met Ile Asn Gln Asn Met Asp Gly Arg
            500                 505                 510
Val Arg Pro Leu Gln Glu Ser Val Glu Leu Ala Pro Lys Leu Glu Ala
        515                 520                 525
Phe Lys Gln Lys Tyr Asp Ser Gly Ala Ser Ile Lys Glu Asp Ala Leu
    530                 535                 540
Glu Leu Ile Ala Glu Phe Thr Asn Leu Gln Lys Ala Ala Asp Tyr Tyr
545                 550                 555                 560
```

```
Lys Asn Asn Pro Gly Asn Glu Arg Thr Arg Asp Gln Ile Ile Tyr Trp
                565                 570                 575
Leu Asn Cys Trp Glu Asp Thr Met Asp Ala Ala Ile Gly Tyr Leu Lys
            580                 585                 590
Ser Ala Ile Ala Ile Glu Glu Gly Asp Asp Glu Ala Ala Trp Ala Asn
        595                 600                 605
Tyr Ser Glu Ala Gln Gly Ala Phe Glu Lys Ser Lys Thr Tyr Gly Phe
    610                 615                 620
His Tyr Val Asp His Thr Glu Tyr Ala Glu Val Gly Val Gln His Ile
625                 630                 635                 640
Val Pro Phe Ile Lys Ser Met Gly Gln Asn Leu Ser Val Val Ile Gly
                645                 650                 655
Ser Ile Val Asp Pro Asn Arg Ile Ile Ala Thr Tyr Ile Ser Asn Arg
            660                 665                 670
Gln Asp Ala Pro Thr Gly Asn Pro Asp Asn Ile Phe Asp Asn Asn Ala
        675                 680                 685
Ser Thr Glu Leu Val Tyr Lys Asn Pro Asn Arg Ile Asp Val Gly Thr
    690                 695                 700
Tyr Val Gly Val Lys Tyr Ser Asn Pro Ile Thr Leu Asn Asn Val Glu
705                 710                 715                 720
Phe Leu Met Gly Ala Asn Ser Asn Pro Asn Asp Thr Met Gln Lys Ala
                725                 730                 735
Lys Ile Gln Tyr Thr Val Asp Gly Arg Glu Trp Ile Asp Leu Glu Glu
            740                 745                 750
Gly Val Glu Tyr Thr Met Pro Gly Ala Ile Lys Val Glu Asn Leu Asp
        755                 760                 765
Leu Lys Val Arg Gly Val Arg Leu Ile Ala Thr Glu Ala Arg Glu Asn
    770                 775                 780
Thr Trp Leu Gly Val Arg Asp Ile Asn Val Asn Lys Lys Glu Asp Ser
785                 790                 795                 800
Asn Ser Gly Val Glu Phe Asn Pro Ser Leu Ile Arg Ser Glu Ser Trp
                805                 810                 815
Gln Val Tyr Glu Gly Asn Glu Ala Asn Leu Leu Asp Gly Asp Asp Asn
            820                 825                 830
Thr Gly Val Trp Tyr Lys Thr Leu Asn Gly Asp Thr Ser Leu Ala Gly
        835                 840                 845
Glu Phe Ile Gly Leu Asp Leu Gly Lys Glu Ile Lys Leu Asp Gly Ile
    850                 855                 860
Arg Phe Val Ile Gly Lys Asn Gly Gly Gly Ser Ser Asp Lys Trp Asn
865                 870                 875                 880
Lys Phe Lys Leu Glu Tyr Ser Leu Asp Asn Glu Ser Trp Thr Thr Ile
                885                 890                 895
Lys Glu Tyr Asp Lys Thr Gly Ala Pro Ala Gly Lys Asp Val Ile Glu
            900                 905                 910
Glu Ser Phe Glu Thr Pro Ile Ser Ala Lys Tyr Ile Arg Leu Thr Asn
        915                 920                 925
Met Glu Asn Ile Asn Lys Trp Leu Thr Phe Ser Glu Phe Ala Ile Ile
    930                 935                 940
Ser Asp Glu Leu Glu Asn Ala Gly Asn Lys Glu Asn Val Tyr Thr Asn
945                 950                 955                 960
Thr Glu Leu Asp Leu Leu Ser Leu Ala Lys Glu Asp Val Thr Lys Leu
                965                 970                 975
Ile Pro Thr Asp Asp Ile Ser Leu Asn His Gly Glu Tyr Ile Gly Val
            980                 985                 990
Lys Leu Asn Arg Ile Lys Asp Leu Ser Asn Ile Asn Leu Glu Ile Ser
        995                 1000                1005
Asn Asp Thr Gly Leu Lys Leu Gln Ser Ser Met Asn Gly Val Glu Trp
    1010                1015                1020
Thr Glu Ile Thr Asp Lys Asn Thr Leu Glu Asp Gly Arg Tyr Val Arg
1025                1030                1035                1040
Leu Ile Asn Thr Ser Asn Glu Ala Val Asn Phe Asn Leu Thr Lys Phe
                1045                1050                1055
Glu Val Asn Ser Asn Glu Val Tyr Glu Pro Ser Leu Val Asp Ala Tyr
            1060                1065                1070
Val Gly Asp Asp Gly Ala Lys Lys Ala Val Asp Gly Asp Leu Lys Thr
```

```
        1075                1080                1085
Arg Val Lys Phe Leu Gly Ala Pro Ser Thr Gly Asp Thr Ile Val Tyr
    1090                1095                1100
Asp Leu Gly Gln Glu Ile Leu Val Asp Asn Leu Lys Tyr Val Val Leu
1105                1110                1115                1120
Asp Thr Glu Val Asp His Val Arg Asp Gly Lys Ile Gln Leu Ser Leu
                1125                1130                1135
Asp Gly Glu Thr Trp Thr Asp Ala Ile Thr Ile Gly Asp Gly Val Glu
            1140                1145                1150
Asn Gly Val Asp Asp Met Phe Ser Thr Pro Leu Lys Asn Gly Tyr Lys
        1155                1160                1165
His Gly Asn Gln Ser Gly Gly Ile Val Pro Ile Asp Ser Ala Tyr Val
    1170                1175                1180
Glu Gly Asp Asn Leu Asn Gln Lys Ala Arg Tyr Val Arg Ile Leu Phe
1185                1190                1195                1200
Thr Ala Pro Tyr Arg His Arg Trp Thr Val Ile Asn Glu Leu Met Ile
                1205                1210                1215
Asn Asn Gly Glu Tyr Ile Ser Thr Val Asn Asp Pro Thr Tyr Ile Ser
            1220                1225                1230
Asn Pro Ile Glu Glu Arg Gly Phe Ala Pro Ser Asn Leu Arg Asp Gly
        1235                1240                1245
Asn Leu Thr Thr Ser Tyr Lys Pro Asn Thr Asn Asn Gly Glu Ile Ser
    1250                1255                1260

Glu Gly Ser Ile Thr Tyr Arg Leu Ser Glu Lys Thr Asp Val Arg Lys
1265                1270                1275                1280
Val Thr Ile Val Gln Ser Gly Ser Ser Ile Ser Asn Ala Lys Val Met
                1285                1290                1295
Ala Arg Val Gly Asp Gly Ser Glu Asn Val Thr Asp Gln Trp Val Gln
            1300                1305                1310
Leu Gly Thr Leu Ser Asn Ser Leu Asn Glu Phe Ile Asn Arg Asp Tyr
        1315                1320                1325
Asn Asn Ile Tyr Glu Ile Lys Ile Glu Trp Thr Asp Val Ala Pro Asn
    1330                1335                1340
Ile Tyr Glu Ile Ile Thr Leu Asn Gln Glu Phe Glu Phe Pro Val Asn
1345                1350                1355                1360
Asp Ser Leu Lys Ala Lys Tyr Asp Glu Leu Ile Asn Leu Ser Gly Asp
                1365                1370                1375
Glu Tyr Thr Leu Ser Ser Phe Glu Thr Leu Lys Glu Ala Leu Asn Glu
            1380                1385                1390
Ala Lys Ser Ile Leu Asp Asp Ser Asn Ser Ser Gln Lys Lys Ile Asp
        1395                1400                1405
Lys Ala Leu Glu Lys Leu Asn Lys Ala Glu Glu Arg Leu Asp Leu Arg
    1410                1415                1420
Ala Thr Asp Phe Glu Asp Phe Asn Lys Val Leu Thr Leu Gly Asn Ser
1425                1430                1435                1440
Leu Val Glu Glu Glu Tyr Thr Ala Glu Ser Trp Ala Leu Phe Ser Glu
                1445                1450                1455
Val Leu Glu Ala Ala Asn Glu Ala Asn Lys Asn Lys Ala Asp Tyr Thr
            1460                1465                1470
Gln Asp Gln Ile Asn Gln Ile Val Ile Asp Leu Asp Ala Ser Ile Lys
        1475                1480                1485
Ala Leu Val Lys Glu Thr Pro Glu Val Asp Lys Thr Asn Leu Gly Glu

    1490                1495                1500
Leu Ile Asn Gln Gly Lys Ser Leu Leu Asp Glu Ser Val Glu Gly Phe
1505                1510                1515                1520
Asn Val Gly Glu Tyr His Lys Gly Ala Lys Asp Gly Leu Thr Val Glu
                1525                1530                1535
Ile Asn Lys Ala Glu Glu Val Phe Asn Lys Glu Asp Ala Thr Glu Glu
            1540                1545                1550
Glu Ile Asn Leu Ala Lys Glu Ser Leu Glu Gly Ala Ile Ala Arg Phe
        1555                1560                1565
Asn Ser Leu Leu Ile Glu Glu Ser Thr Gly Asp Phe Asn Gly Asn Gly
    1570                1575                1580
```

```
Lys Ile Asp Ile Gly Asp Leu Ala Met Val Ser Lys Asn Ile Gly Ser
1585                1590                1595                1600
Thr Thr Asn Thr Ser Leu Asp Leu Asn Lys Asp Gly Ser Ile Asp Glu

                1605                1610                1615
Tyr Glu Ile Ser Phe Ile Asn His Arg Ile Leu Asn
            1620                1625
```

<210> 261
<211> 186
<212> PRT
<213> 小家鼠

<220>
<223> 二氫葉酸還原酶

<400> 261

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

<210> 262
<211> 435
<212> PRT
<213> 現代人

<220>
<223> 玻尿酸酶-1 [前驅體]

<400> 262

```
Met Ala Ala His Leu Leu Pro Ile Cys Ala Leu Phe Leu Thr Leu Leu
 1               5                  10                  15
Asp Met Ala Gln Gly Phe Arg Gly Pro Leu Leu Pro Asn Arg Pro Phe
            20                  25                  30
Thr Thr Val Trp Asn Ala Asn Thr Gln Trp Cys Leu Glu Arg His Gly
        35                  40                  45
Val Asp Val Asp Val Ser Val Phe Asp Val Val Ala Asn Pro Gly Gln
    50                  55                  60
Thr Phe Arg Gly Pro Asp Met Thr Ile Phe Tyr Ser Ser Gln Leu Gly
65                  70                  75                  80
Thr Tyr Pro Tyr Tyr Thr Pro Thr Gly Glu Pro Val Phe Gly Gly Leu
                85                  90                  95
```

```
Pro Gln Asn Ala Ser Leu Ile Ala His Leu Ala Arg Thr Phe Gln Asp
            100                 105                 110
Ile Leu Ala Ala Ile Pro Ala Pro Asp Phe Ser Gly Leu Ala Val Ile
        115                 120                 125
Asp Trp Glu Ala Trp Arg Pro Arg Trp Ala Phe Asn Trp Asp Thr Lys
    130                 135                 140
Asp Ile Tyr Arg Gln Arg Ser Arg Ala Leu Val Gln Ala Gln His Pro
145                 150                 155                 160
Asp Trp Pro Ala Pro Gln Val Glu Ala Val Ala Gln Asp Gln Phe Gln
                165                 170                 175
Gly Ala Ala Arg Ala Trp Met Ala Gly Thr Leu Gln Leu Gly Arg Ala
            180                 185                 190
Leu Arg Pro Arg Gly Leu Trp Gly Phe Tyr Gly Phe Pro Asp Cys Tyr
        195                 200                 205
Asn Tyr Asp Phe Leu Ser Pro Asn Tyr Thr Gly Gln Cys Pro Ser Gly
    210                 215                 220
Ile Arg Ala Gln Asn Asp Gln Leu Gly Trp Leu Trp Gly Gln Ser Arg
225                 230                 235                 240
Ala Leu Tyr Pro Ser Ile Tyr Met Pro Ala Val Leu Glu Gly Thr Gly

                245                 250                 255
Lys Ser Gln Met Tyr Val Gln His Arg Val Ala Glu Ala Phe Arg Val
            260                 265                 270
Ala Val Ala Ala Gly Asp Pro Asn Leu Pro Val Leu Pro Tyr Val Gln
        275                 280                 285
Ile Phe Tyr Asp Thr Thr Asn His Phe Leu Pro Leu Asp Glu Leu Glu
    290                 295                 300
His Ser Leu Gly Glu Ser Ala Ala Gln Gly Ala Ala Gly Val Val Leu
305                 310                 315                 320
Trp Val Ser Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile
                325                 330                 335
Lys Glu Tyr Met Asp Thr Thr Leu Gly Pro Phe Ile Leu Asn Val Thr
            340                 345                 350
Ser Gly Ala Leu Leu Cys Ser Gln Ala Leu Cys Ser Gly His Gly Arg
        355                 360                 365
Cys Val Arg Arg Thr Ser His Pro Lys Ala Leu Leu Leu Leu Asn Pro
    370                 375                 380
Ala Ser Phe Ser Ile Gln Leu Thr Pro Gly Gly Gly Pro Leu Ser Leu
385                 390                 395                 400
Arg Gly Ala Leu Ser Leu Glu Asp Gln Ala Gln Met Ala Val Glu Phe
                405                 410                 415
Lys Cys Arg Cys Tyr Pro Gly Trp Gln Ala Pro Trp Cys Glu Arg Lys
            420                 425                 430
Ser Met Trp
        435
```

<210> 263
<211> 473
<212> PRT
<213> 現代人

<220>
<223> 玻尿酸酶-2 [前驅體]

<400> 263

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

```
Ser Pro Asn Glu Gly Phe Val Asn Gln Asn Ile Thr Ile Phe Tyr Arg
65                  70                  75                  80

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

            420                 425                 430
Trp Ser Gly Glu Gln Cys Gln Trp Asp His Arg Gln Ala Ala Gly Gly
        435                 440                 445
Ala Ser Glu Ala Trp Ala Gly Ser His Leu Thr Ser Leu Leu Ala Leu
    450                 455                 460
Ala Ala Leu Ala Phe Thr Trp Thr Leu
465                 470
```

<210> 264
<211> 417
<212> PRT
<213> 現代人

<220>
<223> 玻尿酸酶-3 [前驅體]

<400> 264
Met Thr Thr Gln Leu Gly Pro Ala Leu Val Leu Gly Val Ala Leu Cys
1 5 10 15
Leu Gly Cys Gly Gln Pro Leu Pro Gln Val Pro Glu Arg Pro Phe Ser
20 25 30
Val Leu Trp Asn Val Pro Ser Ala His Cys Glu Ala Arg Phe Gly Val
35 40 45
His Leu Pro Leu Asn Ala Leu Gly Ile Ile Ala Asn Arg Gly Gln His
50 55 60
Phe His Gly Gln Asn Met Thr Ile Phe Tyr Lys Asn Gln Leu Gly Leu
65 70 75 80
Tyr Pro Tyr Phe Gly Pro Arg Gly Thr Ala His Asn Gly Gly Ile Pro
85 90 95
Gln Ala Leu Pro Leu Asp Arg His Leu Ala Leu Ala Ala Tyr Gln Ile
100 105 110
His His Ser Leu Arg Pro Gly Phe Ala Gly Pro Ala Val Leu Asp Trp
115 120 125
Glu Glu Trp Cys Pro Leu Trp Ala Gly Asn Trp Gly Arg Arg Arg Ala
130 135 140
Tyr Gln Ala Ala Ser Trp Ala Trp Ala Gln Gln Val Phe Pro Asp Leu
145 150 155 160
Asp Pro Gln Glu Gln Leu Tyr Lys Ala Tyr Thr Gly Phe Glu Gln Ala
165 170 175
Ala Arg Ala Leu Met Glu Asp Thr Leu Arg Val Ala Gln Ala Leu Arg
180 185 190
Pro His Gly Leu Trp Gly Phe Tyr His Tyr Pro Ala Cys Gly Asn Gly
195 200 205
Trp His Ser Met Ala Ser Asn Tyr Thr Gly Arg Cys His Ala Ala Thr
210 215 220
Leu Ala Arg Asn Thr Gln Leu His Trp Leu Trp Ala Ala Ser Ser Ala
225 230 235 240
Leu Phe Pro Ser Ile Tyr Leu Pro Pro Arg Leu Pro Pro Ala His His
245 250 255
Gln Ala Phe Val Arg His Arg Leu Glu Glu Ala Phe Arg Val Ala Leu
260 265 270
Val Gly His Arg His Pro Leu Pro Val Leu Ala Tyr Val Arg Leu Thr
275 280 285
His Arg Arg Ser Gly Arg Phe Leu Ser Gln Asp Asp Leu Val Gln Ser
290 295 300
Ile Gly Val Ser Ala Ala Leu Gly Ala Ala Gly Val Val Leu Trp Gly
305 310 315 320
Asp Leu Ser Leu Ser Ser Ser Glu Glu Glu Cys Trp His Leu His Asp
325 330 335
Tyr Leu Val Asp Thr Leu Gly Pro Tyr Val Ile Asn Val Thr Arg Ala
340 345 350
Ala Met Ala Cys Ser His Gln Arg Cys His Gly His Gly Arg Cys Ala
355 360 365
Arg Arg Asp Pro Gly Gln Met Glu Ala Phe Leu His Leu Trp Pro Asp
370 375 380
Gly Ser Leu Gly Asp Trp Lys Ser Phe Ser Cys His Cys Tyr Trp Gly
385 390 395 400
Trp Ala Gly Pro Thr Cys Gln Glu Pro Arg Pro Gly Pro Lys Glu Ala
405 410 415
Val

<210> 265
<211> 481
<212> PRT
<213> 現代人

<220>
<223> 玻尿酸酶-4

<400> 265

```
Met Lys Val Leu Ser Glu Gly Gln Leu Lys Leu Cys Val Val Gln Pro
 1               5                  10                  15
Val His Leu Thr Ser Trp Leu Leu Ile Phe Phe Ile Leu Lys Ser Ile
            20                  25                  30
Ser Cys Leu Lys Pro Ala Arg Leu Pro Ile Tyr Gln Arg Lys Pro Phe
        35                  40                  45
Ile Ala Ala Trp Asn Ala Pro Thr Asp Gln Cys Leu Ile Lys Tyr Asn
    50                  55                  60
Leu Arg Leu Asn Leu Lys Met Phe Pro Val Ile Gly Ser Pro Leu Ala
65                  70                  75                  80
Lys Ala Arg Gly Gln Asn Val Thr Ile Phe Tyr Val Asn Arg Leu Gly
                85                  90                  95
Tyr Tyr Pro Trp Tyr Thr Ser Gln Gly Val Pro Ile Asn Gly Gly Leu
            100                 105                 110
Pro Gln Asn Ile Ser Leu Gln Val His Leu Glu Lys Ala Asp Gln Asp
        115                 120                 125
Ile Asn Tyr Tyr Ile Pro Ala Glu Asp Phe Ser Gly Leu Ala Val Ile
    130                 135                 140
Asp Trp Glu Tyr Trp Arg Pro Gln Trp Ala Arg Asn Trp Asn Ser Lys
145                 150                 155                 160
Asp Val Tyr Arg Gln Lys Ser Arg Lys Leu Ile Ser Asp Met Gly Lys
                165                 170                 175
Asn Val Ser Ala Thr Asp Ile Glu Tyr Leu Ala Lys Val Thr Phe Glu
            180                 185                 190
Glu Ser Ala Lys Ala Phe Met Lys Glu Thr Ile Lys Leu Gly Ile Lys
        195                 200                 205
Ser Arg Pro Lys Gly Leu Trp Gly Tyr Tyr Leu Tyr Pro Asp Cys His
    210                 215                 220
Asn Tyr Asn Val Tyr Ala Pro Asn Tyr Ser Gly Ser Cys Pro Glu Asp
225                 230                 235                 240
Glu Val Leu Arg Asn Asn Glu Leu Ser Trp Leu Trp Asn Ser Ser Ala
                245                 250                 255
Ala Leu Tyr Pro Ser Ile Gly Val Trp Lys Ser Leu Gly Asp Ser Glu
            260                 265                 270
Asn Ile Leu Arg Phe Ser Lys Phe Arg Val His Glu Ser Met Arg Ile
        275                 280                 285
Ser Thr Met Thr Ser His Asp Tyr Ala Leu Pro Val Phe Val Tyr Thr
    290                 295                 300
Arg Leu Gly Tyr Arg Asp Glu Pro Leu Phe Phe Leu Ser Lys Gln Asp
305                 310                 315                 320
Leu Val Ser Thr Ile Gly Glu Ser Ala Ala Leu Gly Ala Ala Gly Ile
                325                 330                 335
Val Ile Trp Gly Asp Met Asn Leu Thr Ala Ser Lys Ala Asn Cys Thr
            340                 345                 350
Lys Val Lys Gln Phe Val Ser Ser Asp Leu Gly Ser Tyr Ile Ala Asn
        355                 360                 365
Val Thr Arg Ala Ala Glu Val Cys Ser Leu His Leu Cys Arg Asn Asn
    370                 375                 380
Gly Arg Cys Ile Arg Lys Met Trp Asn Ala Pro Ser Tyr Leu His Leu
385                 390                 395                 400
Asn Pro Ala Ser Tyr His Ile Glu Ala Ser Glu Asp Gly Glu Phe Thr
                405                 410                 415
Val Lys Gly Lys Ala Ser Asp Thr Asp Leu Ala Val Met Ala Asp Thr
            420                 425                 430

Phe Ser Cys His Cys Tyr Gln Gly Tyr Glu Gly Ala Asp Cys Arg Glu
        435                 440                 445
Ile Lys Thr Ala Asp Gly Cys Ser Gly Val Ser Pro Ser Pro Gly Ser
    450                 455                 460
Leu Met Thr Leu Cys Leu Leu Leu Leu Ala Ser Tyr Arg Ser Ile Gln
465                 470                 475                 480
Leu
```

<210> 266

<211> 553
<212> PRT
<213> 西藏黃牛 (Bos taurus)

<220>
<223> PH20

<400> 266

```
Met Arg Met Leu Arg Arg His His Ile Ser Phe Arg Ser Phe Ala Gly
 1               5                  10                  15
Ser Ser Gly Thr Pro Gln Ala Val Phe Thr Phe Leu Leu Leu Pro Cys
            20                  25                  30
Cys Leu Ala Leu Asp Phe Arg Ala Pro Pro Leu Ile Ser Asn Thr Ser
        35                  40                  45
Phe Leu Trp Ala Trp Asn Ala Pro Val Glu Arg Cys Val Asn Arg Arg
    50                  55                  60
Phe Gln Leu Pro Pro Asp Leu Arg Leu Phe Ser Val Lys Gly Ser Pro
65                  70                  75                  80
Gln Lys Ser Ala Thr Gly Gln Phe Ile Thr Leu Phe Tyr Ala Asp Arg
                85                  90                  95
Leu Gly Tyr Tyr Pro His Ile Asp Glu Lys Thr Gly Lys Thr Val Phe
            100                 105                 110
Gly Gly Ile Pro Gln Leu Gly Asn Leu Lys Ser His Met Glu Lys Ala
        115                 120                 125
Lys Asn Asp Ile Ala Tyr Tyr Ile Pro Asn Asp Ser Val Gly Leu Ala
    130                 135                 140
Val Ile Asp Trp Glu Asn Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys
145                 150                 155                 160
Pro Lys Asp Val Tyr Arg Asp Glu Ser Val Glu Leu Val Leu Gln Lys
                165                 170                 175
Asn Pro Gln Leu Ser Phe Pro Glu Ala Ser Lys Ile Ala Lys Val Asp
            180                 185                 190
Phe Glu Thr Ala Gly Lys Ser Phe Met Gln Glu Thr Leu Lys Leu Gly
        195                 200                 205
Lys Leu Leu Arg Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp
    210                 215                 220
Cys Tyr Asn His Asn His Asn Gln Pro Thr Tyr Asn Gly Asn Cys Pro
225                 230                 235                 240
Asp Val Glu Lys Arg Arg Asn Asp Asp Leu Glu Trp Leu Trp Lys Glu
                245                 250                 255
Ser Thr Ala Leu Phe Pro Ser Val Tyr Leu Asn Ile Arg Leu Lys Ser
            260                 265                 270
Thr Gln Asn Ala Ala Leu Tyr Val Arg Asn Arg Val Gln Glu Ala Ile
        275                 280                 285
Arg Leu Ser Lys Ile Ala Ser Val Glu Ser Pro Leu Pro Val Phe Val
    290                 295                 300
Tyr Ala Arg Pro Val Phe Thr Asp Gly Ser Ser Thr Tyr Leu Ser Gln
305                 310                 315                 320
Gly Asp Leu Val Asn Ser Val Gly Glu Ile Val Ser Leu Gly Ala Ser
                325                 330                 335
Gly Ile Ile Met Trp Gly Ser Leu Asn Leu Ser Leu Ser Met Gln Ser
            340                 345                 350
Cys Met Asn Leu Gly Thr Tyr Leu Asn Thr Thr Leu Asn Pro Tyr Ile
        355                 360                 365
Ile Asn Val Thr Leu Ala Ala Lys Met Cys Ser Gln Val Leu Cys His
    370                 375                 380
Asn Glu Gly Val Cys Thr Arg Lys His Trp Asn Ser Ser Asp Tyr Leu
385                 390                 395                 400
His Leu Asn Pro Met Asn Phe Ala Ile Gln Thr Gly Glu Gly Gly Lys
                405                 410                 415
Tyr Thr Val Pro Gly Thr Val Thr Leu Glu Asp Leu Gln Lys Phe Ser
            420                 425                 430
Asp Thr Phe Tyr Cys Ser Cys Tyr Ala Asn Ile His Cys Lys Lys Arg
        435                 440                 445
Val Asp Ile Lys Asn Val His Ser Val Asn Val Cys Met Ala Glu Asp
```

```
    450                 455                 460
Ile Cys Ile Asp Ser Pro Val Lys Leu Gln Pro Ser Asp His Ser Ser
465                 470                 475                 480
Ser Gln Glu Ala Ser Thr Thr Thr Phe Ser Ser Ile Ser Pro Ser Thr
                485                 490                 495
Thr Thr Ala Thr Val Ser Pro Cys Thr Pro Glu Lys His Ser Pro Glu
            500                 505                 510
Cys Leu Lys Val Arg Cys Ser Glu Val Ile Pro Asn Val Thr Gln Lys
        515                 520                 525
Ala Cys Gln Ser Val Lys Leu Lys Asn Ile Ser Tyr Gln Ser Pro Ile
    530                 535                 540
Gln Asn Ile Lys Asn Gln Thr Thr Tyr
545                 550
```

<210> 267
<211> 114
<212> PRT
<213> 綿羊 (Ovis aries)

<220>
<223> PH20部分序列

<400> 267

```
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Leu Ser Lys Ile
 1               5                  10                  15
Ala Ser Val Glu Ser Pro Leu Pro Val Phe Val Tyr His Arg Pro Val
            20                  25                  30
Phe Thr Asp Gly Ser Ser Thr Tyr Leu Ser Gln Gly Asp Leu Val Asn
        35                  40                  45
Ser Val Gly Glu Ile Val Ala Leu Gly Ala Ser Gly Ile Ile Met Trp
    50                  55                  60
Gly Ser Leu Asn Leu Ser Leu Thr Met Gln Ser Cys Met Asn Leu Gly
65                  70                  75                  80
Asn Tyr Leu Asn Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
                85                  90                  95
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
            100                 105                 110
Ile Arg
```

<210> 268
<211> 1446
<212> DNA
<213> 現代人

<220>
<223> 編碼可溶性rHuPH20「前驅體」之DNA

<400> 268

```
atgggagtgc taaaattcaa gcacatcttt ttcagaagct ttgttaaatc aagtggagta 60
tcccagatag ttttcacctt ccttctgatt ccatgttgct tgactctgaa tttcagagca 120
cctcctgtta ttccaaatgt gcctttcctc tgggcctgga atgccccaag tgaattttgt 180
cttggaaaat ttgatgagcc actagatatg agcctcttct ctttcatagg aagcccccga 240
ataaacgcca ccgggcaagg tgttacaata ttttatgttg atagacttgg ctactatcct 300
tacatagatt caatcacagg agtaactgtg aatggaggaa tcccccagaa gatttcctta 360
caagaccatc tggacaaagc taagaaagac attacatttt atatgccagt agacaatttg 420
ggaatggctg ttattgactg ggaagaatgg agacccactt gggcaagaaa ctggaaacct 480
aaagatgttt acaagaatag gtctattgaa ttggttcagc aacaaaatgt acaacttagt 540
ctcacagagg ccactgagaa agcaaaacaa gaatttgaaa aggcagggaa ggatttcctg 600
gtagagacta taaaattggg aaaattactt cggccaaatc acttgtgggg ttattatctt 660
tttccggatt gttacaacca tcactataag aaacccggtt acaatggaag ttgcttcaat 720
gtagaaataa aaagaaatga tgatctcagc tggttgtgga atgaaagcac tgctctttac 780
ccatccattt atttgaacac tcagcagtct cctgtagctg ctacactcta tgtgcgcaat 840
cgagttcggg aagccatcag agtttccaaa atacctgatg caaaaagtcc acttccggtt 900
tttgcatata cccgcatagt ttttactgat caagttttga aattcctttc tcaagatgaa 960
cttgtgtata catttggcga aactgttgct ctgggtgctt ctggaattgt aatatgggga 1020
```

accctcagta taatgcgaag tatgaaatct tgcttgctcc tagacaatta catggagact 1080
atactgaatc cttacataat caacgtcaca ctagcagcca aaatgtgtag ccaagtgctt 1140
tgccaggagc aaggagtgtg tataaggaaa aactggaatt caagtgacta tcttcacctc 1200
aacccagata attttgctat tcaacttgag aaaggtggaa agttcacagt acgtggaaaa 1260
ccgacacttg aagacctgga gcaatttttct gaaaaatttt attgcagctg ttatagcacc 1320
ttgagttgta aggagaaagc tgatgtaaaa gacactgatg ctgttgatgt gtgtattgct 1380
gatggtgtct gtatagatgc ttttctaaaa cctcccatgg agacagaaga acctcaaatt 1440
ttctac 1446

<210> 269
<211> 509
<212> PRT
<213> 現代人

<220>
<223> PH20變異體P48A

<400> 269

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

```
    370                 375                 380
Gly Val Cys Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu
385                 390                 395                 400
Asn Pro Asp Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr
                405                 410                 415
Val Arg Gly Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys
            420                 425                 430
Phe Tyr Cys Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp
        435                 440                 445
Val Lys Asp Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys
    450                 455                 460
Ile Asp Ala Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile
465                 470                 475                 480
Phe Tyr Asn Ala Ser Pro Ser Thr Leu Ser Ala Thr Met Phe Ile Val
                485                 490                 495
Ser Ile Leu Phe Leu Ile Ile Ser Ser Val Ala Ser Leu
            500                 505
```

<210> 270
<211> 509
<212> PRT
<213> 現代人

<220>
<223> 前驅體PH20變異體L499W

<400> 270

```
Met Gly Val Leu Lys Phe Lys His Ile Phe Phe Arg Ser Phe Val Lys
 1               5                  10                  15
Ser Ser Gly Val Ser Gln Ile Val Phe Thr Phe Leu Leu Ile Pro Cys
            20                  25                  30
Cys Leu Thr Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro
        35                  40                  45
Phe Leu Trp Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe
    50                  55                  60
Asp Glu Pro Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg
65                  70                  75                  80
Ile Asn Ala Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu
                85                  90                  95
Gly Tyr Tyr Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly
            100                 105                 110
Gly Ile Pro Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys
        115                 120                 125
Lys Asp Ile Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val
    130                 135                 140
Ile Asp Trp Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro
145                 150                 155                 160
Lys Asp Val Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn
                165                 170                 175
Val Gln Leu Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe
            180                 185                 190
Glu Lys Ala Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys
        195                 200                 205
Leu Leu Arg Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys
    210                 215                 220
Tyr Asn His His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn
225                 230                 235                 240
Val Glu Ile Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser
                245                 250                 255
Thr Ala Leu Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val
            260                 265                 270
Ala Ala Thr Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val
        275                 280                 285
Ser Lys Ile Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr
```

```
    290                 295                 300
Arg Ile Val Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu
305                 310                 315                 320
Leu Val Tyr Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile
                325                 330                 335
Val Ile Trp Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu
            340                 345                 350
Leu Leu Asp Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn
        355                 360                 365
Val Thr Leu Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln
    370                 375                 380
Gly Val Cys Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu
385                 390                 395                 400
Asn Pro Asp Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr
                405                 410                 415
Val Arg Gly Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys
            420                 425                 430
Phe Tyr Cys Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp
        435                 440                 445
Val Lys Asp Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys
    450                 455                 460
Ile Asp Ala Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile
465                 470                 475                 480
Phe Tyr Asn Ala Ser Pro Ser Thr Leu Ser Ala Thr Met Phe Ile Val
                485                 490                 495
Ser Ile Trp Phe Leu Ile Ile Ser Ser Val Ala Ser Leu
            500                 505
```

<210> 271
<211> 520
<212> PRT
<213> 綿羊 (Ovis aries)

<400> 271

```
Leu Asp Phe Pro Ala Pro Pro Leu Ile Ser Asn Thr Ser Phe Leu Trp
 1                5                  10                  15
Ala Trp Asn Ala Pro Ala Glu Arg Cys Val Lys Ile Phe Lys Leu Pro
            20                  25                  30
Pro Asp Leu Arg Leu Phe Ser Val Lys Gly Ser Pro Gln Lys Ser Ala
        35                  40                  45
Thr Gly Gln Phe Ile Thr Leu Phe Tyr Ala Asp Arg Leu Gly Tyr Tyr
    50                  55                  60
Pro His Ile Asp Glu Lys Thr Gly Asn Thr Val Tyr Gly Gly Ile Pro
65                  70                  75                  80
Gln Leu Gly Asn Leu Lys Asn His Leu Glu Lys Ala Lys Lys Asp Ile
                85                  90                  95
Ala Tyr Tyr Ile Pro Asn Asp Ser Val Gly Leu Ala Val Ile Asp Trp
            100                 105                 110
Glu Asn Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
        115                 120                 125
Tyr Arg Asp Glu Ser Val Glu Leu Val Leu Gln Lys Asn Pro Gln Leu
    130                 135                 140
Ser Phe Pro Glu Ala Ser Lys Ile Ala Lys Val Asp Phe Glu Thr Ala
145                 150                 155                 160
Gly Lys Ser Phe Met Gln Glu Thr Leu Lys Leu Gly Lys Leu Leu Arg
                165                 170                 175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
            180                 185                 190
Asn Tyr Asn Gln Pro Thr Tyr Asn Gly Asn Cys Ser Asp Leu Glu Lys
        195                 200                 205
Arg Arg Asn Asp Asp Leu Asp Trp Leu Trp Lys Glu Ser Thr Ala Leu
    210                 215                 220
Phe Pro Ser Val Tyr Leu Asn Ile Lys Leu Lys Ser Thr Pro Lys Ala
225                 230                 235                 240
```

```
Ala Phe Tyr Val Arg Asn Arg Val Gln Glu Ala Ile Arg Leu Ser Lys
                245                 250                 255
Ile Ala Ser Val Glu Ser Pro Leu Pro Val Phe Val Tyr His Arg Pro
            260                 265                 270
Val Phe Thr Asp Gly Ser Ser Thr Tyr Leu Ser Gln Gly Asp Leu Val
        275                 280                 285
Asn Ser Val Gly Glu Ile Val Ala Leu Gly Ala Ser Gly Ile Ile Met
    290                 295                 300
Trp Gly Ser Leu Asn Leu Ser Leu Thr Met Gln Ser Cys Met Asn Leu
305                 310                 315                 320
Gly Asn Tyr Asn Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
                325                 330                 335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys His Asp Glu Gly Val Cys
            340                 345                 350
Thr Arg Lys Gln Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Ile
        355                 360                 365
Met Asn Phe Ala Ile Gln Thr Gly Lys Gly Gly Lys Tyr Thr Val Pro
    370                 375                 380
Gly Lys Val Thr Leu Glu Asp Leu Gln Thr Phe Ser Asp Lys Phe Tyr
385                 390                 395                 400
Cys Ser Cys Tyr Ala Asn Ile Asn Cys Lys Lys Arg Val Asp Ile Lys
                405                 410                 415
Asn Val His Ser Val Asn Val Cys Met Ala Glu Asp Ile Cys Ile Glu
            420                 425                 430
Gly Pro Val Lys Leu Gln Pro Ser Asp His Ser Ser Ser Gln Asn Glu
        435                 440                 445
Ala Ser Thr Thr Thr Val Ser Ser Ile Ser Pro Ser Thr Thr Ala Thr
    450                 455                 460
Thr Val Val Ser Pro Cys Thr Pro Glu Lys Gln Ser Pro Glu Cys Leu
465                 470                 475                 480
Lys Val Arg Cys Leu Glu Ala Ile Ala Asn Val Thr Gln Thr Gly Cys
                485                 490                 495
Gln Gly Val Lys Trp Lys Asn Thr Ser Ser Gln Ser Gln Ser Ser Ile
            500                 505                 510
Gln Asn Ile Lys Asn Gln Thr Thr
        515                 520
```

<210> 272
<211> 474
<212> PRT
<213> 西藏黃牛（Bos taurus）

<220>
<223> PH20

<400> 272

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

```
Val Ile Asp Trp Glu Asn Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys
145                 150                 155                 160
Pro Lys Asp Val Tyr Arg Asp Glu Ser Val Glu Leu Val Leu Gln Lys
                165                 170                 175
Asn Pro Gln Leu Ser Phe Pro Glu Ala Ser Lys Ile Ala Lys Val Asp
            180                 185                 190
Phe Glu Thr Ala Gly Lys Ser Phe Met Gln Glu Thr Leu Lys Leu Gly
        195                 200                 205
Lys Leu Leu Arg Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp
    210                 215                 220
Cys Tyr Asn His Asn His Asn Gln Pro Thr Tyr Asn Gly Asn Cys Pro
225                 230                 235                 240
Asp Val Glu Lys Arg Arg Asn Asp Asp Leu Glu Trp Leu Trp Lys Glu
                245                 250                 255
Ser Thr Ala Leu Phe Pro Ser Val Tyr Leu Asn Ile Arg Leu Lys Ser
            260                 265                 270
Thr Gln Asn Ala Ala Leu Tyr Val Arg Asn Arg Val Gln Glu Ala Ile
        275                 280                 285
Arg Leu Ser Lys Ile Ala Ser Val Glu Ser Pro Leu Pro Val Phe Val
    290                 295                 300
Tyr Ala Arg Pro Val Phe Thr Asp Gly Ser Ser Thr Tyr Leu Ser Gln
305                 310                 315                 320
Gly Asp Leu Val Asn Ser Val Gly Glu Ile Val Ser Leu Gly Ala Ser

                325                 330                 335
Gly Ile Ile Met Trp Gly Ser Leu Asn Leu Ser Leu Ser Val Gln Ser
            340                 345                 350
Cys Met Asn Leu Gly Thr Tyr Leu Asn Thr Thr Leu Asn Pro Tyr Ile
        355                 360                 365
Ile Asn Val Thr Leu Ala Ala Lys Met Cys Ser Gln Val Leu Cys His
    370                 375                 380
Asp Gly Gly Val Cys Thr Arg Lys His Trp Asn Ser Ser Asp Tyr Leu
385                 390                 395                 400
His Leu Asn Pro Met Asn Phe Ala Ile Gln Thr Gly Glu Gly Gly Lys
                405                 410                 415
Tyr Thr Val Pro Gly Thr Leu Thr Leu Glu Asp Leu Gln Lys Phe Ser
            420                 425                 430
Asp Thr Phe Tyr Cys Ser Cys Tyr Ser Asn Leu Ser Cys Lys Lys Arg
        435                 440                 445
Val Asp Ile Lys Asn Val His Ser Val Asp Val Cys Met Ala Glu Asp
    450                 455                 460
Val Cys Ile Asp Ala Phe Leu Lys Pro Pro
465                 470

<210> 273
<211> 517
<212> PRT
<213> 綿羊 (Ovis aries)

<400> 273
Asp Phe Arg Ala Pro Pro Leu Ile Ser Asn Thr Ser Phe Leu Trp Ala
 1               5                  10                  15
Trp Asn Ala Pro Ala Glu Arg Cys Ile Lys Ile Phe Lys Leu Pro Pro
            20                  25                  30
Asp Leu Arg Leu Phe Ser Val Lys Gly Ser Pro Gln Lys Ser Ala Thr
        35                  40                  45
Gly Gln Phe Ile Thr Leu Phe Tyr Ala Asp Arg Leu Gly Tyr Tyr Pro
    50                  55                  60
His Ile Asp Glu Lys Thr Gly Asn Thr Val Tyr Gly Gly Ile Pro Gln
65                  70                  75                  80
Leu Gly Asn Leu Lys Asn His Leu Glu Lys Ala Lys Lys Asp Ile Ala
                85                  90                  95
Tyr Tyr Ile Pro Asn Asp Ser Val Gly Leu Ala Val Ile Asp Trp Glu
            100                 105                 110
Asn Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr
```

```
        115                 120                 125
Arg Asp Glu Ser Val Glu Leu Val Leu Gln Lys Asn Pro Gln Leu Ser
    130                 135                 140
Phe Pro Glu Ala Ser Lys Ile Ala Lys Val Asp Phe Glu Thr Ala Gly
145                 150                 155                 160
Lys Ser Phe Met Gln Glu Thr Leu Lys Leu Gly Lys Leu Leu Arg Pro
                165                 170                 175
Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His Asn
            180                 185                 190
Tyr Asn Gln Pro Thr Tyr Asn Gly Asn Cys Ser Asp Leu Glu Lys Arg
        195                 200                 205
Arg Asn Asp Asp Leu Asp Trp Leu Trp Lys Glu Ser Thr Ala Leu Phe
    210                 215                 220
Pro Ser Val Tyr Leu Asn Ile Lys Leu Lys Ser Thr Pro Lys Ala Ala
225                 230                 235                 240
Phe Tyr Val Arg Asn Arg Val Gln Glu Ala Ile Arg Leu Ser Lys Ile
                245                 250                 255
Ala Ser Val Glu Ser Pro Leu Pro Val Phe Val Tyr His Arg Pro Val
            260                 265                 270
Phe Thr Asp Gly Ser Ser Thr Tyr Leu Ser Gln Gly Asp Leu Val Asn
        275                 280                 285
Ser Val Gly Glu Ile Val Ala Leu Gly Ala Ser Gly Ile Ile Met Trp
    290                 295                 300
Gly Ser Leu Asn Leu Ser Leu Thr Met Gln Ser Cys Met Asn Leu Gly
305                 310                 315                 320
Asn Tyr Leu Asn Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
                325                 330                 335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys His Asp Glu Gly Val Cys
            340                 345                 350
Thr Arg Lys Gln Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Met
        355                 360                 365
Asn Phe Ala Ile Gln Thr Gly Lys Gly Gly Lys Tyr Thr Val Pro Gly
    370                 375                 380
Lys Val Thr Leu Glu Asp Leu Gln Thr Phe Ser Asp Lys Phe Tyr Cys
385                 390                 395                 400
Ser Cys Tyr Ala Asn Ile Asn Cys Lys Lys Arg Val Asp Ile Lys Asn
                405                 410                 415
Val His Ser Val Asn Val Cys Met Ala Glu Asp Ile Cys Ile Glu Gly
            420                 425                 430
Pro Val Lys Leu Gln Pro Ser Asp His Ser Ser Ser Gln Asn Glu Ala
        435                 440                 445
Ser Thr Thr Thr Val Ser Ser Ile Ser Pro Ser Thr Thr Ala Thr Thr
    450                 455                 460
Val Ser Pro Cys Thr Pro Glu Lys Gln Ser Pro Glu Cys Leu Lys Val
465                 470                 475                 480
Arg Cys Leu Glu Ala Ile Ala Asn Val Thr Gln Thr Gly Cys Gln Gly
                485                 490                 495
Val Lys Trp Lys Asn Thr Ser Ser Gln Ser Ser Ile Gln Asn Ile Lys
            500                 505                 510
Asn Gln Thr Thr Tyr
        515
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<210> 274
<211> 1620
<212> DNA
<213> 綿羊 (Ovis aries)

<400> 274
ttttccgtgt tggttggctc tggacttcag agcacccccct ctcatttcaa acacttcttt 60
cctctgggcc tggaatgccc cagctgaacg ttgtattaaa atctttaaac tacctccaga 120
tctgagactc ttctctgtaa aaggaagccc ccaaaaaagt gctacgggac aatttattac 180
attattttat gctgatagac ttggctacta tcctcatata gatgaaaaaa caggcaacac 240
tgtatatgga ggaattcccc agttgggaaa cttaaaaaat catttggaaa aagccaaaaa 300
agacattgcc tattacatac caaatgacag cgtgggcttg gcggtcattg actgggaaaa 360

ctggaggcct acctgggcaa gaaactggaa acctaaagat gtttacaggg atgagtctgt 420
tgagttggtt ctgcaaaaaa atccacaact cagtttccca gaggcttcca agattgcaaa 480
agtggatttt gagacagcag gaaagagttt catgcaagag actttaaaac tgggaaaatt 540
acttcggcca aatcacttat ggggttatta tctttttcct gattgttaca atcataatta 600
taaccagcct acttacaatg gaaattgctc tgatttagaa aaaaggagaa atgatgatct 660
cgactggttg tggaaggaaa gcactgccct tttcccttct gtttatttga atatcaagtt 720
aaaatctact ccaaaagctg ccttctatgt tcgtaatcgt gtccaggaag ccattcggtt 780
gtctaaaata gcgagtgttg aaagtccact tcccgttttt gtatatcacc gtccagtttt 840
tactgatggg tcttcaacat acctttctca gggtgacctt gtgaattcgg ttggtgagat 900
cgttgctcta ggtgcctctg ggattataat gtggggcagt ctcaatctaa gcctaactat 960
gcaatcttgc atgaacctag gcaattactt gaacactaca ctgaatcctt acataatcaa 1020
cgtcacccta gcagccaaaa tgtgcagcca agtgctttgc cacgatgaag gagtgtgtac 1080
aaggaaacaa tggaattcaa gcgactatct tcacctgaac ccaatgaatt ttgctattca 1140
aactgggaaa ggtggaaaat acacagtacc tgggaaagtc acacttgaag acctgcaaac 1200
gttttctgat aaattttatt gcagttgtta tgccaacatc aactgtaaga agagagttga 1260
tataaaaaat gttcatagtg ttaatgtatg tatggcagaa gacatttgta tagagggccc 1320
tgtgaagtta caacccagtg atcattcctc tagccagaat gaggcatcta ctaccaccgt 1380
cagcagtatc tcaccctcta ctacagccac cacagtatct ccatgtactc ctgagaaaca 1440
gtcccctgag tgcctcaaag tcaggtgttt ggaagccatc gccaacgtca cccaaacggg 1500
gtgtcaaggt gttaaatgga agaacacttc cagtcagtca agtattcaaa atattaaaaa 1560
tcaaacaacc tattaaaata taaattcagt gcttataaaa aaaaaaaaaa aaaaaaaaaa 1620

<210> 275
<211> 793
<212> PRT
<213> 節桿菌屬（Arthrobacter sp.）（菌株FB24）

<220>
<223> 玻尿酸解離酶

<400> 275

Met	Thr	Arg	Glu	Phe	Ser	Arg	Arg	Thr	Ala	Leu	Lys	Gly	Ala	Ala	Leu
1				5				10					15		
Ser	Gly	Leu	Leu	Leu	Ala	Met	Val	His	Gly	Pro	Ala	His	Ala	Ala	Ala
			20					25					30		
Thr	Ala	Asn	Ala	Thr	Leu	Thr	Pro	Ala	Asp	Phe	Ala	Gly	Leu	Arg	Gln
		35					40					45			
Arg	Trp	Val	Asp	Gln	Ile	Thr	Gly	Arg	Lys	Val	Leu	Val	Ala	Gly	Asp
	50					55					60				
Asn	Asp	Phe	Val	Thr	Ala	Leu	Ala	Ala	Leu	Asp	Lys	Lys	Ala	Arg	Thr
65					70					75					80
Ala	Ile	Asp	Leu	Leu	Glu	Arg	Ser	Ala	Gly	Arg	Leu	Thr	Val	Phe	Ser
				85					90					95	
Asp	Leu	Ser	Leu	Ala	Lys	Asp	Thr	Asp	Leu	Val	Thr	Thr	His	Thr	Arg
			100					105					110		
Leu	Ala	Thr	Met	Ala	Thr	Ala	Trp	Ala	Thr	Pro	Gly	Ser	Glu	His	Phe
		115					120					125			
Ala	Asp	Ala	Gly	Leu	Leu	Ala	Ala	Ile	Arg	Ala	Gly	Leu	Ala	Asp	Ala
	130					135					140				
Asn	Ser	Leu	Cys	Tyr	Asn	Ala	Ser	Lys	Glu	Glu	Gln	Gly	Asn	Trp	Trp
145					150					155					160
Ser	Trp	Glu	Ile	Gly	Thr	Pro	Lys	Ala	Leu	Ala	Asp	Thr	Met	Val	Leu
				165					170					175	
Leu	His	Ala	Glu	Leu	Thr	Ala	Ala	Glu	Arg	Ala	Ala	Tyr	Cys	Ala	Ala
			180					185					190		
Ile	Asp	His	Phe	Val	Pro	Asp	Pro	Trp	Gln	Gln	Phe	Pro	Pro	Lys	Arg
		195					200					205			
Gly	Lys	Ile	Thr	Ser	Val	Gly	Ala	Asn	Arg	Val	Asp	Leu	Cys	Gln	Ala
	210					215					220				
Val	Thr	Ile	Arg	Ser	Leu	Val	Asp	Glu	Asp	Ala	Glu	Lys	Leu	Thr	His
225					230					235					240
Ala	Val	Ala	Gly	Leu	Ser	Glu	Val	Trp	Gln	Tyr	Val	Ser	Ala	Gly	Asn
				245					250					255	

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Gly Phe Phe Thr Asp Gly Ser Phe Ile Gln His Ser Thr Thr Pro Tyr
                260                 265                 270
Thr Gly Ser Tyr Gly Val Val Leu Leu Thr Gly Leu Ser Lys Leu Phe
        275                 280                 285
Ala Leu Leu Gly Gly Thr Gly Ala Glu Val Ser Asp Pro Ser Arg Asp
    290                 295                 300
Ile Leu Phe Lys Thr Val Glu Gly Ser Phe Ala Pro Phe Met Val Ala
305                 310                 315                 320
Gly Ala Met Ala Asp Ser Val Arg Gly Arg Ser Ile Ser Arg Glu Ser
                325                 330                 335
Asn Thr Gly Phe Asp Leu Gly Ala Ser Thr Ile Glu Ser Ile Leu Leu
            340                 345                 350
Leu Ala Arg Ala Val Asp Pro Val Thr Ala Arg Arg Trp Arg Ser Leu
        355                 360                 365
Cys Leu Ala Trp Ile Asn Gln Asn Arg Lys Ala Pro Ile Leu Ala Asp
    370                 375                 380
Ala Gly Val Gly Arg Thr Ala Leu Val Lys Glu Leu Leu Ala Met Gly
385                 390                 395                 400
Leu Thr Glu Thr Asp Leu Pro Gly Gly His Tyr Leu Phe Pro Ala Met
                405                 410                 415
Asp Arg Thr Met His His Ser Gln Gly Trp Thr Leu Ser Thr Ala Met
            420                 425                 430
Ala Ser Ser Arg Ile Ala Trp Tyr Glu Cys Gly Asn Gly Glu Asn Asn
        435                 440                 445
Arg Gly Tyr His Thr Gly Ser Gly Met Thr Tyr Val Tyr Asp Gly Asp
    450                 455                 460
Leu Gly Gln Tyr Asp Asp Ala Phe Trp Ala Thr Ala Asn His Cys Arg
465                 470                 475                 480
Leu Pro Gly Ile Thr Val Asp Thr Ser Ser Leu Pro Asp Lys Val Glu
                485                 490                 495
Gly Glu Trp Gly Ala Ala Thr Pro Ala Asn Glu Trp Thr Gly Ser Thr
            500                 505                 510
Ala Tyr Gly Asp Val Ala Ala Val Gly Gln His Leu Ile Gly Pro Gly
        515                 520                 525
Gly Thr Gly Leu Thr Ala Arg Lys Ser Trp Phe Val Ser Lys Asp Val
    530                 535                 540
Ile Val Cys Leu Gly Ala Asp Ile Arg Thr Gly Ser Gly Ser Arg Ile
545                 550                 555                 560
Glu Thr Val Val Asp His Arg Asn Leu His Ala Gly Phe Asn Ala Met
                565                 570                 575
Gly Thr Ala Ala Gly Thr Val Ala Ala Thr Pro Gly His Pro Glu Val
            580                 585                 590
Leu Thr Val Asp Arg Trp Val His Leu Glu Gly Phe Gly Gly Tyr Val
        595                 600                 605
Val Leu Asp Ala Ala Pro Leu Gln Val Leu Arg Glu Gln Arg Glu Gly
    610                 615                 620
Ser Trp Ser Glu Val Asn Val Lys Gly Ser Ala Ala Arg Gln Thr Arg
625                 630                 635                 640
Asn Tyr Ala Thr Leu Tyr Phe Asp His Gly His Glu Pro Glu Ala Ala
                645                 650                 655
Ser Tyr Ala Tyr Leu Val Ala Pro Gly Ala Ser Ala Ser Met Thr Ser
            660                 665                 670
Ser Leu Ser Gly Gln Ser Phe His Thr Val Leu Arg Asn Asp Glu Val
        675                 680                 685
Ala Gln Ala Val Lys Phe Lys Lys Glu Lys Thr Thr Ala Ala Thr Phe
    690                 695                 700
Trp Arg Pro Gly Thr Val Gly Asp Leu Ala Leu Ser Gly Pro Ala Cys
705                 710                 715                 720
Val Val Val Lys Glu Val Gly Asp Arg Leu Ser Ile Ala Val Ser Asp
                725                 730                 735
Pro Thr Gln Asn Ala Ser Thr Leu Thr Leu Arg Leu Lys Thr Lys Arg
            740                 745                 750
Phe Phe Arg Ile Ile Glu Gly Gln Gly Ala Ser Leu Ser His Gly Ala
        755                 760                 765
Asp Gly Phe Thr Val Leu Glu Val Asp Ile Ala Asn His Ala Gly Arg
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770 775 780
Thr Lys Gln Ile Glu Leu Ser Ala Glu
785 790

<210> 276
<211> 557
<212> PRT
<213> 噬菌蛭弧菌（Bdellovibrio bacteriovorus）

<220>
<223> 玻尿酸解離酶

<400> 276
Met Thr Lys Phe Phe Phe Leu Leu Thr Leu Ile Ser Ala Thr Ala Phe
1 5 10 15
Ala Gln Ser Glu Pro Asp Trp Thr Ala Gly Val Pro Val Pro Pro Gly
20 25 30
Gly Arg Ser Asn Ile Tyr Ser Trp Asn Asp Phe Asp Phe Gln Ala Thr
35 40 45
Leu Asn Lys Gly Lys Ile His Ala Gln Val Tyr Pro Val Thr Val Thr
50 55 60
Gly Met Leu Pro Pro Tyr Glu Pro Val Arg Arg Leu Ile Glu Glu Lys
65 70 75 80
Asn Ser Asn Pro Leu Arg Lys Trp Ile Gln Ser Leu Met Lys Gly Leu
85 90 95
Ser Gly Phe Arg Ser Phe Glu Asp Val Leu Lys Asn Leu Gly Leu His
100 105 110
Lys Tyr Pro Leu Glu Asn Glu Arg Gly Val Tyr Ala Val Pro Tyr Pro
115 120 125
Asn Glu Ile Arg Pro Asp Thr Leu Met Gly Phe Gly Leu Ile Glu Arg
130 135 140
Asn Gly Ala Glu Gly Phe Thr Phe Ser Cys Ala Ala Cys His Ser Ser
145 150 155 160
Asn Leu Phe Gly Lys Thr Val Leu Gly Met Thr Asn Arg Phe Pro Arg
165 170 175
Ala Asn Glu Phe Phe Ile Lys Ala Lys Lys Val Met Pro Leu Met Asp
180 185 190
Pro His Ile Phe Gln Ala Tyr Thr Arg Ala Thr Asp Ala Glu Thr Ala
195 200 205
Leu Leu Val Glu Ser Lys Glu Arg Leu Lys Ser Val Ala Leu Lys Gln
210 215 220
Pro Ile Ala Leu Gly Leu Asp Thr Ser Leu Ala Gln Val Ser Leu Ser
225 230 235 240
Leu Asn Arg Arg Ala Lys Asp Gly Tyr Ala Asn Tyr Ser Asp Lys Ala
245 250 255
Ala Arg Ser Pro Arg Ala Asp Ala Tyr Leu Asp Asn Lys Pro Ala Asp
260 265 270
Ser Lys Pro Ala Val Trp Trp Asn Val Lys Tyr Lys Asn Arg Trp Leu
275 280 285
Ser Asp Gly Ser Val Leu Ser Gly Asn Pro Ile Phe Thr Asn Leu Ile
290 295 300
Trp Asn Glu Ile Gly Arg Gly Ala Asp Leu His Glu Leu Glu Gln Trp
305 310 315 320
Leu Ala Asp Asn Asp His Ile Ile Lys Glu Leu Thr Thr Ala Val Phe
325 330 335
Ala Ser Glu Ala Pro His Ile Thr Asp Phe Tyr Pro Ala Glu Lys Ile
340 345 350
Asp Leu Gly Arg Ala Lys Ala Gly Glu Gln Ile Phe Lys Asn Thr Cys
355 360 365
Ala Lys Cys His Gly His Tyr Glu Lys Ala Trp Asn Leu Pro Gln Ala
370 375 380
Leu Val Leu Ser Ala Ala Glu Arg Leu Lys Thr Val Glu Val Arg Tyr
385 390 395 400
Lys Glu Lys Thr Pro Val Val Asn Val Gly Thr Asp Pro Phe Arg Arg

405 410 415
Gln Gly Met Lys Ser Leu Glu Gln Leu Asn Asp Leu Glu Ile Ser Lys
420 425 430
Lys Asn Gly Ile Val Ile Lys Ala Gln Glu Gly Tyr Val Pro Pro Pro
435 440 445
Leu Val Gly Ile Trp Ala Arg Trp Pro Tyr Met His Asn Asn Ser Ile
450 455 460
Pro Asn Leu Cys Val Leu Leu Thr Pro Ala Lys Lys Arg Pro Ser Ile
465 470 475 480
Tyr Tyr Ser Gly Glu Ala Leu Asn Lys Asp Thr Asp Tyr Asp Phe Ser
485 490 495
Cys Gly Gly Tyr Pro Ile Gly Asp Lys Thr Pro Lys Ala Trp Lys Thr
500 505 510
Arg Glu His Leu Tyr Asp Thr Arg Asn Pro Gly Met Gly Asn Met Gly
515 520 525
His Asp Glu Gly Ile Phe Ile Lys Asp Gly Lys Glu Ile Leu Ser Ala
530 535 540
Glu Asp Lys Tyr Asn Leu Ile Gln Phe Leu Gln Thr Leu
545 550 555

<210> 277
<211> 813
<212> PRT
<213> 痤皰丙酸桿菌（Propionibacterium acnes）

<220>
<223> 玻尿酸解離酶

<400> 277
Met Phe Gly Thr Pro Ser Arg Arg Thr Phe Leu Thr Ala Ser Ala Leu
1 5 10 15
Ser Ala Met Ala Leu Ala Ala Ser Pro Thr Val Thr Asp Ala Ile Ala
20 25 30
Ala Pro Gly Pro Asp Ser Trp Ser Ala Leu Cys Glu Arg Trp Ile Asp
35 40 45
Ile Ile Thr Gly Arg Arg Ala Ala Arg Thr Ser Asp Pro Arg Ala Arg
50 55 60
Ala Ile Ile Ala Lys Thr Asp Arg Lys Val Ala Glu Ile Leu Thr Asp
65 70 75 80
Leu Val Ser Gly Ser Ser Arg Gln Thr Val Leu Ile Ser Ala Asp Leu
85 90 95
Arg Lys Glu Gln Ser Pro Phe Ile Thr Lys Thr Ala Arg Ala Ile Glu
100 105 110
Ser Met Ala Cys Ala Trp Ala Thr Pro Gly Ser Ser Tyr His Lys Asp
115 120 125
Pro Glu Ile Leu Ser Ala Cys Ile Glu Gly Leu Arg Asp Phe Cys Arg
130 135 140
Leu Arg Tyr Asn Pro Ser Gln Asp Glu Tyr Gly Asn Trp Trp Asp Trp
145 150 155 160
Glu Asp Gly Ala Ser Arg Ala Val Ala Asp Val Met Cys Ile Leu His
165 170 175
Asp Val Leu Pro Pro Glu Val Met Ser Ala Ala Ala Ala Gly Ile Asp
180 185 190
His Phe Ile Pro Asp Pro Trp Phe Gln Gln Pro Ala Ser Val Lys Pro
195 200 205
Thr Ala Asn Pro Val Gln Pro Val Val Ser Thr Gly Ala Asn Arg Met
210 215 220
Asp Leu Thr Arg Ala Val Met Cys Arg Ser Ile Ala Thr Gly Asp Glu
225 230 235 240
Lys Arg Leu Arg His Ala Val Asp Gly Leu Pro Asp Ala Trp Arg Val
245 250 255
Thr Thr Glu Gly Asp Gly Phe Arg Ala Asp Gly Gly Phe Ile Gln His
260 265 270
Ser His Ile Pro Tyr Thr Gly Gly Tyr Gly Asp Val Leu Phe Ser Gly

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        275                 280                 285
Leu Ala Met Leu Phe Pro Leu Val Ser Gly Met Arg Phe Asp Ile Val
    290                 295                 300
Glu Ser Ala Arg Lys Ala Phe His Asp Gln Val Glu Arg Gly Phe Ile
305                 310                 315                 320
Pro Val Met Tyr Asn Gly Gln Ile Leu Asp Asp Val Arg Gly Arg Ser
                325                 330                 335
Ile Ser Arg Ile Asn Glu Ser Ala Ala Met His Gly Ile Ser Ile Ala
            340                 345                 350
Arg Ala Met Leu Met Met Ala Asp Ala Leu Pro Thr His Arg Ala Glu
        355                 360                 365
Gln Trp Arg Gly Ile Val His Gly Trp Met Ala Arg Asn Thr Phe Asp
    370                 375                 380
His Leu Ser Glu Pro Ser Thr Leu Val Asp Ile Ser Leu Phe Asp Ala
385                 390                 395                 400
Ala Ala Lys Ala Arg Pro Val Pro Glu Ser Ser Thr Pro Ser Tyr Phe
                405                 410                 415
Ala Ser Met Asp Arg Leu Val His Arg Thr Ala Asp Trp Leu Ile Thr
            420                 425                 430
Val Ser Asn Cys Ser Asp Arg Ile Ala Trp Tyr Glu Tyr Gly Asn Gly
        435                 440                 445
Glu Asn Glu Trp Ala Ser Arg Thr Ser Gln Gly Met Arg Tyr Leu Leu
    450                 455                 460
Leu Pro Gly Asp Met Gly Gln Tyr Glu Asp Gly Tyr Trp Ala Thr Val
465                 470                 475                 480
Asp Tyr Ser Ala Pro Thr Gly Thr Thr Val Asp Ser Thr Pro Leu Lys
                485                 490                 495
Arg Ala Val Gly Ala Ser Trp Ala Ala Lys Thr Pro Thr Asn Glu Trp
            500                 505                 510
Ser Gly Gly Leu Ala Ser Gly Ser Trp Ser Ala Ala Ala Ser His Ile
        515                 520                 525
Thr Ser Gln Asp Ser Ala Leu Lys Ala Arg Arg Leu Trp Val Gly Leu
    530                 535                 540
Lys Asp Ala Met Val Glu Leu Thr Thr Asp Val Thr Thr Asp Ala Ser
545                 550                 555                 560
Arg Ala Ile Thr Val Val Glu His Arg Lys Val Ala Ser Ser Ser Thr
                565                 570                 575
Lys Leu Leu Val Asp Gly Asn Arg Val Ser Ser Ala Thr Ser Phe Gln
            580                 585                 590
Asn Pro Arg Trp Ala His Leu Asp Gly Val Gly Gly Tyr Val Phe Ala
        595                 600                 605
Thr Asp Thr Asp Leu Ser Ala Asp Val Ala Thr Arg Lys Gly Thr Trp
    610                 615                 620
Ile Asp Val Asn Pro Ser Arg Lys Val Lys Gly Ala Asp Glu Val Ile
625                 630                 635                 640
Glu Arg Ala Tyr Ala Ser Leu His Val Thr His His Asp Arg Pro Val
                645                 650                 655
Ala Trp Ala Leu Leu Pro Thr Ala Ser Arg Ser His Thr Met Ala Leu
            660                 665                 670
Ala Thr Arg Pro Gly Val Glu Pro Phe Thr Val Leu Arg Asn Asp Ala
        675                 680                 685
Thr Val Gln Ala Val Arg Ser Ala Gly Ala Leu Leu Thr Lys Asp Pro
    690                 695                 700
Thr Val Val Thr Thr Leu Ala Phe Trp Lys Pro Ala Thr Cys Gly Gly
705                 710                 715                 720
Val Ala Val Asn Arg Pro Ala Leu Val Gln Thr Arg Glu Ser Ala Asn
                725                 730                 735
Gln Met Glu Val Val Ile Val Glu Pro Thr Gln Lys Arg Gly Ser Leu
            740                 745                 750
Thr Val Thr Ile Glu Gly Ser Trp Lys Val Lys Thr Ala Asp Ser His
        755                 760                 765
Val Asp Val Ser Cys Glu Asn Ala Ala Gly Thr Leu His Val Asp Thr
    770                 775                 780
Ala Gly Leu Gly Gly Gln Ser Val Arg Val Thr Leu Ala Arg Gln Val
785                 790                 795                 800
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Thr Gln Thr Pro Ser Gly Gly Gly Arg His Asp Arg Ala
                805                 810


<210> 278
<211> 1072
<212> PRT
<213> 無乳鏈球菌 (Streptococcus agalactiae)

<220>
<223> 玻尿酸解離酶

<400> 278
Met Glu Ile Lys Lys Lys Tyr Arg Ile Met Leu Tyr Ser Ala Leu Ile
 1               5                  10                  15
Leu Gly Thr Ile Leu Val Asn Asn Ser Tyr Gln Ala Lys Ala Glu Glu
            20                  25                  30
Leu Thr Lys Thr Thr Ser Thr Ser Gln Ile Arg Asp Thr Gln Thr Asn
        35                  40                  45
Asn Ile Glu Val Leu Gln Thr Glu Ser Thr Thr Val Lys Glu Thr Ser
    50                  55                  60
Thr Thr Thr Thr Gln Gln Asp Leu Ser Asn Pro Thr Ala Ser Thr Ala
65                  70                  75                  80
Thr Ala Thr Ala Thr His Ser Thr Met Lys Gln Val Val Asp Asn Gln
                85                  90                  95
Thr Gln Asn Lys Glu Leu Val Lys Asn Gly Asp Phe Asn Gln Thr Asn
            100                 105                 110
Pro Val Ser Gly Ser Trp Ser His Thr Ser Ala Arg Glu Trp Ser Ala
        115                 120                 125
Trp Ile Asp Lys Glu Asn Thr Ala Asp Lys Ser Pro Ile Ile Gln Arg
    130                 135                 140
Thr Glu Gln Gly Gln Val Ser Leu Ser Ser Asp Lys Gly Phe Arg Gly
145                 150                 155                 160
Ala Val Thr Gln Lys Val Asn Ile Asp Pro Thr Lys Lys Tyr Glu Val
                165                 170                 175
Lys Phe Asp Ile Glu Thr Ser Asn Lys Ala Gly Gln Ala Phe Leu Arg
            180                 185                 190
Ile Met Glu Lys Lys Asp Asn Asn Thr Arg Leu Trp Leu Ser Glu Met
        195                 200                 205
Thr Ser Gly Thr Thr Asn Lys His Thr Leu Thr Lys Ile Tyr Asn Pro
    210                 215                 220
Lys Leu Asn Val Ser Glu Val Thr Leu Glu Leu Tyr Tyr Glu Lys Gly
225                 230                 235                 240
Thr Gly Ser Ala Thr Phe Asp Asn Ile Ser Met Lys Ala Lys Gly Pro
                245                 250                 255
Lys Asp Ser Glu His Pro Gln Pro Val Thr Thr Gln Ile Glu Glu Ser
            260                 265                 270
Val Asn Thr Ala Leu Asn Lys Asn Tyr Val Phe Asn Lys Ala Asp Tyr
        275                 280                 285
Gln Tyr Thr Leu Thr Asn Pro Ser Leu Gly Lys Ile Val Gly Gly Ile
    290                 295                 300
Leu Tyr Pro Asn Ala Thr Gly Ser Thr Thr Val Lys Ile Ser Asp Lys
305                 310                 315                 320
Ser Gly Lys Ile Ile Lys Glu Val Pro Leu Ser Val Thr Ala Ser Thr
                325                 330                 335

Glu Asp Lys Phe Thr Lys Leu Leu Asp Lys Trp Asn Asp Val Thr Ile
            340                 345                 350
Gly Asn His Val Tyr Asp Thr Asn Asp Ser Asn Met Gln Lys Ile Asn
        355                 360                 365
Gln Lys Leu Asp Glu Thr Asn Ala Lys Asn Ile Lys Thr Ile Lys Leu
    370                 375                 380
Asp Ser Asn His Thr Phe Leu Trp Lys Asp Leu Asp Asn Leu Asn Asn
385                 390                 395                 400
Ser Ala Gln Leu Thr Ala Thr Tyr Arg Arg Leu Glu Asp Leu Ala Lys
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405 410 415

Gln Ile Thr Asn Pro His Ser Thr Ile Tyr Lys Asn Glu Lys Ala Ile

420 425 430

Arg Thr Val Lys Glu Ser Leu Ala Trp Leu His Gln Asn Phe Tyr Asn

435 440 445

Val Asn Lys Asp Ile Glu Gly Ser Ala Asn Trp Trp Asp Phe Glu Ile

450 455 460

Gly Val Pro Arg Ser Ile Thr Ala Thr Leu Ala Leu Met Asn Asn Tyr

465 470 475 480

Phe Thr Asp Ala Glu Ile Lys Thr Tyr Thr Asp Pro Ile Glu His Phe

485 490 495

Val Pro Asp Ala Gly Tyr Phe Arg Lys Thr Leu Asp Asn Pro Phe Lys

500 505 510

Ala Leu Gly Gly Asn Leu Val Asp Met Gly Arg Val Lys Ile Ile Glu

515 520 525

Gly Leu Leu Arg Lys Asp Asn Thr Ile Ile Glu Lys Thr Ser His Ser

530 535 540

Leu Lys Asn Leu Phe Thr Thr Ala Thr Lys Ala Glu Gly Phe Tyr Ala

545 550 555 560

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

565 570 575

Gly Asn Val Leu Ile Asp Gly Leu Thr Gln Leu Leu Pro Ile Ile Gln

580 585 590

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

595 600 605

Trp Ile Asn Gln Ser Phe Leu Pro Leu Ile Val Lys Gly Glu Leu Met

610 615 620

Asp Met Ser Arg Gly Arg Ser Ile Ser Arg Glu Ala Ala Ser Ser His

625 630 635 640

Ala Ala Ala Val Glu Val Leu Arg Gly Phe Leu Arg Leu Ala Asn Met

645 650 655

Ser Asn Glu Glu Arg Asn Leu Asp Leu Lys Ser Thr Ile Lys Thr Ile

660 665 670

Ile Thr Ser Asn Lys Phe Tyr Asn Val Phe Asn Asn Leu Lys Ser Tyr

675 680 685

Ser Asp Ile Ala Asn Met Asn Lys Met Leu Asn Asp Ser Thr Val Ala

690 695 700

Thr Lys Pro Leu Lys Ser Asn Leu Ser Thr Phe Asn Ser Met Asp Arg

705 710 715 720

Leu Ala Tyr Tyr Asn Ala Glu Lys Asp Phe Gly Phe Ala Leu Ser Leu

725 730 735

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

740 745 750

Arg Gly Trp Tyr Thr Gly Asp Gly Met Phe Tyr Leu Tyr Asn Ser Asp

755 760 765

Gln Ser His Tyr Ser Asn His Phe Trp Pro Thr Val Asn Pro Tyr Lys

770 775 780

Met Ala Gly Thr Thr Glu Lys Asp Ala Lys Arg Glu Asp Thr Thr Lys

785 790 795 800

Glu Phe Met Ser Lys His Ser Lys Asp Ala Lys Glu Lys Thr Gly Gln

805 810 815

Val Thr Gly Thr Ser Asp Phe Val Gly Ser Val Lys Leu Asn Asp His

820 825 830

Phe Ala Leu Ala Ala Met Asp Phe Thr Asn Trp Asp Arg Thr Leu Thr

835 840 845

Ala Gln Lys Gly Trp Val Ile Leu Asn Asp Lys Ile Val Phe Leu Gly

850 855 860

Ser Asn Ile Lys Asn Thr Asn Gly Ile Gly Asn Val Ser Thr Thr Ile

865 870 875 880

Asp Gln Arg Lys Asp Asp Ser Lys Thr Pro Tyr Thr Thr Tyr Val Asn

885 890 895

Gly Lys Thr Ile Asp Leu Lys Gln Ala Ser Ser Gln Gln Phe Thr Asp

900 905 910

Thr Lys Ser Val Phe Leu Glu Ser Lys Glu Pro Gly Arg Asn Ile Gly

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        915                 920                 925
Tyr Ile Phe Phe Lys Asn Ser Thr Ile Asp Ile Glu Arg Lys Glu Gln
    930                 935                 940
Thr Gly Thr Trp Asn Ser Ile Asn Arg Thr Ser Lys Asn Thr Ser Ile
945                 950                 955                 960
Val Ser Asn Pro Phe Ile Thr Ile Ser Gln Lys His Asp Asn Lys Gly
                965                 970                 975
Asp Ser Tyr Gly Tyr Met Met Val Pro Asn Ile Asp Arg Thr Ser Phe
            980                 985                 990
Asp Lys Leu Ala Asn Ser Lys Glu Val Glu Leu Leu Glu Asn Ser Ser
        995                 1000                1005
Lys Gln Gln Val Ile Tyr Asp Lys Asn Ser Gln Thr Trp Ala Val Ile
    1010                1015                1020
Lys His Asp Asn Gln Glu Ser Leu Ile Asn Asn Gln Phe Lys Met Asn
1025                1030                1035                1040
Lys Ala Gly Leu Tyr Leu Val Gln Lys Val Gly Asn Asp Tyr Gln Asn
                1045                1050                1055
Val Tyr Tyr Gln Pro Gln Thr Met Thr Lys Thr Asp Gln Leu Ala Ile
            1060                1065                1070


<210> 279
<211> 1072
<212> PRT
<213> 無乳鏈球菌18RS21

<220>
<223> 玻尿酸解離酶

<400> 279
Met Glu Ile Lys Lys Lys His Arg Ile Met Leu Tyr Ser Ala Leu Ile
 1                5                  10                  15
Leu Gly Thr Ile Leu Val Asn Asn Ser Tyr Gln Ala Lys Ala Glu Glu
            20                  25                  30
Leu Thr Lys Thr Thr Ser Thr Ser Gln Ile Arg Asp Thr Gln Thr Asn
        35                  40                  45
Asn Ile Glu Val Leu Gln Thr Glu Ser Thr Thr Val Lys Glu Thr Ser
    50                  55                  60
Thr Thr Thr Thr Gln Gln Asp Leu Ser Asn Pro Thr Ala Ser Thr Ala
65                  70                  75                  80
Thr Ala Thr Ala Thr His Ser Thr Met Lys Gln Val Val Asp Asn Gln
                85                  90                  95
Thr Gln Asn Lys Glu Leu Val Lys Asn Gly Asp Phe Asn Gln Thr Asn
            100                 105                 110
Pro Val Ser Gly Ser Trp Ser His Thr Ser Ala Arg Glu Trp Ser Ala
        115                 120                 125
Trp Ile Asp Lys Glu Asn Thr Ala Asp Lys Ser Pro Ile Ile Gln Arg
    130                 135                 140
Thr Glu Gln Gly Gln Val Ser Leu Ser Ser Asp Lys Gly Phe Arg Gly
145                 150                 155                 160
Ala Val Thr Gln Lys Val Asn Ile Asp Pro Thr Lys Lys Tyr Glu Val
                165                 170                 175
Lys Phe Asp Ile Glu Thr Ser Asn Lys Ala Gly Gln Ala Phe Leu Arg
            180                 185                 190
Ile Met Glu Lys Lys Asp Asn Asn Thr Arg Leu Trp Leu Ser Glu Met
        195                 200                 205
Thr Ser Gly Thr Thr Asn Lys His Thr Leu Thr Lys Ile Tyr Asn Pro
    210                 215                 220
Lys Leu Asn Val Ser Glu Val Thr Leu Glu Leu Tyr Tyr Glu Lys Gly
225                 230                 235                 240
Thr Gly Ser Ala Thr Phe Asp Asn Ile Ser Met Lys Ala Lys Gly Pro
                245                 250                 255
Lys Asp Ser Glu His Pro Gln Pro Val Thr Thr Gln Ile Glu Glu Ser
            260                 265                 270
Val Asn Thr Ala Leu Asn Lys Asn Tyr Val Phe Asn Lys Ala Asp Tyr
```

```
          275                 280                 285
Gln Tyr Thr Leu Thr Asn Pro Ser Leu Gly Lys Ile Val Gly Gly Ile
     290                 295                 300
Leu Tyr Pro Asn Ala Thr Gly Ser Thr Thr Val Lys Ile Ser Asp Lys


305                 310                 315                 320
Ser Gly Lys Ile Ile Lys Glu Val Pro Leu Ser Val Thr Ala Ser Thr
                325                 330                 335
Glu Asp Lys Phe Thr Lys Leu Leu Asp Lys Trp Asn Asp Val Thr Ile
            340                 345                 350
Gly Asn His Val Tyr Asp Thr Asn Asp Ser Asn Met Gln Lys Ile Asn
        355                 360                 365
Gln Lys Leu Asp Glu Thr Asn Ala Lys Asn Ile Lys Thr Ile Lys Leu
    370                 375                 380
Asp Ser Asn His Thr Phe Leu Trp Lys Asp Leu Asp Asn Leu Asn Asn
385                 390                 395                 400
Ser Ala Gln Leu Thr Ala Thr Tyr Arg Arg Leu Glu Asp Leu Ala Lys
                405                 410                 415
Gln Ile Thr Asn Pro His Ser Thr Ile Tyr Lys Asn Glu Lys Ala Ile
            420                 425                 430
Arg Thr Val Lys Glu Ser Leu Ala Trp Leu His Gln Asn Phe Tyr Asn
        435                 440                 445
Val Asn Lys Asp Ile Glu Gly Ser Ala Asn Trp Trp Asp Phe Glu Ile
    450                 455                 460
Gly Val Pro Arg Ser Ile Thr Ala Thr Leu Ala Leu Met Asn Asn Tyr
465                 470                 475                 480
Phe Thr Asp Ala Glu Ile Lys Thr Tyr Thr Asp Pro Ile Glu His Phe
                485                 490                 495
Val Pro Asp Ala Gly Tyr Phe Arg Lys Thr Leu Asp Asn Pro Phe Lys
            500                 505                 510
Ala Leu Gly Gly Asn Leu Val Asp Met Gly Arg Val Lys Ile Ile Glu
        515                 520                 525
Gly Leu Leu Arg Lys Asp Asn Thr Ile Ile Glu Lys Thr Ser His Ser
    530                 535                 540
Leu Lys Asn Leu Phe Thr Thr Ala Thr Lys Ala Glu Gly Phe Tyr Ala
545                 550                 555                 560
Asp Gly Ser Tyr Ile Asp His Thr Asn Val Ala Tyr Thr Gly Ala Tyr
                565                 570                 575
Gly Asn Val Leu Ile Asp Gly Leu Thr Gln Leu Leu Pro Ile Ile Gln
            580                 585                 590
Glu Thr Asp Tyr Lys Ile Ser Asn Gln Glu Leu Asp Met Val Tyr Lys
        595                 600                 605
Trp Ile Asn Gln Ser Phe Leu Pro Leu Ile Val Lys Gly Glu Leu Met
    610                 615                 620
Asp Met Ser Arg Gly Arg Ser Ile Ser Arg Glu Ala Ala Ser Ser His
625                 630                 635                 640
Ala Ala Ala Val Glu Val Leu Arg Gly Phe Leu Arg Leu Ala Asn Met
                645                 650                 655
Ser Asn Glu Glu Arg Asn Leu Asp Leu Ile Ser Thr Ile Lys Thr Ile
            660                 665                 670
Ile Thr Ser Asn Lys Phe Tyr Asn Val Phe Asn Asn Leu Lys Ser Tyr
        675                 680                 685
Ser Asp Ile Ala Asn Met Asn Lys Met Leu Asn Asp Ser Thr Val Ala
    690                 695                 700
Thr Lys Pro Leu Lys Ser Asn Leu Ser Thr Phe Asn Ser Met Asp Arg
705                 710                 715                 720
Leu Ala Tyr Tyr Asn Ala Glu Lys Asp Phe Gly Phe Ala Leu Ser Leu
                725                 730                 735
His Ser Lys Arg Thr Leu Asn Tyr Glu Gly Met Asn Asp Glu Asn Thr
            740                 745                 750
Arg Gly Trp Tyr Thr Gly Asp Gly Met Phe Tyr Leu Tyr Asn Ser Asp
        755                 760                 765
Gln Ser His Tyr Ser Asn His Phe Trp Pro Thr Val Asn Pro Tyr Lys
    770                 775                 780
```

```
Met Ala Gly Thr Thr Glu Lys Asp Ala Lys Arg Glu Asp Thr Thr Lys
785                 790                 795                 800
Glu Phe Met Ser Lys His Ser Lys Asp Ala Lys Glu Lys Thr Gly Gln
                805                 810                 815
Val Thr Gly Thr Ser Asp Phe Val Gly Ser Val Lys Leu Asn Asp His
            820                 825                 830
Phe Ala Leu Ala Ala Met Asp Phe Thr Asn Trp Asp Arg Thr Leu Thr
        835                 840                 845
Ala Gln Lys Gly Trp Val Ile Leu Asn Asp Lys Ile Val Phe Leu Gly
    850                 855                 860
Ser Asn Ile Lys Asn Thr Asn Gly Ile Gly Asn Val Ser Thr Thr Ile
865                 870                 875                 880
Asp Gln Arg Lys Asp Asp Ser Lys Thr Pro Tyr Thr Thr Tyr Val Asn
                885                 890                 895
Gly Lys Thr Ile Asp Leu Lys Gln Ala Ser Ser Gln Gln Phe Thr Asp
            900                 905                 910
Thr Lys Ser Val Phe Leu Glu Ser Lys Glu Pro Gly Arg Asn Ile Gly
        915                 920                 925
Tyr Ile Phe Phe Lys Asn Ser Thr Ile Asp Ile Glu Arg Lys Glu Gln
    930                 935                 940
Thr Gly Thr Trp Asn Ser Ile Asn Arg Thr Ser Lys Asn Thr Ser Ile
945                 950                 955                 960
Val Ser Asn Pro Phe Ile Thr Ile Ser Gln Lys His Asp Asn Lys Gly
                965                 970                 975
Asp Ser Tyr Gly Tyr Met Met Val Pro Asn Ile Asp Arg Thr Ser Phe
            980                 985                 990
Asp Lys Leu Ala Asn Ser Lys Glu Val Glu Leu Leu Glu Asn Ser Ser
        995                 1000                1005
Lys Gln Gln Val Ile Tyr Asp Lys Asn Ser Gln Thr Trp Ala Val Ile
    1010                1015                1020
Lys His Asp Asn Gln Glu Ser Leu Ile Asn Asn Gln Phe Lys Met Asn
1025                1030                1035                1040
Lys Ala Gly Leu Tyr Leu Val Gln Lys Val Gly Asn Asp Tyr Gln Asn
                1045                1050                1055
Val Tyr Tyr Gln Pro Gln Thr Met Thr Lys Thr Asp Gln Leu Ala Ile
            1060                1065                1070
```

<210> 280
<211> 1081
<212> PRT
<213> 無乳鏈球菌血清型Ia

<220>
<223> 玻尿酸解離酶

<400> 280

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

```
Ser Pro Ile Ile Gln Arg Thr Glu Gln Gly Gln Val Ser Leu Ser Ser
145                 150                 155                 160
Asp Lys Gly Phe Arg Gly Ala Val Thr Gln Lys Val Asn Ile Asp Pro
                165                 170                 175
Thr Lys Lys Tyr Glu Val Lys Phe Asp Ile Glu Thr Ser Asn Lys Val
            180                 185                 190
Gly Gln Ala Phe Leu Arg Ile Met Lys Lys Lys Asp Lys Asn Thr Arg
        195                 200                 205
Leu Trp Leu Ser Glu Met Thr Ser Gly Thr Thr Asn Lys His Thr Leu
    210                 215                 220
Thr Lys Ile Tyr Asn Pro Lys Leu Asn Val Ser Glu Val Thr Leu Glu
225                 230                 235                 240
Leu Tyr Tyr Glu Lys Gly Thr Gly Ser Val Thr Phe Asp Asn Ile Ser
                245                 250                 255
Met Lys Ala Lys Gly Pro Lys Asp Ser Glu His Pro Gln Pro Val Thr
            260                 265                 270
Thr Gln Ile Glu Glu Ser Val Asn Thr Ala Leu Asn Lys Asn Tyr Val
        275                 280                 285
Phe Asn Lys Ala Asp Tyr Gln Tyr Thr Leu Thr Asn Pro Ser Leu Gly
    290                 295                 300
Lys Ile Val Gly Gly Ile Leu Tyr Pro Ser Ala Thr Gly Ser Thr Thr
305                 310                 315                 320
Val Lys Ile Ser Asp Lys Ser Gly Lys Ile Ile Lys Glu Val Pro Leu
                325                 330                 335
Ser Val Thr Ala Ser Thr Glu Asp Asn Phe Thr Lys Leu Leu Asp Lys
            340                 345                 350
Trp Asn Asp Val Thr Ile Gly Asn His Val Tyr Asp Thr Asn Asp Ser
        355                 360                 365
Asn Met Gln Lys Leu Asn Gln Lys Leu Asp Glu Thr Asn Ala Lys Asn
    370                 375                 380
Ile Lys Asp Ile Lys Leu Asp Ser Asn Arg Thr Phe Leu Trp Glu Asp
385                 390                 395                 400
Leu Lys Gly Leu Asn Asn Ser Ala Gln Leu Thr Ala Thr Tyr Arg Arg
                405                 410                 415
Leu Glu Asp Leu Ala Lys Gln Ile Thr Asn Pro His Ser Thr Ile Tyr
            420                 425                 430
Lys Asn Glu Lys Ala Ile Arg Thr Val Lys Glu Ser Leu Ala Trp Leu
        435                 440                 445
His Gln Asn Phe Tyr Asn Val Asn Lys Asp Ile Glu Gly Ser Ala Asn
    450                 455                 460
Trp Trp Asp Phe Glu Ile Gly Val Pro Arg Ser Ile Thr Ala Thr Leu
465                 470                 475                 480
Ala Leu Met Asn Asn Tyr Phe Thr Asp Ala Glu Ile Lys Thr Tyr Thr
                485                 490                 495
Asp Pro Ile Glu His Phe Val Pro Asp Ala Gly Tyr Phe Arg Lys Thr
            500                 505                 510
Leu Val Asn Pro Phe Lys Ala Leu Gly Gly Asn Leu Val Asp Met Gly
        515                 520                 525
Arg Val Lys Ile Ile Glu Gly Leu Leu Arg Lys Asp Asn Thr Ile Ile
    530                 535                 540
Lys Lys Thr Ser His Ser Leu Lys Asn Leu Phe Thr Thr Ala Thr Lys
545                 550                 555                 560
Ala Glu Gly Phe Tyr Ala Asp Gly Ser Tyr Ile Asp His Thr Asn Val
                565                 570                 575
Ala Tyr Thr Gly Ala Tyr Gly Asn Val Leu Ile Asp Gly Leu Thr Gln
            580                 585                 590
Leu Leu Pro Ile Ile Gln Glu Thr Asp Tyr Lys Ile Ser Asn Gln Glu
        595                 600                 605
Leu Asp Met Val Tyr Lys Trp Ile Asn Gln Ser Phe Leu Pro Leu Ile
    610                 615                 620
Val Lys Gly Glu Leu Met Asp Met Ser Arg Gly Arg Ser Ile Ser Arg
625                 630                 635                 640
Glu Ala Ala Ser Ser His Ala Ala Ala Val Glu Val Leu Arg Gly Phe
                645                 650                 655
Leu Arg Leu Ala Asn Met Ser Asn Glu Glu Arg Asn Leu Asp Leu Lys
```

660 665 670
Ser Thr Ile Lys Thr Ile Ile Thr Ser Asn Lys Phe Tyr Asn Val Phe
675 680 685
Asn Asn Leu Lys Ser Tyr Ser Asp Ile Ala Asn Met Asn Lys Leu Leu
690 695 700
Asn Asp Ser Thr Val Ala Thr Lys Pro Leu Lys Ser Asn Leu Ser Thr
705 710 715 720
Phe Asn Ser Met Asp Arg Leu Ala Tyr Tyr Asn Ala Glu Lys Asp Phe
725 730 735
Gly Phe Ala Leu Ser Leu His Ser Lys Arg Thr Leu Asn Tyr Glu Gly
740 745 750
Met Asn Asp Glu Asn Thr Arg Gly Trp Tyr Thr Gly Asp Gly Met Phe
755 760 765
Tyr Leu Tyr Asn Ser Asp Gln Ser His Tyr Ser Asn His Phe Trp Pro
770 775 780
Thr Val Asn Pro Tyr Lys Met Ala Gly Thr Thr Glu Lys Asp Thr Gly
785 790 795 800
Arg Glu Asp Thr Ile Lys Lys Leu Met Asn Arg Tyr Asp Lys Thr Asn
805 810 815
Lys Asn Ser Lys Val Met Thr Gly Gln Val Thr Gly Thr Ser Asp Phe
820 825 830
Val Gly Ser Val Lys Leu Asn Asp His Phe Ala Leu Ala Ala Met Asp
835 840 845
Phe Thr Asn Trp Asp Arg Thr Leu Thr Ala Gln Lys Gly Trp Val Ile
850 855 860
Leu Asn Asp Lys Ile Val Phe Leu Gly Ser Asn Ile Lys Asn Thr Asn
865 870 875 880
Gly Val Gly Asn Val Ser Thr Thr Ile Asp Gln Arg Lys Asp Asp Ser
885 890 895
Lys Thr Pro Tyr Thr Thr Tyr Val Asn Gly Lys Thr Val Asp Leu Lys
900 905 910
Gln Ala Ser Ser Gln Gln Phe Thr Asp Thr Lys Ser Val Phe Leu Glu
915 920 925
Ser Lys Glu Pro Gly Arg Asn Ile Gly Tyr Ile Phe Phe Lys Asn Ser
930 935 940
Thr Ile Asp Ile Glu Arg Lys Glu Gln Thr Gly Thr Trp Asn Ser Ile
945 950 955 960
Asn Arg Thr Ser Lys Asn Thr Ser Ile Val Ser Asn Pro Phe Ile Thr
965 970 975
Ile Ser Gln Lys His Asp Asn Lys Gly Asp Ser Tyr Gly Tyr Met Met
980 985 990
Val Pro Asn Ile Asp Arg Thr Ser Phe Asp Lys Leu Ala Asn Ser Lys
995 1000 1005
Glu Val Glu Leu Leu Glu Asn Ser Ser Lys Gln Gln Val Ile Tyr Asp
1010 1015 1020
Lys Asn Ser Gln Thr Trp Ala Val Ile Lys His Asp Asn Gln Glu Ser
1025 1030 1035 1040
Leu Ile Asn Asn Gln Phe Lys Met Asn Lys Ala Gly Leu Tyr Leu Val
1045 1050 1055
Gln Lys Val Gly Asn Asp Tyr Gln Asn Val Tyr Tyr Gln Pro Gln Thr
1060 1065 1070
Met Thr Lys Thr Asp Gln Leu Ala Ile
1075 1080

<210> 281
<211> 984
<212> PRT
<213> 無乳鏈球菌血清型III

<220>
<223> 玻尿酸解離酶

<400> 281
Met Lys Gln Val Val Asp Asn Gln Thr Gln Asn Lys Glu Leu Val Lys

```
 1               5                  10                  15
Asn Gly Asp Phe Asn Gln Thr Asn Pro Val Ser Gly Ser Trp Ser His
            20                  25                  30
Thr Ser Ala Arg Glu Trp Ser Ala Trp Ile Asp Lys Glu Asn Thr Ala
        35                  40                  45
Asp Lys Ser Pro Ile Ile Gln Arg Thr Glu Gln Gly Gln Val Ser Leu
    50                  55                  60
Ser Ser Asp Lys Gly Phe Arg Gly Ala Val Thr Gln Lys Val Asn Ile
65                  70                  75                  80
Asp Pro Thr Lys Lys Tyr Glu Val Lys Phe Asp Ile Glu Thr Ser Asn
                85                  90                  95
Lys Ala Gly Gln Ala Phe Leu Arg Ile Met Glu Lys Lys Asp Asn Asn
            100                 105                 110
Thr Arg Leu Trp Leu Ser Glu Met Thr Ser Gly Thr Thr Asn Lys His
        115                 120                 125
Thr Leu Thr Lys Ile Tyr Asn Pro Lys Leu Asn Val Ser Glu Val Thr
    130                 135                 140
Leu Glu Leu Tyr Tyr Glu Lys Gly Thr Gly Ser Ala Thr Phe Asp Asn
145                 150                 155                 160
Ile Ser Met Lys Ala Lys Gly Pro Lys Asp Ser Glu His Pro Gln Pro
                165                 170                 175
Val Thr Thr Gln Ile Glu Glu Ser Val Asn Thr Ala Leu Asn Lys Asn
            180                 185                 190
Tyr Val Phe Asn Lys Ala Asp Tyr Gln Tyr Thr Leu Thr Asn Pro Ser
        195                 200                 205
Leu Gly Lys Ile Val Gly Gly Ile Leu Tyr Pro Asn Ala Thr Gly Ser
    210                 215                 220
Thr Thr Val Lys Ile Ser Asp Lys Ser Gly Lys Ile Ile Lys Glu Val
225                 230                 235                 240
Pro Leu Ser Val Thr Ala Ser Thr Glu Asp Lys Phe Thr Lys Leu Leu
                245                 250                 255
Asp Lys Trp Asn Asp Val Thr Ile Gly Asn His Val Tyr Asp Thr Asn
            260                 265                 270
Asp Ser Asn Met Gln Lys Ile Asn Gln Lys Leu Asp Glu Thr Asn Ala
        275                 280                 285
Lys Asn Ile Lys Thr Ile Lys Leu Asp Ser Asn His Thr Phe Leu Trp
    290                 295                 300
Lys Asp Leu Asp Asn Leu Asn Asn Ser Ala Gln Leu Thr Ala Thr Tyr
305                 310                 315                 320
Arg Arg Leu Glu Asp Leu Ala Lys Gln Ile Thr Asn Pro His Ser Thr
                325                 330                 335
Ile Tyr Lys Asn Glu Lys Ala Ile Arg Thr Val Lys Glu Ser Leu Ala
            340                 345                 350
Trp Leu His Gln Asn Phe Tyr Asn Val Asn Lys Asp Ile Glu Gly Ser
        355                 360                 365
Ala Asn Trp Trp Asp Phe Glu Ile Gly Val Pro Arg Ser Ile Thr Ala
    370                 375                 380
Thr Leu Ala Leu Met Asn Asn Tyr Phe Thr Asp Ala Glu Ile Lys Thr
385                 390                 395                 400
Tyr Thr Asp Pro Ile Glu His Phe Val Pro Asp Ala Gly Tyr Phe Arg
                405                 410                 415
Lys Thr Leu Asp Asn Pro Phe Lys Ala Leu Gly Gly Asn Leu Val Asp
            420                 425                 430
Met Gly Arg Val Lys Ile Ile Glu Gly Leu Leu Arg Lys Asp Asn Thr
        435                 440                 445
Ile Ile Glu Lys Thr Ser His Ser Leu Lys Asn Leu Phe Thr Thr Ala
    450                 455                 460
Thr Lys Ala Glu Gly Phe Tyr Ala Asp Gly Ser Tyr Ile Asp His Thr
465                 470                 475                 480
Asn Val Ala Tyr Thr Gly Ala Tyr Gly Asn Val Leu Ile Asp Gly Leu
                485                 490                 495
Thr Gln Leu Leu Pro Ile Ile Gln Glu Thr Asp Tyr Lys Ile Ser Asn
            500                 505                 510
Gln Glu Leu Asp Met Val Tyr Lys Trp Ile Asn Gln Ser Phe Leu Pro
        515                 520                 525
```

```
Leu Ile Val Lys Gly Glu Leu Met Asp Met Ser Arg Gly Arg Ser Ile
    530                 535                 540
Ser Arg Glu Ala Ala Ser Ser His Ala Ala Ala Val Glu Val Leu Arg
545                 550                 555                 560
Gly Phe Leu Arg Leu Ala Asn Met Ser Asn Glu Glu Arg Asn Leu Asp
                565                 570                 575
Leu Lys Ser Thr Ile Lys Thr Ile Ile Thr Ser Asn Lys Phe Tyr Asn
            580                 585                 590
Val Phe Asn Asn Leu Lys Ser Tyr Ser Asp Ile Ala Asn Met Asn Lys
        595                 600                 605
Met Leu Asn Asp Ser Thr Val Ala Thr Lys Pro Leu Lys Ser Asn Leu
    610                 615                 620
Ser Thr Phe Asn Ser Met Asp Arg Leu Ala Tyr Tyr Asn Ala Glu Lys
625                 630                 635                 640
Asp Phe Gly Phe Ala Leu Ser Leu His Ser Lys Arg Thr Leu Asn Tyr
                645                 650                 655
Glu Gly Met Asn Asp Glu Asn Thr Arg Asp Trp Tyr Thr Gly Asp Gly
            660                 665                 670
Met Phe Tyr Leu Tyr Asn Ser Asp Gln Ser His Tyr Ser Asn His Phe
        675                 680                 685
Trp Pro Thr Val Asn Pro Tyr Lys Met Ala Gly Thr Thr Glu Lys Asp
    690                 695                 700
Ala Lys Arg Glu Asp Thr Thr Lys Glu Phe Met Ser Lys His Ser Lys
705                 710                 715                 720
Asp Ala Lys Glu Lys Thr Gly Gln Val Thr Gly Thr Ser Asp Phe Val
                725                 730                 735
Gly Ser Val Lys Leu Asn Asp His Phe Ala Leu Ala Ala Met Asp Phe
            740                 745                 750
Thr Asn Trp Asp Arg Thr Leu Thr Ala Gln Lys Gly Trp Val Ile Leu
        755                 760                 765
Asn Asp Lys Ile Val Phe Leu Gly Ser Asn Ile Lys Asn Thr Asn Gly
    770                 775                 780
Ile Gly Asn Val Ser Thr Thr Ile Asp Gln Arg Lys Asp Asp Ser Lys
785                 790                 795                 800
Thr Pro Tyr Thr Thr Tyr Val Asn Gly Lys Thr Ile Asp Leu Lys Gln
                805                 810                 815

Ala Ser Ser Gln Gln Phe Thr Asp Thr Lys Ser Val Phe Leu Glu Ser
            820                 825                 830
Lys Glu Pro Gly Arg Asn Ile Gly Tyr Ile Phe Phe Lys Asn Ser Thr
        835                 840                 845

Ile Asp Ile Glu Arg Lys Glu Gln Thr Gly Thr Trp Asn Ser Ile Asn
    850                 855                 860
Arg Thr Ser Lys Asn Thr Ser Ile Val Ser Asn Pro Phe Ile Thr Ile
865                 870                 875                 880
Ser Gln Lys His Asp Asn Lys Gly Asp Ser Tyr Gly Tyr Met Met Val
                885                 890                 895
Pro Asn Ile Asp Arg Thr Ser Phe Asp Lys Leu Ala Asn Ser Lys Glu
            900                 905                 910
Val Glu Leu Leu Glu Asn Ser Ser Lys Gln Gln Val Ile Tyr Asp Lys
        915                 920                 925
Asn Ser Gln Thr Trp Ala Val Ile Lys His Asp Asn Gln Glu Ser Leu
    930                 935                 940
Ile Asn Asn Gln Phe Lys Met Asn Lys Ala Gly Leu Tyr Leu Val Gln
945                 950                 955                 960
Lys Val Gly Asn Asp Tyr Gln Asn Val Tyr Tyr Gln Pro Gln Thr Met
                965                 970                 975
Thr Lys Thr Asp Gln Leu Ala Ile
            980
```

<210> 282
<211> 807
<212> PRT

<213> 金黃色葡萄球菌(菌株COL)

<220>
<223> 玻尿酸解離酶

<400> 282

```
Met Thr Tyr Arg Ile Lys Lys Trp Gln Lys Leu Ser Thr Ile Thr Leu
 1               5                  10                  15
Leu Met Ala Gly Val Ile Thr Leu Asn Gly Gly Glu Phe Arg Ser Val
            20                  25                  30
Asp Lys His Gln Ile Ala Val Ala Asp Thr Asn Val Gln Thr Pro Asp
        35                  40                  45
Tyr Glu Lys Leu Arg Asn Thr Trp Leu Asp Val Asn Tyr Gly Tyr Asp
    50                  55                  60
Lys Tyr Asp Glu Asn Asn Pro Asp Met Lys Lys Lys Phe Asp Ala Thr
65                  70                  75                  80
Glu Lys Glu Ala Thr Asn Leu Leu Lys Glu Met Lys Thr Glu Ser Gly
                85                  90                  95
Arg Lys Tyr Leu Trp Ser Gly Ala Glu Thr Leu Glu Thr Asn Ser Ser
            100                 105                 110
His Met Thr Arg Thr Tyr Arg Asn Ile Glu Lys Ile Ala Glu Ala Met
        115                 120                 125
Arg Asn Pro Lys Thr Thr Leu Asn Thr Asp Glu Asn Lys Lys Lys Val
    130                 135                 140
Lys Asp Ala Leu Glu Trp Leu His Lys Asn Ala Tyr Gly Lys Glu Pro
145                 150                 155                 160
Asp Lys Lys Val Lys Glu Leu Ser Glu Asn Phe Thr Lys Thr Thr Gly
                165                 170                 175
Lys Asn Thr Asn Leu Asn Trp Trp Asp Tyr Glu Ile Gly Thr Pro Lys
            180                 185                 190
Ser Leu Thr Asn Thr Leu Ile Leu Leu Asn Asp Gln Phe Ser Asn Glu
        195                 200                 205
Glu Lys Lys Lys Phe Thr Ala Pro Ile Lys Thr Phe Ala Pro Asp Ser
    210                 215                 220
Asp Lys Ile Leu Ser Ser Val Gly Lys Ala Glu Leu Ala Lys Gly Gly
225                 230                 235                 240
Asn Leu Val Asp Ile Ser Lys Val Lys Leu Leu Glu Cys Ile Ile Glu
                245                 250                 255
Glu Asp Lys Asp Met Met Lys Lys Ser Ile Asp Ser Phe Asn Lys Val
            260                 265                 270
Phe Thr Tyr Val Gln Asp Ser Ala Thr Gly Lys Glu Arg Asn Gly Phe
        275                 280                 285
Tyr Lys Asp Gly Ser Tyr Ile Asp His Gln Asp Val Pro Tyr Thr Gly
    290                 295                 300
Ala Tyr Gly Val Val Leu Leu Glu Gly Ile Ser Gln Met Met Pro Met
305                 310                 315                 320
Ile Lys Glu Thr Pro Phe Asn Asp Lys Thr Gln Asn Asp Thr Thr Leu
                325                 330                 335
Lys Ser Trp Ile Asp Asp Gly Phe Met Pro Leu Ile Tyr Lys Gly Glu
            340                 345                 350
Met Met Asp Leu Ser Arg Gly Arg Ala Ile Ser Arg Glu Asn Glu Thr
        355                 360                 365
Ser His Ser Ala Ser Ala Thr Val Met Lys Ser Leu Leu Arg Leu Ser
    370                 375                 380
Asp Ala Met Asp Asp Ser Thr Lys Ala Lys Tyr Lys Lys Ile Val Lys
385                 390                 395                 400
Ser Ser Val Glu Ser Asp Ser Ser Tyr Lys Gln Asn Asp Tyr Leu Asn
                405                 410                 415
Ser Tyr Ser Asp Ile Asp Lys Met Lys Ser Leu Met Thr Asp Asn Ser
            420                 425                 430
Ile Ser Lys Asn Gly Leu Thr Gln Gln Leu Lys Ile Tyr Asn Asp Met
        435                 440                 445
Asp Arg Val Thr Tyr His Asn Lys Asp Leu Asp Phe Ala Phe Gly Leu
    450                 455                 460
Ser Met Thr Ser Lys Asn Val Ala Arg Tyr Glu Ser Ile Asn Gly Glu
```

```
465                 470                 475                 480
Asn Leu Lys Gly Trp His Thr Gly Ala Gly Met Ser Tyr Leu Tyr Asn
                485                 490                 495
Ser Asp Val Lys His Tyr His Asp Asn Phe Trp Val Thr Ala Asp Met
            500                 505                 510
Lys Arg Leu Ser Gly Thr Thr Thr Leu Asp Asn Glu Ile Leu Lys Asp
        515                 520                 525
Thr Asp Asp Lys Lys Ser Ser Lys Thr Phe Val Gly Gly Thr Lys Val
    530                 535                 540
Asp Asp Gln His Ala Ser Ile Gly Met Asp Phe Glu Asn Gln Asp Lys
545                 550                 555                 560
Thr Leu Thr Ala Lys Lys Ser Tyr Phe Ile Leu Asn Asp Lys Ile Val
                565                 570                 575
Phe Leu Gly Thr Gly Ile Lys Ser Thr Asp Ser Ser Lys Asn Pro Val
            580                 585                 590
Thr Thr Ile Glu Asn Arg Lys Ala Asn Gly Tyr Thr Leu Tyr Thr Asp
        595                 600                 605
Asp Lys Gln Thr Thr Asn Ser Asp Asn Gln Glu Asn Asn Ser Val Phe
    610                 615                 620
Leu Glu Ser Thr Asp Thr Lys Lys Asn Ile Gly Tyr His Phe Leu Asn
625                 630                 635                 640
Lys Pro Lys Ile Thr Val Lys Lys Glu Ser His Thr Gly Lys Trp Lys
                645                 650                 655
Glu Ile Asn Lys Ser Gln Lys Asp Thr Gln Lys Thr Asp Glu Tyr Tyr
            660                 665                 670
Glu Val Thr Gln Lys His Ser Asn Ser Asp Asn Lys Tyr Gly Tyr Val
        675                 680                 685
Leu Tyr Pro Gly Leu Ser Lys Asp Val Phe Lys Thr Lys Lys Asp Glu
    690                 695                 700
Val Thr Val Val Lys Gln Glu Asp Asp Phe His Val Val Lys Asp Asn
705                 710                 715                 720
Glu Ser Val Trp Ala Gly Val Asn Tyr Ser Asn Ser Thr Gln Thr Phe
                725                 730                 735
Asp Ile Asn Asn Thr Lys Val Glu Val Lys Ala Lys Gly Met Phe Ile
            740                 745                 750
Leu Lys Lys Lys Asp Asp Asn Thr Tyr Glu Cys Ser Phe Tyr Asn Pro
        755                 760                 765
Glu Ser Thr Asn Ser Ala Ser Asp Ile Glu Ser Lys Ile Ser Met Thr
    770                 775                 780
Gly Tyr Ser Ile Thr Asn Lys Asn Thr Ser Thr Ser Asn Glu Ser Gly
785                 790                 795                 800
Val His Phe Glu Leu Thr Lys
                805
```

<210> 283
<211> 420
<212> PRT
<213> 金黃色葡萄球菌(菌株MRSA252)

<220>
<223> 玻尿酸解離酶

<400> 283

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

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

<210> 284
<211> 806
<212> PRT
<213> 金黃色葡萄球菌(菌株MRSA252)

<220>
<223> 玻尿酸解離酶

<400> 284

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

```
                85                  90                  95
Arg Thr Tyr Leu Trp Ser Gly Ala Glu Asn Leu Glu Thr Asn Ser Ser
            100                 105                 110
His Met Thr Lys Thr Tyr Arg Asn Ile Glu Lys Ile Ala Glu Ser Met
        115                 120                 125
Gln His Lys Asn Thr Val Leu Lys Thr Val Glu Asn Lys Leu Lys Ile
    130                 135                 140
Lys Glu Ala Leu Asp Trp Met His Lys Asn Val Tyr Gly Lys Asn Pro
145                 150                 155                 160
Ser Gln Lys Val Glu Asp Leu Thr Lys Asn Arg Lys Gly Gln Thr Thr
                165                 170                 175
Pro Lys Asn Asn Ser Leu Asn Trp Trp Asp Tyr Glu Ile Gly Thr Pro
            180                 185                 190
Arg Ala Leu Thr Asn Thr Leu Leu Leu Met Asp Asp Met Leu Thr Lys
        195                 200                 205
Asp Glu Met Lys Asn Tyr Ser Lys Pro Ile Ser Thr Tyr Ala Pro Ser
    210                 215                 220
Ser Asp Lys Ile Leu Ser Ser Val Gly Glu Ser Glu Asp Ala Lys Gly
225                 230                 235                 240
Gly Asn Leu Val Asp Ile Ser Lys Val Lys Leu Leu Glu Ser Val Ile
                245                 250                 255
Glu Glu Asp Val Asp Met Leu Lys Lys Ser Ile Asp Ser Phe Asn Lys
            260                 265                 270
Val Phe Thr Tyr Val Gln Asp Ser Ala Thr Gly Lys Gly Arg Asn Gly
        275                 280                 285
Phe Tyr Lys Asp Gly Ser Tyr Ile Asp His Gln Asp Val Pro Tyr Thr
    290                 295                 300
Gly Ala Tyr Gly Val Val Leu Leu Glu Gly Ile Ser Gln Met Met Pro
305                 310                 315                 320
Met Ile Lys Glu Ser Pro Phe Lys Thr Thr Gln Asp Asn Ala Thr Leu
                325                 330                 335
Ser Asn Trp Ile Asp Glu Gly Phe Met Pro Leu Ile Tyr Lys Gly Glu
            340                 345                 350
Met Met Asp Leu Ser Arg Gly Arg Ala Ile Ser Arg Glu Asn Glu Thr
        355                 360                 365
Ser His Thr Ala Ser Ala Thr Val Met Lys Ser Leu Leu Arg Leu Asn
    370                 375                 380
Asp Thr Met Asp Asp Ser Thr Lys Thr Arg Tyr Lys Gln Ile Val Lys
385                 390                 395                 400
Thr Ser Val Asn Ser Asp Ser Ser Tyr Asn Gln Asn Asn Tyr Leu Asn
                405                 410                 415
Ser Tyr Ser Asp Ile Ala Lys Met Lys Lys Leu Met Asn Asp Ser Thr
            420                 425                 430
Ile Ser Lys Asn Asp Leu Thr Gln Gln Leu Lys Ile Tyr Asn Asp Met
        435                 440                 445
Asp Arg Val Thr Tyr His Asn Lys Asp Leu Asp Phe Ala Phe Gly Leu
    450                 455                 460
Ser Met Thr Ser Lys Asn Ile Ala Arg Tyr Glu Asn Ile Asn Gly Glu
465                 470                 475                 480
Asn Leu Lys Gly Trp His Thr Gly Ala Gly Met Ser Tyr Leu Tyr Asn
                485                 490                 495
Ser Asp Val Lys His Tyr Arg Asp Asn Phe Trp Ala Thr Ala Asp Met
            500                 505                 510
Thr Cys Leu Pro Gly Thr Thr Thr Leu Asn Asp Met Pro Ser Thr Asn
        515                 520                 525
Thr Lys Asn Asp Lys Ser Phe Val Gly Gly Thr Lys Leu Asn Asn Lys
    530                 535                 540
Tyr Ala Ser Ile Gly Met Asp Phe Glu Asn Gln Asp Lys Thr Leu Thr
545                 550                 555                 560
Ala Lys Lys Ser Tyr Phe Ile Leu Asn Asp Lys Ile Val Phe Leu Gly
                565                 570                 575
Thr Gly Ile Lys Ser Thr Asp Ser Ser Lys Asn Pro Val Thr Ser Val
            580                 585                 590
Glu Asn Arg Lys Ala Asn Gly Tyr Lys Leu Phe Lys Asp Asp Ile Glu
        595                 600                 605
```

```
Ile Thr Thr Ser Asp Val Asn Ala Gln Glu Thr His Ser Val Phe Leu
    610                 615                 620
Glu Ser Asn Asp Thr Lys Lys Asn Ile Gly Tyr His Phe Leu Asp Lys
625                 630                 635                 640
Pro Lys Ile Thr Val Lys Lys Glu Ser His Thr Gly Lys Trp Ser Glu
                645                 650                 655
Ile Asn Lys Ser Gln Lys Lys Asp Asp Lys Lys Asp Glu Tyr Tyr Glu
            660                 665                 670
Val Thr Gln Thr His Asn Thr Ser Asp Ser Lys Tyr Ala Tyr Val Leu
        675                 680                 685
Tyr Pro Gly Leu Ser Lys Ser Asp Phe Lys Ser Lys Asn Asn Asn Val
    690                 695                 700
Ser Ile Val Lys Gln Asp Glu Asp Phe His Val Ile Lys Asp Asn Asp
705                 710                 715                 720
Gly Val Phe Ala Gly Val Asn Tyr Ser Asp Asn Thr Lys Ser Phe Asp
                725                 730                 735
Ile Asn Gly Ile Thr Val Glu Leu Lys Glu Lys Gly Met Phe Val Ile
            740                 745                 750
Lys Lys Lys Asp Asp Lys Ala Tyr Lys Cys Ser Phe Tyr Asn Pro Glu
        755                 760                 765
Thr Thr Asn Thr Ala Ser Asn Ile Glu Ser Lys Ile Phe Ile Lys Gly
    770                 775                 780
Tyr Thr Ile Thr Asn Lys Ser Val Ile Asn Ser Asn Asp Ala Gly Val
785                 790                 795                 800
Asn Phe Glu Leu Thr Lys
                805
```

<210> 285
<211> 815
<212> PRT
<213> 金黃色葡萄球菌(菌株MSSA476)

<220>
<223> 玻尿酸解離酶

<400> 285

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

```
Asp Lys Ile Leu Ser Ser Val Gly Gln Pro Glu Gln Ala Lys Gly Gly
225                 230                 235                 240
Asn Leu Val Asp Ile Ala Lys Val Lys Leu Leu Glu Ser Ile Ile Glu
                245                 250                 255
Glu Asp Lys Asp Ile Thr Lys Asn Ser Ile Asp Ala Phe Asn Lys Val
            260                 265                 270
Phe Thr Tyr Val Gln Ser Asn Ala Thr Gly Lys Glu Arg Asn Gly Phe
        275                 280                 285
Tyr Lys Asp Gly Ser Tyr Ile Asp His Gln Asp Val Pro Tyr Thr Gly
    290                 295                 300
Ala Tyr Gly Val Val Leu Leu Glu Gly Ile Ser Gln Met Met Pro Met
305                 310                 315                 320
Ile Lys Glu Thr Pro Phe Asn Asp Lys Thr Gln Asn Asp Thr Thr Leu
                325                 330                 335
Lys Ser Trp Ile Asp Asp Gly Phe Met Pro Leu Ile Tyr Lys Gly Glu
            340                 345                 350
Met Met Asp Leu Ser Arg Gly Arg Ala Ile Ser Arg Glu Asn Glu Thr
        355                 360                 365
Ser His Thr Ala Ser Ala Thr Val Met Lys Ser Leu Leu Arg Leu Ser
    370                 375                 380
Asp Ala Met Asp Asp Ser Thr Lys Ala Lys Tyr Lys Gln Ile Val Lys
385                 390                 395                 400
Thr Ser Val Lys Ser Asp Ser Ser Tyr Gly Gln Asn Asp Thr Leu Ser
                405                 410                 415
Ser Tyr Ser Asp Ile Ser Lys Met Lys Ser Leu Met Glu Asp Ser Thr
            420                 425                 430
Ile Ser Thr Asn Gly Leu Thr Gln Gln Leu Lys Ile Tyr Asn Asp Met
        435                 440                 445
Asp Arg Val Thr Tyr His Asn Lys Asp Leu Asp Phe Ala Phe Gly Leu
    450                 455                 460
Ser Met Thr Ser Lys Asn Val Ala Arg Tyr Glu Ser Ile Asn Gly Glu
465                 470                 475                 480
Asn Leu Lys Gly Trp His Thr Gly Ala Gly Met Ser Tyr Leu Tyr Asn
                485                 490                 495
Ser Asp Val Lys His Tyr Arg Asp Asn Phe Trp Ala Thr Ala Asp Met
            500                 505                 510
Lys Arg Leu Ala Gly Thr Thr Thr Leu Glu Asn Glu Glu Pro Lys Gly
        515                 520                 525
Thr Asp Val Lys Lys Ser Ser Lys Thr Phe Val Gly Gly Thr Lys Phe
    530                 535                 540
Asp Asp Gln His Ala Ser Ile Gly Met Asp Phe Glu Asn Gln Asp Lys
545                 550                 555                 560
Thr Leu Thr Ala Lys Lys Ser Tyr Phe Ile Leu Asn Asp Lys Ile Val
                565                 570                 575
Phe Leu Gly Thr Gly Ile Lys Ser Thr Asp Ser Ser Lys Asn Pro Val
            580                 585                 590
Thr Thr Ile Glu Asn Arg Lys Ala Asn Gly Tyr Thr Leu Tyr Thr Asp
        595                 600                 605
Asp Lys Gln Thr Thr Ala Ser Asp Asn Gln Gly Thr Asn Ser Val Phe
    610                 615                 620
Leu Glu Ser Thr Asn Lys Pro Lys Asn Asn Ile Gly Tyr His Phe Leu
625                 630                 635                 640
Asn Glu Ser Lys Ile Thr Val Lys Lys Glu Ser His Thr Gly Lys Trp
                645                 650                 655
Ser Asp Ile Asn Lys Ser Gln Lys Gln Asp Ser Lys Thr Asn Gln Tyr
            660                 665                 670
Tyr Glu Val Thr Gln Lys His Ser Asn Thr Asp Ser Lys Tyr Ala Tyr
        675                 680                 685
Val Leu Tyr Pro Gly Leu Ser Lys Asp Asp Phe Asn Thr Lys Lys Asp
    690                 695                 700
Lys Val Thr Val Val Lys Gln Asp Asp Asp Phe His Val Val Lys Asp
705                 710                 715                 720
Asn Glu Ser Val Trp Ala Gly Val Asn Tyr Ser Asp Ser Thr Gln Thr
                725                 730                 735
Phe Ile Ile Asn Asn Thr Lys Val Glu Val Lys Ala Lys Gly Met Phe
```

```
            740                 745                 750
Ile Leu Lys Lys Lys Asp Asp Lys Thr Tyr Glu Cys Ser Phe Tyr Asn
        755                 760                 765
Pro Glu Ser Thr Asn Thr Ala Ser Asp Ile Glu Ser Lys Ile Ser Met
    770                 775                 780
Thr Gly Tyr Ser Ile Thr Asn Lys Asn Thr Ser Thr Ser Asn Glu Ser
785                 790                 795                 800
Gly Val Arg Phe Glu Leu Gln Gln Thr Leu Asn Lys Asp Asp Asn
                805                 810                 815
```

<210> 286
<211> 807
<212> PRT
<213> 金黃色葡萄球菌(菌株NCTC 8325)

<220>
<223> 玻尿酸解離酶

```
<400> 286
Met Thr Tyr Arg Ile Lys Lys Trp Gln Lys Leu Ser Thr Ile Thr Leu
 1               5                  10                  15
Leu Met Ala Gly Val Ile Thr Leu Asn Gly Gly Glu Phe Arg Ser Val
            20                  25                  30
Asp Lys His Gln Ile Ala Val Ala Asp Thr Asn Val Gln Thr Pro Asp
        35                  40                  45
Tyr Glu Lys Leu Arg Asn Thr Trp Leu Asp Val Asn Tyr Gly Tyr Asp
    50                  55                  60
Lys Tyr Asp Glu Asn Asn Pro Asp Met Lys Lys Lys Phe Asp Ala Thr
65                  70                  75                  80
Glu Lys Glu Ala Thr Asn Leu Leu Lys Glu Met Lys Thr Glu Ser Gly
                85                  90                  95
Arg Lys Tyr Leu Trp Ser Gly Ala Glu Thr Leu Glu Thr Asn Ser Ser
            100                 105                 110
His Met Thr Arg Thr Tyr Arg Asn Ile Glu Lys Ile Ala Glu Ala Met
        115                 120                 125
Arg Asn Pro Lys Thr Thr Leu Asn Thr Asp Glu Asn Lys Lys Lys Val
    130                 135                 140
Lys Asp Ala Leu Glu Trp Leu His Lys Asn Ala Tyr Gly Lys Glu Pro
145                 150                 155                 160
Asp Lys Lys Val Lys Glu Leu Ser Glu Asn Phe Thr Lys Thr Thr Gly
                165                 170                 175
Lys Asn Thr Asn Leu Asn Trp Trp Asp Tyr Glu Ile Gly Thr Pro Lys
            180                 185                 190
Ser Leu Thr Asn Thr Leu Ile Leu Leu Asn Asp Gln Phe Ser Asn Glu
        195                 200                 205
Glu Lys Lys Lys Phe Thr Ala Pro Ile Lys Thr Phe Ala Pro Asp Ser
    210                 215                 220
Asp Lys Ile Leu Ser Ser Val Gly Lys Ala Glu Leu Ala Lys Gly Gly
225                 230                 235                 240
Asn Leu Val Asp Ile Ser Lys Val Lys Leu Leu Glu Cys Ile Ile Glu
                245                 250                 255
Glu Asp Lys Asp Met Met Lys Lys Ser Ile Asp Ser Phe Asn Lys Val
            260                 265                 270
Phe Thr Tyr Val Gln Asp Ser Ala Thr Gly Lys Glu Arg Asn Gly Phe
        275                 280                 285
Tyr Lys Asp Gly Ser Tyr Ile Asp His Gln Asp Val Pro Tyr Thr Gly
    290                 295                 300
Ala Tyr Gly Val Val Leu Leu Glu Gly Ile Ser Gln Met Met Pro Met
305                 310                 315                 320
Ile Lys Glu Thr Pro Phe Asn Asp Lys Thr Gln Asn Asp Thr Thr Leu
                325                 330                 335
Lys Ser Trp Ile Asp Asp Gly Phe Met Pro Leu Ile Tyr Lys Gly Glu
            340                 345                 350
Met Met Asp Leu Ser Arg Gly Arg Ala Ile Ser Arg Glu Asn Glu Thr
```

```
        355                 360                 365
Ser His Ser Ala Ser Ala Thr Val Met Lys Ser Leu Leu Arg Leu Ser
    370                 375                 380
Asp Ala Met Asp Asp Ser Thr Lys Ala Lys Tyr Lys Lys Ile Val Lys
385                 390                 395                 400
Ser Ser Val Glu Ser Asp Ser Ser Tyr Lys Gln Asn Asp Tyr Leu Asn
                405                 410                 415
Ser Tyr Ser Asp Ile Asp Lys Met Lys Ser Leu Met Thr Asp Asn Ser
            420                 425                 430
Ile Ser Lys Asn Gly Leu Thr Gln Gln Leu Lys Ile Tyr Asn Asp Met
        435                 440                 445
Asp Arg Val Thr Tyr His Asn Lys Asp Leu Asp Phe Ala Phe Gly Leu
    450                 455                 460
Ser Met Thr Ser Lys Asn Val Ala Arg Tyr Glu Ser Ile Asn Gly Glu
465                 470                 475                 480
Asn Leu Lys Gly Trp His Thr Gly Ala Gly Met Ser Tyr Leu Tyr Asn
                485                 490                 495
Ser Asp Val Lys His Tyr His Asp Asn Phe Trp Val Thr Ala Asp Met
            500                 505                 510
Lys Arg Leu Ser Gly Thr Thr Thr Leu Asp Asn Glu Ile Leu Lys Asp
        515                 520                 525
Thr Asp Asp Lys Lys Ser Ser Lys Thr Phe Val Gly Gly Thr Lys Val
    530                 535                 540
Asp Asp Gln His Ala Ser Ile Gly Met Asp Phe Glu Asn Gln Asp Lys
545                 550                 555                 560
Thr Leu Thr Ala Lys Lys Ser Tyr Phe Ile Leu Asn Asp Lys Ile Val
                565                 570                 575
Phe Leu Gly Thr Gly Ile Lys Ser Thr Asp Ser Ser Lys Asn Pro Val
            580                 585                 590
Thr Thr Ile Glu Asn Arg Lys Ala Asn Gly Tyr Thr Leu Tyr Thr Asp
        595                 600                 605
Asp Lys Gln Thr Thr Asn Ser Asp Asn Gln Glu Asn Asn Ser Val Phe
    610                 615                 620
Leu Glu Ser Thr Asp Thr Lys Lys Asn Ile Gly Tyr His Phe Leu Asn
625                 630                 635                 640
Lys Pro Lys Ile Thr Val Lys Lys Glu Ser His Thr Gly Lys Trp Lys
                645                 650                 655
Glu Ile Asn Lys Ser Gln Lys Asp Thr Gln Lys Thr Asp Glu Tyr Tyr
            660                 665                 670
Glu Val Thr Gln Lys His Ser Asn Ser Asp Asn Lys Tyr Gly Tyr Val
        675                 680                 685
Leu Tyr Pro Gly Leu Ser Lys Asp Val Phe Lys Thr Lys Lys Asp Glu
    690                 695                 700
Val Thr Val Val Lys Gln Glu Asp Asp Phe His Val Val Lys Asp Asn
705                 710                 715                 720
Glu Ser Val Trp Ala Gly Val Asn Tyr Ser Asn Ser Thr Gln Thr Phe
                725                 730                 735
Asp Ile Asn Asn Thr Lys Val Glu Val Lys Ala Lys Gly Met Phe Ile
            740                 745                 750
Leu Lys Lys Lys Asp Asp Asn Thr Tyr Glu Cys Ser Phe Tyr Asn Pro
        755                 760                 765
Glu Ser Thr Asn Ser Ala Ser Asp Ile Glu Ser Lys Ile Ser Met Thr
    770                 775                 780
Gly Tyr Ser Ile Thr Asn Lys Asn Thr Ser Thr Ser Asn Glu Ser Gly
785                 790                 795                 800
Val His Phe Glu Leu Thr Lys
                805
```

<210> 287
<211> 809
<212> PRT
<213> 金黃色葡萄球菌(菌株bovine RF122)

<220>

<223> 玻尿酸解離酶

<400> 287

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

Gln Lys Asn Thr Asn Leu Asn Trp Trp Asp Tyr Glu Ile Gly Thr Pro
            180                 185                 190
Arg Ala Leu Thr Asn Thr Leu Ile Leu Leu Lys Glu Asp Phe Thr Asp
        195                 200                 205
Glu Glu Lys Lys Lys Tyr Thr Ala Pro Ile Lys Thr Phe Ala Pro Lys
    210                 215                 220
Ser Asp Glu Ile Leu Ser Ser Val Gly Lys Ala Glu Pro Ala Lys Gly
225                 230                 235                 240
Gly Asn Leu Val Asp Ile Ser Lys Val Lys Leu Leu Glu Ser Ile Ile
                245                 250                 255
Glu Glu Asp Lys Asp Met Met Lys Asn Ser Ile Asp Ser Phe Asn Lys
            260                 265                 270
Val Phe Thr Tyr Val Gln Asp Ser Ala Thr Asp Lys Glu Arg Asn Gly
        275                 280                 285
Phe Tyr Lys Asp Gly Ser Tyr Ile Asp His Lys Asp Val Pro Tyr Thr
    290                 295                 300
Gly Ala Tyr Gly Val Val Leu Leu Glu Gly Ile Ser Gln Met Met Pro
305                 310                 315                 320
Met Ile Lys Glu Thr Pro Phe Asn Asp Lys Thr Gln Asn Asn Thr Thr
                325                 330                 335
Leu Thr Ser Trp Ile Asp Asp Gly Phe Met Pro Leu Ile Tyr Lys Gly
            340                 345                 350
Glu Met Met Asp Leu Ser Arg Gly Arg Ala Ile Ser Arg Glu Asn Glu
        355                 360                 365
Thr Ser His Ser Ala Ser Ala Thr Val Met Lys Ser Leu Leu Arg Leu
    370                 375                 380
Ser Asp Ala Met Asp Glu Ser Thr Lys Ala Lys Tyr Lys Gln Ile Val
385                 390                 395                 400
Lys Asn Ser Val Lys Ser Asp Ser Ser Tyr Gly Gln Asn Asp Thr Leu
                405                 410                 415
Ser Ser Tyr Ser Asp Ile Asp Lys Met Lys Ser Leu Met Thr Asp Ser
            420                 425                 430
Thr Ile Ser Thr Asn Gly Leu Thr Gln Gln Leu Lys Ile Tyr Asn Ala
        435                 440                 445
Met Asp Arg Val Thr Tyr His Asn Lys Asp Leu Asp Phe Ala Phe Gly
    450                 455                 460
Leu Ser Met Thr Ser Lys Asn Val Ala Arg Tyr Glu Asn Ile Asn Gly
465                 470                 475                 480
Glu Asn Leu Lys Gly Trp His Thr Gly Ala Gly Met Ser Tyr Leu Tyr
```

```
                485                 490                 495
Asn Ser Asp Val Arg His Tyr Arg Asp Asn Phe Trp Ala Thr Ala Asp
            500                 505                 510
Met Lys Arg Leu Ala Asp Thr Thr Thr Leu Glu Asn Glu Glu Pro Lys

        515                 520                 525
Gly Thr Asp Val Lys Lys Ser Ser Lys Thr Phe Val Gly Gly Thr Lys
    530                 535                 540
Phe Asp Asp Gln His Ala Ser Ile Gly Met Asp Phe Glu Asn Gln Asp
545                 550                 555                 560
Lys Thr Leu Thr Ala Lys Lys Ser Tyr Phe Ile Leu Asn Asp Lys Ile
                565                 570                 575
Val Phe Leu Gly Thr Gly Ile Lys Thr Thr Asp Ser Ser Lys Asn Pro
            580                 585                 590
Val Thr Thr Ile Glu Asn Arg Lys Ala His Gly Tyr Thr Leu Tyr Thr
        595                 600                 605
Asp Asp Lys Gln Thr Thr Asn Ser Asn Asn Gln Glu Thr Asn Ser Val
    610                 615                 620
Phe Leu Glu Ser Thr Asn Ser Thr Gln Asn Asn Ile Gly Tyr His Phe
625                 630                 635                 640
Leu Asn Lys Ser Lys Ile Thr Val Lys Lys Glu Ser His Thr Gly Lys
                645                 650                 655
Trp Ser Asp Ile Asn Lys Ser Gln Lys Asp Thr Gln Lys Thr Asp Glu
            660                 665                 670
Tyr Tyr Glu Val Thr Gln Lys His Ser Asn Thr Asp Asp Lys Tyr Ala
        675                 680                 685
Tyr Val Leu Tyr Pro Gly Ile Thr Lys Asp Asn Phe Lys Ser Lys Ala
    690                 695                 700
Ser Gln Val Thr Val Val Lys Gln Asp Asp Asp Phe His Val Val Lys
705                 710                 715                 720
Asp Asn Glu Ser Val Trp Ala Gly Val Asn Tyr Ser Asp Ser Thr Gln
                725                 730                 735
Thr Phe Asp Ile Asn Gly Thr Lys Val Glu Val Lys Ala Lys Gly Met
            740                 745                 750
Phe Ile Leu Lys Lys Lys Asp Asp Asn Thr Tyr Glu Cys Ser Phe Tyr
        755                 760                 765
Asn Pro Glu Ser Thr Asn Ser Ala Ser Asp Ile Glu Ser Lys Ile Ser
    770                 775                 780
Met Thr Gly Tyr Ser Ile Thr Asn Lys Asn Thr Ser Asn Thr Asn Glu
785                 790                 795                 800
Ser Gly Val Arg Phe Glu Leu Thr Lys
                805
```

<210> 288
<211> 807
<212> PRT
<213> 金黃色葡萄球菌(菌株bovine RF122)

<220>
<223> 玻尿酸解離酶

<400> 288

```
Met Thr Tyr Lys Met Lys Lys Trp Gln Lys Leu Ser Thr Ile Thr Leu
 1               5                  10                  15
Leu Met Ala Gly Val Ile Thr Leu Asn Asn Gly Glu Phe Arg Asn Val
            20                  25                  30
Asp Lys His Gln Ile Ala Val Ala Asp Thr Asn Val Gln Thr Pro Asp
        35                  40                  45
Tyr Glu Lys Leu Lys Lys Thr Trp Leu Asp Val Asn Tyr Gly Asn Asp
    50                  55                  60
Gln Tyr Asp Glu Asn Asn Gln Asp Met Lys Lys Lys Phe Asp Ala Lys
65                  70                  75                  80
Glu Asn Glu Ala Lys Lys Leu Leu Glu Asp Met Lys Thr Asp Thr Asn
                85                  90                  95
```

Arg Thr Tyr Leu Trp Ser Gly Ala Glu Asn Leu Glu Thr Asn Ser Ser
100 105 110
His Met Thr Lys Thr Tyr Arg Asn Ile Glu Lys Ile Ala Glu Ala Met
115 120 125
Arg His Lys Asn Thr Ser Leu Lys Thr Asp Glu Asn Lys Leu Lys Ile
130 135 140
Lys Asp Ala Ile Lys Trp Leu His His Asn Val Tyr Gly Lys Asp Pro
145 150 155 160
Asp Lys Lys Val Ala Asp Leu Thr Thr Asn Arg Lys Glu Lys Asp Ser
165 170 175
Ser Lys Lys Asn Asn Ser Leu Asn Trp Trp Asp Tyr Glu Ile Gly Thr
180 185 190
Pro Arg Ala Leu Thr Asn Thr Leu Leu Leu Met Asp Asn Met Leu Thr
195 200 205
Lys Asp Glu Met Lys Asn Tyr Ser Lys Pro Ile Ser Ile Tyr Ser Pro
210 215 220
Ser Ser Tyr Lys Ile Leu Ser Ser Val Gly Glu Ser Glu Asp Ala Lys
225 230 235 240
Gly Gly Asn Leu Val Asp Ile Ala Lys Val Lys Phe Leu Glu Ser Val
245 250 255
Ile Glu Glu Asp Val Asp Met Met Lys Lys Ser Ile Asp Ser Phe Asn
260 265 270
Lys Val Phe Thr Tyr Val Gln Asp Ser Ala Thr Gly Lys Ala Arg Asn
275 280 285
Gly Phe Tyr Lys Asp Gly Ser Tyr Ile Asp His Gln Asp Val Pro Tyr
290 295 300
Thr Gly Ala Tyr Gly Val Val Leu Leu Glu Gly Ile Ser Gln Met Met
305 310 315 320
Pro Met Ile Lys Glu Ser Pro Phe Lys His Thr Gln Asp Lys Ala Thr
325 330 335
Leu Ser Asn Trp Ile Asp Glu Gly Phe Met Pro Leu Ile Tyr Lys Gly
340 345 350
Glu Met Met Asp Leu Ser Arg Gly Arg Ala Ile Ser Arg Glu Asn Glu
355 360 365
Thr Ser His Thr Ala Ser Ala Thr Val Met Lys Ser Leu Leu Arg Leu
370 375 380
Ser Asp Thr Met Asp Glu Ser Thr Lys Thr Lys Tyr Lys Gln Ile Val
385 390 395 400
Lys Thr Ser Val Lys Ser Asp Ser Ser Tyr Asp Ser Asn Asp Thr Leu
405 410 415
Asn Ser Tyr Ser Asp Ile Asp Lys Met Lys Lys Leu Met Asn Asp Ser
420 425 430
Thr Ile Ser Lys Asn Asp Leu Thr Gln Gln Leu Lys Ile Tyr Asn Asp
435 440 445
Met Asp Arg Val Thr Tyr His Asn Lys Glu Leu Asp Phe Ala Phe Gly
450 455 460
Leu Ser Met Thr Ser Lys Asn Ile Ala Arg Tyr Glu Asn Ile Asn Gly
465 470 475 480
Glu Asn Leu Lys Gly Trp His Thr Gly Ala Gly Met Ser Tyr Leu Tyr
485 490 495
Asn Ser Asp Val Lys His Tyr Arg Asp Asn Phe Trp Ala Thr Ala Asp
500 505 510
Met Thr Arg Leu Pro Gly Thr Thr Thr Leu Asn Asp Met Pro Ser Thr
515 520 525
Asn Thr Lys Asn Asp Lys Ser Phe Val Gly Gly Thr Lys Leu Asn Asn
530 535 540
Lys Tyr Ala Ser Ile Gly Met Asp Phe Glu Asn Gln Asp Lys Thr Leu
545 550 555 560
Thr Ala Lys Lys Ser Tyr Phe Ile Leu Asn Asp Lys Ile Val Phe Ile
565 570 575
Gly Thr Gly Ile Lys Ser Thr Asp Ser Ser Lys Asn Pro Val Thr Ser
580 585 590
Val Glu Asn Arg Lys Ala Asn Gly Tyr Lys Leu Phe Lys Gly Asp Ile
595 600 605
Glu Ile Thr Thr Ser Asp Val Asn Ala Gln Glu Thr His Ser Val Phe

```
    610                 615                 620
Leu Glu Ser Asn Asp Thr Lys Lys Asn Ile Gly Tyr His Phe Leu Asp
625                 630                 635                 640
Lys Pro Lys Ile Thr Val Lys Lys Glu Ser His Thr Gly Lys Trp Ser
                645                 650                 655
Glu Ile Asn Lys Ser Gln Lys Thr Asp Asp Lys Lys Asp Glu Tyr Tyr
            660                 665                 670
Glu Val Thr Gln Thr His Asn Thr Ser Asp Ser Lys Tyr Ala Tyr Val
        675                 680                 685
Leu Tyr Pro Gly Leu Ser Lys Ser Asp Phe Lys Ser Lys Asn Asn Asn
    690                 695                 700
Val Ser Ile Val Lys Gln Asp Glu Asp Phe His Val Ile Lys Asp Asn
705                 710                 715                 720
Asp Gly Val Phe Ala Gly Val Asn Tyr Ser Asp Ser Thr Lys Ser Phe
                725                 730                 735
Asp Ile Asn Gly Thr Ile Val Glu Leu Lys Glu Lys Gly Met Phe Val
            740                 745                 750
Ile Lys Lys Lys Asp Asp Asn Thr Tyr Glu Cys Ser Phe Tyr Asn Pro
        755                 760                 765
Thr Ser Thr Asn Ser Thr Ser Asn Lys Glu Ser Lys Ile Ser Val Thr
    770                 775                 780
Gly Tyr Thr Ile Thr Asn Gln Ser Val Ser Asn Phe Lys Glu Ser Asp
785                 790                 795                 800
Ile His Phe Glu Leu Thr Lys
                805
```

<210> 289
<211> 807
<212> PRT
<213> 金黃色葡萄球菌(菌株USA300)

<220>
<223> 玻尿酸解離酶

<400> 289

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

```
225                 230                 235                 240
Asn Leu Val Asp Ile Ser Lys Val Lys Leu Leu Glu Cys Ile Ile Glu
                245                 250                 255
Glu Asp Lys Asp Met Met Lys Lys Ser Ile Asp Ser Phe Asn Lys Val
            260                 265                 270
Phe Thr Tyr Val Gln Asp Ser Ala Thr Gly Lys Glu Arg Asn Gly Phe
        275                 280                 285
Tyr Lys Asp Gly Ser Tyr Ile Asp His Gln Asp Val Pro Tyr Thr Gly
    290                 295                 300
Ala Tyr Gly Val Val Leu Leu Glu Gly Ile Ser Gln Met Met Pro Met
305                 310                 315                 320
Ile Lys Glu Thr Pro Phe Asn Asp Lys Thr Gln Asn Asp Thr Thr Leu
                325                 330                 335
Lys Ser Trp Ile Asp Asp Gly Phe Met Pro Leu Ile Tyr Lys Gly Glu
            340                 345                 350
Met Met Asp Leu Ser Arg Gly Arg Ala Ile Ser Arg Glu Asn Glu Thr
        355                 360                 365
Ser His Ser Ala Ser Ala Thr Val Met Lys Ser Leu Leu Arg Leu Ser
    370                 375                 380
Asp Ala Met Asp Asp Ser Thr Lys Ala Lys Tyr Lys Lys Ile Val Lys
385                 390                 395                 400
Ser Ser Val Glu Ser Asp Ser Ser Tyr Lys Gln Asn Asp Tyr Leu Asn
                405                 410                 415
Ser Tyr Ser Asp Ile Asp Lys Met Lys Ser Leu Met Thr Asp Asn Ser
            420                 425                 430
Ile Ser Lys Asn Gly Leu Thr Gln Gln Leu Lys Ile Tyr Asn Asp Met
        435                 440                 445
Asp Arg Val Thr Tyr His Asn Lys Asp Leu Asp Phe Ala Phe Gly Leu
    450                 455                 460
Ser Met Thr Ser Lys Asn Val Ala Arg Tyr Glu Ser Ile Asn Gly Glu
465                 470                 475                 480
Asn Leu Lys Gly Trp His Thr Gly Ala Gly Met Ser Tyr Leu Tyr Asn
                485                 490                 495
Ser Asp Val Lys His Tyr His Asp Asn Phe Trp Val Thr Ala Asp Met
            500                 505                 510
Lys Arg Leu Ser Gly Thr Thr Thr Leu Asp Asn Glu Ile Leu Lys Asp
        515                 520                 525
Thr Asp Asp Lys Lys Ser Ser Lys Thr Phe Val Gly Gly Thr Lys Val
    530                 535                 540
Asp Asp Gln His Ala Ser Ile Gly Met Asp Phe Glu Asn Gln Asp Lys
545                 550                 555                 560
Thr Leu Thr Ala Lys Lys Ser Tyr Phe Ile Leu Asn Asp Lys Ile Val
                565                 570                 575
Phe Leu Gly Thr Gly Ile Lys Ser Thr Asp Ser Ser Lys Asn Pro Val
            580                 585                 590
Thr Thr Ile Glu Asn Arg Lys Ala Asn Gly Tyr Thr Leu Tyr Thr Asp
        595                 600                 605
Asp Lys Gln Thr Thr Asn Ser Asp Asn Gln Glu Asn Asn Ser Val Phe
    610                 615                 620
Leu Glu Ser Thr Asp Thr Lys Lys Asn Ile Gly Tyr His Phe Leu Asn
625                 630                 635                 640
Lys Pro Lys Ile Thr Val Lys Lys Glu Ser His Thr Gly Lys Trp Lys
                645                 650                 655
Glu Ile Asn Lys Ser Gln Lys Asp Thr Gln Lys Thr Asp Glu Tyr Tyr
            660                 665                 670
Glu Val Thr Gln Lys His Ser Asn Ser Asp Asn Lys Tyr Gly Tyr Val
        675                 680                 685
Leu Tyr Pro Gly Leu Ser Lys Asp Val Phe Lys Thr Lys Lys Asp Glu
    690                 695                 700
Val Thr Val Val Lys Gln Glu Asp Asp Phe His Val Val Lys Asp Asn
705                 710                 715                 720
Glu Ser Val Trp Ala Gly Val Asn Tyr Ser Asn Ser Thr Gln Thr Phe
                725                 730                 735
Asp Ile Asn Asn Thr Lys Val Glu Val Lys Ala Lys Gly Met Phe Ile
            740                 745                 750
```

```
Leu Lys Lys Lys Asp Asp Asn Thr Tyr Glu Cys Ser Phe Tyr Asn Pro
        755                 760                 765
Glu Ser Thr Asn Ser Ala Ser Asp Ile Glu Ser Lys Ile Ser Met Thr
    770                 775                 780
Gly Tyr Ser Ile Thr Asn Lys Asn Thr Ser Thr Ser Asn Glu Ser Gly
785                 790                 795                 800
Val His Phe Glu Leu Thr Lys
                805
```

<210> 290
<211> 1066
<212> PRT
<213> 肺炎鏈球菌（Streptococcus pneumoniae）

<220>
<223> 玻尿酸解離酶

<400> 290

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

Pro Thr Leu Asp Val Asp Lys Ile Lys Leu Glu Leu Phe Tyr Glu Thr
            180                 185                 190
Gly Thr Gly Thr Val Ser Phe Lys Asp Ile Glu Leu Val Glu Val Ala
        195                 200                 205
Asp Gln Leu Ser Glu Asp Ser Gln Thr Asp Lys Gln Leu Glu Glu Lys
    210                 215                 220
Ile Asp Leu Pro Ile Gly Lys Lys His Val Phe Ser Leu Ala Asp Tyr
225                 230                 235                 240
Thr Tyr Lys Val Glu Asn Pro Asp Val Ala Ser Val Lys Asn Gly Ile
                245                 250                 255
Leu Glu Pro Leu Lys Glu Gly Thr Thr Asn Val Ile Val Ser Lys Asp
            260                 265                 270
Gly Lys Glu Val Lys Lys Ile Pro Leu Lys Ile Leu Ala Ser Val Lys
        275                 280                 285
Asp Ala Tyr Thr Asp Arg Leu Asp Asp Trp Asn Gly Ile Ile Ala Gly
    290                 295                 300
Asn Gln Tyr Tyr Asp Ser Lys Asn Glu Gln Met Ala Lys Leu Asn Gln
305                 310                 315                 320
Glu Leu Glu Gly Lys Val Ala Asp Ser Leu Ser Ser Ile Ser Ser Gln
                325                 330                 335
Ala Asp Arg Thr Tyr Leu Trp Glu Lys Phe Ser Asn Tyr Lys Thr Ser
            340                 345                 350
Ala Asn Leu Thr Ala Thr Tyr Arg Lys Leu Glu Glu Met Ala Lys Gln
```

```
        355                 360                 365
Val Thr Asn Pro Ser Ser Arg Tyr Tyr Gln Asp Glu Thr Val Val Arg
    370                 375                 380
Thr Val Arg Asp Ser Met Glu Trp Met His Lys His Val Tyr Asn Ser
385                 390                 395                 400
Glu Lys Ser Ile Val Gly Asn Trp Trp Asp Tyr Glu Ile Gly Thr Pro
                405                 410                 415
Arg Ala Ile Asn Asn Thr Leu Ser Leu Met Lys Glu Tyr Phe Ser Asp
            420                 425                 430
Glu Glu Ile Lys Lys Tyr Thr Asp Val Ile Glu Lys Phe Val Pro Asp
        435                 440                 445
Pro Glu His Phe Arg Lys Thr Thr Asp Asn Pro Phe Lys Ala Leu Gly
    450                 455                 460
Gly Asn Leu Val Asp Met Gly Arg Val Lys Val Ile Ala Gly Leu Leu
465                 470                 475                 480
Arg Lys Asp Asp Gln Glu Ile Ser Ser Thr Ile Arg Ser Ile Glu Gln
                485                 490                 495
Val Phe Lys Leu Val Asp Gln Gly Glu Gly Phe Tyr Gln Asp Gly Ser
            500                 505                 510
Tyr Ile Asp His Thr Asn Val Ala Tyr Thr Gly Ala Tyr Gly Asn Val

        515                 520                 525
Leu Ile Asp Gly Leu Ser Gln Leu Leu Pro Val Ile Gln Lys Thr Lys
    530                 535                 540
Asn Pro Ile Asp Lys Asp Lys Met Gln Thr Met Tyr His Trp Ile Asp
545                 550                 555                 560
Lys Ser Phe Ala Pro Leu Leu Val Asn Gly Glu Leu Met Asp Met Ser
                565                 570                 575
Arg Gly Arg Ser Ile Ser Arg Ala Asn Ser Glu Gly His Val Ala Ala
            580                 585                 590
Val Glu Val Leu Arg Gly Ile His Arg Ile Ala Asp Met Ser Glu Gly
        595                 600                 605
Glu Thr Lys Gln Cys Leu Gln Ser Leu Val Lys Thr Ile Val Gln Ser
    610                 615                 620
Asp Ser Tyr Tyr Asp Val Phe Lys Asn Leu Lys Thr Tyr Lys Asp Ile
625                 630                 635                 640
Ser Leu Met Gln Ser Leu Leu Ser Asp Ala Gly Val Ala Ser Val Pro
                645                 650                 655
Arg Pro Ser Tyr Leu Ser Ala Phe Asn Lys Met Asp Lys Thr Ala Met
            660                 665                 670
Tyr Asn Ala Glu Lys Gly Phe Gly Phe Gly Leu Ser Leu Phe Ser Ser
        675                 680                 685
Arg Thr Leu Asn Tyr Glu His Met Asn Lys Glu Asn Lys Arg Gly Trp
    690                 695                 700
Tyr Thr Ser Asp Gly Met Phe Tyr Leu Tyr Asn Gly Asp Leu Ser His
705                 710                 715                 720
Tyr Ser Asp Gly Tyr Trp Pro Thr Val Asn Pro Tyr Lys Met Pro Gly
                725                 730                 735
Thr Thr Glu Thr Asp Ala Lys Arg Ala Asp Ser Asp Thr Gly Lys Val
            740                 745                 750
Leu Pro Ser Ala Phe Val Gly Thr Ser Lys Leu Asp Asp Ala Asn Ala
        755                 760                 765
Thr Ala Thr Met Asp Phe Thr Asn Trp Asn Gln Thr Leu Thr Ala His
    770                 775                 780
Lys Ser Trp Phe Met Leu Lys Asp Lys Ile Ala Phe Leu Gly Ser Asn
785                 790                 795                 800
Ile Gln Asn Thr Ser Thr Asp Thr Ala Ala Thr Thr Ile Asp Gln Arg
                805                 810                 815
Lys Leu Glu Ser Gly Asn Pro Tyr Lys Val Tyr Val Asn Asp Lys Glu
            820                 825                 830
Ala Ser Leu Thr Glu Gln Glu Lys Asp Tyr Pro Glu Thr Gln Ser Val
        835                 840                 845
Phe Leu Glu Ser Phe Asp Ser Lys Lys Asn Ile Gly Tyr Phe Phe Phe
    850                 855                 860
Lys Lys Ser Ser Ile Ser Met Ser Lys Ala Leu Gln Lys Gly Ala Trp
```

865 870 875 880
Lys Asp Ile Asn Glu Gly Gln Ser Asp Lys Glu Val Glu Asn Glu Phe
885 890 895
Leu Thr Ile Ser Gln Ala His Lys Gln Asn Arg Asp Ser Tyr Gly Tyr
900 905 910
Met Leu Ile Pro Asn Val Asp Arg Ala Thr Phe Asn Gln Met Ile Lys
915 920 925
Glu Leu Glu Ser Ser Leu Ile Glu Asn Asn Glu Thr Leu Gln Ser Val
930 935 940
Tyr Asp Ala Lys Gln Gly Val Trp Gly Ile Val Lys Tyr Asp Asp Ser
945 950 955 960
Val Ser Thr Ile Ser Asn Gln Phe Gln Val Leu Lys Arg Gly Val Tyr
965 970 975
Thr Ile Arg Lys Glu Gly Asp Glu Tyr Lys Ile Ala Tyr Tyr Asn Pro
980 985 990
Glu Thr Gln Glu Ser Ala Pro Asp Gln Glu Val Phe Lys Lys Leu Glu
995 1000 1005
Gln Ala Ala Gln Pro Gln Val Gln Asn Ser Lys Glu Lys Glu Lys Ser
1010 1015 1020
Glu Glu Glu Lys Asn His Ser Asp Gln Lys Asn Leu Pro Gln Thr Gly
1025 1030 1035 1040
Glu Gly Gln Ser Ile Leu Ala Ser Leu Gly Phe Leu Leu Leu Gly Ala
1045 1050 1055
Phe Tyr Leu Phe Arg Arg Gly Lys Asn Asn
1060 1065

<210> 291
<211> 1078
<212> PRT
<213> 肺炎鏈球菌(菌株ATCC BAA-255/R6)

<220>
<223> 玻尿酸解離酶

<400> 291
Met Ile Leu Gln Tyr Val Tyr Trp Ser Val Tyr Met Gln Thr Lys Thr
1 5 10 15
Lys Lys Leu Ile Val Ser Leu Ser Ser Leu Val Leu Ser Gly Phe Leu
20 25 30
Leu Asn His Tyr Met Thr Val Gly Ala Glu Glu Thr Thr Thr Asn Thr
35 40 45
Ile Gln Gln Ser Gln Lys Glu Val Gln Tyr Gln Gln Arg Asp Thr Lys
50 55 60
Asn Leu Val Glu Asn Gly Asp Phe Gly Gln Thr Glu Asp Gly Ser Ser
65 70 75 80
Pro Trp Thr Gly Ser Lys Ala Gln Gly Trp Ser Ala Trp Val Asp Gln
85 90 95
Lys Asn Ser Ser Ala Asp Ala Ser Thr Arg Val Ile Glu Ala Lys Asp
100 105 110
Gly Ala Ile Thr Ile Ser Ser Pro Glu Lys Leu Arg Ala Ala Val His
115 120 125
Arg Met Val Pro Ile Glu Ala Lys Lys Lys Tyr Lys Leu Arg Phe Lys
130 135 140
Ile Lys Thr Asp Asn Lys Val Gly Ile Ala Lys Val Arg Ile Ile Glu
145 150 155 160
Glu Ser Gly Lys Asp Lys Arg Leu Trp Asn Ser Ala Thr Thr Ser Gly
165 170 175
Thr Lys Asp Trp Gln Thr Ile Glu Ala Asp Tyr Ser Pro Thr Leu Asp
180 185 190
Val Asp Lys Ile Lys Leu Glu Leu Phe Tyr Glu Thr Gly Thr Gly Thr
195 200 205
Val Ser Phe Lys Asp Ile Glu Leu Val Glu Val Ala Asp Gln Pro Ser
210 215 220
Glu Asp Ser Gln Thr Asp Lys Gln Leu Glu Glu Lys Ile Asp Leu Pro

225 230 235 240
Ile Gly Lys Lys His Val Phe Ser Leu Ala Asp Tyr Thr Tyr Lys Val
245 250 255
Glu Asn Pro Asp Val Ala Ser Val Lys Asn Gly Ile Leu Glu Pro Leu
260 265 270
Lys Glu Gly Thr Thr Asn Val Ile Val Ser Lys Asp Gly Lys Glu Val
275 280 285
Lys Lys Ile Pro Leu Lys Ile Leu Ala Ser Val Lys Asp Thr Tyr Thr
290 295 300
Asp Arg Leu Asp Asp Trp Asn Gly Ile Ile Ala Gly Asn Gln Tyr Tyr

305 310 315 320
Asp Ser Lys Asn Glu Gln Met Ala Lys Leu Asn Gln Glu Leu Glu Gly
325 330 335
Lys Val Ala Asp Ser Leu Ser Ser Ile Ser Ser Gln Ala Asp Arg Ile
340 345 350
Tyr Leu Trp Glu Lys Phe Ser Asn Tyr Lys Thr Ser Ala Asn Leu Thr
355 360 365
Ala Thr Tyr Arg Lys Leu Glu Glu Met Ala Lys Gln Val Thr Asn Pro
370 375 380
Ser Ser Arg Tyr Tyr Gln Asp Glu Thr Val Val Arg Thr Val Arg Asp
385 390 395 400
Ser Met Glu Trp Met His Lys His Val Tyr Asn Ser Glu Lys Ser Ile
405 410 415
Val Gly Asn Trp Trp Asp Tyr Glu Ile Gly Thr Pro Arg Ala Ile Asn
420 425 430
Asn Thr Leu Ser Leu Met Lys Glu Tyr Phe Ser Asp Glu Glu Ile Lys
435 440 445
Lys Tyr Thr Asp Val Ile Glu Lys Phe Val Pro Asp Pro Glu His Phe
450 455 460
Arg Lys Thr Thr Asp Asn Pro Phe Lys Ala Leu Gly Gly Asn Leu Val
465 470 475 480
Asp Met Gly Arg Val Lys Val Ile Ala Gly Leu Leu Arg Lys Asp Asp
485 490 495
Gln Glu Ile Ser Ser Thr Ile Arg Ser Ile Glu Gln Val Phe Lys Leu
500 505 510
Val Asp Gln Gly Glu Gly Phe Tyr Gln Asp Gly Ser Tyr Ile Asp His
515 520 525
Thr Asn Val Ala Tyr Thr Gly Ala Tyr Gly Asn Val Leu Ile Asp Gly
530 535 540
Leu Ser Gln Leu Leu Pro Val Ile Gln Lys Thr Lys Asn Pro Ile Asp
545 550 555 560
Lys Asp Lys Met Gln Thr Met Tyr His Trp Ile Asp Lys Ser Phe Ala
565 570 575
Pro Leu Leu Val Asn Gly Glu Leu Met Asp Met Ser Arg Gly Arg Ser
580 585 590
Ile Ser Arg Ala Asn Ser Glu Gly His Val Ala Ala Val Glu Val Leu
595 600 605
Arg Gly Ile His Arg Ile Ala Asp Met Ser Glu Gly Glu Thr Lys Gln
610 615 620
Arg Leu Gln Ser Leu Val Lys Thr Ile Val Gln Ser Asp Ser Tyr Tyr
625 630 635 640
Asp Val Phe Lys Asn Leu Lys Thr Tyr Lys Asp Ile Ser Leu Met Gln
645 650 655
Ser Leu Leu Ser Asp Ala Gly Val Ala Ser Val Pro Arg Thr Ser Tyr
660 665 670
Leu Ser Ala Phe Asn Lys Met Asp Lys Thr Ala Met Tyr Asn Ala Glu
675 680 685
Lys Gly Phe Gly Phe Gly Leu Ser Leu Phe Ser Ser Arg Thr Leu Asn
690 695 700
Tyr Glu His Met Asn Lys Glu Asn Lys Arg Gly Trp Tyr Thr Ser Asp
705 710 715 720
Gly Met Phe Tyr Leu Tyr Asn Gly Asp Leu Ser His Tyr Ser Asp Gly
725 730 735
Tyr Trp Pro Thr Val Asn Pro Tyr Lys Met Pro Gly Thr Thr Glu Thr

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            740                 745                 750
Asp Ala Lys Arg Ala Asp Ser Asp Thr Gly Lys Val Leu Pro Ser Ala
        755                 760                 765
Phe Val Gly Thr Ser Lys Leu Asp Asp Ala Asn Ala Thr Ala Thr Met
    770                 775                 780
Asp Phe Thr Asn Trp Asn Gln Thr Leu Thr Ala His Lys Ser Trp Phe
785                 790                 795                 800
Met Leu Lys Asp Lys Ile Ala Phe Leu Gly Ser Asn Ile Gln Asn Thr
                805                 810                 815
Ser Thr Asp Thr Ala Ala Thr Thr Ile Asp Gln Arg Lys Leu Glu Ser
            820                 825                 830
Ser Asn Pro Tyr Lys Val Tyr Val Asn Asp Lys Glu Ala Ser Leu Thr
        835                 840                 845
Glu Gln Glu Lys Asp Tyr Pro Glu Thr Gln Ser Val Phe Leu Glu Ser
    850                 855                 860
Ser Asp Ser Lys Lys Asn Ile Gly Tyr Phe Phe Phe Lys Lys Ser Ser
865                 870                 875                 880
Ile Ser Met Ser Lys Ala Leu Gln Lys Gly Ala Trp Lys Asp Ile Asn
                885                 890                 895
Glu Gly Gln Ser Asp Lys Glu Val Glu Asn Glu Phe Leu Thr Ile Ser
            900                 905                 910
Gln Ala His Lys Gln Asn Gly Asp Ser Tyr Gly Tyr Met Leu Ile Pro
        915                 920                 925
Asn Val Asp Arg Ala Thr Phe Asn Gln Met Ile Lys Glu Leu Glu Ser
    930                 935                 940
Ser Leu Ile Glu Asn Asn Glu Thr Leu Gln Ser Val Tyr Asp Ala Lys
945                 950                 955                 960
Gln Gly Val Trp Gly Ile Val Lys Tyr Asp Asp Ser Val Ser Thr Ile
                965                 970                 975
Ser Asn Gln Phe Gln Val Leu Lys Arg Gly Val Tyr Thr Ile Arg Lys
            980                 985                 990
Glu Gly Asp Glu Tyr Lys Ile Ala Tyr Tyr Asn Pro Glu Thr Gln Glu
        995                 1000                1005
Ser Ala Pro Asp Gln Glu Val Phe Lys Lys Leu Glu Gln Ala Ala Gln
    1010                1015                1020
Pro Gln Val Gln Asn Ser Lys Glu Lys Glu Lys Ser Glu Glu Glu Lys
1025                1030                1035                1040
Asn His Ser Asp Gln Lys Asn Leu Pro Gln Thr Gly Glu Gly Gln Ser
                1045                1050                1055
Ile Leu Ala Ser Leu Gly Phe Leu Leu Leu Gly Ala Phe Tyr Leu Phe
            1060                1065                1070
Arg Arg Gly Lys Asn Asn
        1075
```

<210> 292
<211> 1067
<212> PRT
<213> 肺炎鏈球菌血清型2 (菌株D39/NCTC 7466)

<220>
<223> 玻尿酸解離酶

<400> 292

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

```
                85                  90                  95
Ile Glu Ala Lys Asp Gly Ala Ile Thr Ile Ser Ser Pro Glu Lys Leu
            100                 105                 110
Arg Ala Ala Val His Arg Met Val Pro Ile Glu Ala Lys Lys Lys Tyr
        115                 120                 125
Lys Leu Arg Phe Lys Ile Lys Thr Asp Asn Lys Val Gly Ile Ala Lys
    130                 135                 140
Val Arg Ile Ile Glu Glu Ser Gly Lys Asp Lys Arg Leu Trp Asn Ser
145                 150                 155                 160
Ala Thr Thr Ser Gly Thr Lys Asp Trp Gln Thr Ile Glu Ala Asp Tyr
                165                 170                 175
Ser Pro Thr Leu Asp Val Asp Lys Ile Lys Leu Glu Leu Phe Tyr Glu
            180                 185                 190
Thr Gly Thr Gly Thr Val Ser Phe Lys Asp Ile Glu Leu Val Glu Val
        195                 200                 205
Ala Asp Gln Pro Ser Glu Asp Ser Gln Thr Asp Lys Gln Leu Glu Glu
    210                 215                 220
Lys Ile Asp Leu Pro Ile Gly Lys Lys His Val Phe Ser Leu Ala Asp
225                 230                 235                 240
Tyr Thr Tyr Lys Val Glu Asn Pro Asp Val Ala Ser Val Lys Asn Gly
                245                 250                 255
Ile Leu Glu Pro Leu Lys Glu Gly Thr Thr Asn Val Ile Val Ser Lys
            260                 265                 270
Asp Gly Lys Glu Val Lys Lys Ile Pro Leu Lys Ile Leu Ala Ser Val
        275                 280                 285
Lys Asp Thr Tyr Thr Asp Arg Leu Asp Asp Trp Asn Gly Ile Ile Ala
    290                 295                 300
Gly Asn Gln Tyr Tyr Asp Ser Lys Asn Glu Gln Met Ala Lys Leu Asn
305                 310                 315                 320
Gln Glu Leu Glu Gly Lys Val Ala Asp Ser Leu Ser Ser Ile Ser Ser
                325                 330                 335
Gln Ala Asp Arg Ile Tyr Leu Trp Glu Lys Phe Ser Asn Tyr Lys Thr
            340                 345                 350
Ser Ala Asn Leu Thr Ala Thr Tyr Arg Lys Leu Glu Glu Met Ala Lys
        355                 360                 365
Gln Val Thr Asn Pro Ser Ser Arg Tyr Tyr Gln Asp Glu Thr Val Val
    370                 375                 380
Arg Thr Val Arg Asp Ser Met Glu Trp Met His Lys His Val Tyr Asn
385                 390                 395                 400
Ser Glu Lys Ser Ile Val Gly Asn Trp Trp Asp Tyr Glu Ile Gly Thr
                405                 410                 415
Pro Arg Ala Ile Asn Asn Thr Leu Ser Leu Met Lys Glu Tyr Phe Ser
            420                 425                 430
Asp Glu Glu Ile Lys Lys Tyr Thr Asp Val Ile Glu Lys Phe Val Pro
        435                 440                 445
Asp Pro Glu His Phe Arg Lys Thr Thr Asp Asn Pro Phe Lys Ala Leu
    450                 455                 460
Gly Gly Asn Leu Val Asp Met Gly Arg Val Lys Val Ile Ala Gly Leu
465                 470                 475                 480
Leu Arg Lys Asp Asp Gln Glu Ile Ser Ser Thr Ile Arg Ser Ile Glu
                485                 490                 495
Gln Val Phe Lys Leu Val Asp Gln Gly Glu Gly Phe Tyr Gln Asp Gly
            500                 505                 510
Ser Tyr Ile Asp His Thr Asn Val Ala Tyr Thr Gly Ala Tyr Gly Asn
        515                 520                 525
Val Leu Ile Asp Gly Leu Ser Gln Leu Leu Pro Val Ile Gln Lys Thr
    530                 535                 540
Lys Asn Pro Ile Asp Lys Asp Lys Met Gln Thr Met Tyr His Trp Ile
545                 550                 555                 560
Asp Lys Ser Phe Ala Pro Leu Leu Val Asn Gly Glu Leu Met Asp Met
                565                 570                 575
Ser Arg Gly Arg Ser Ile Ser Arg Ala Asn Ser Glu Gly His Val Ala
            580                 585                 590
Ala Val Glu Val Leu Arg Gly Ile His Arg Ile Ala Asp Met Ser Glu
        595                 600                 605
```

```
Gly Glu Thr Lys Gln Arg Leu Gln Ser Leu Val Lys Thr Ile Val Gln
    610                 615                 620
Ser Asp Ser Tyr Tyr Asp Val Phe Lys Asn Leu Lys Thr Tyr Lys Asp
625                 630                 635                 640
Ile Ser Leu Met Gln Ser Leu Leu Ser Asp Ala Gly Val Ala Ser Val
                645                 650                 655
Pro Arg Thr Ser Tyr Leu Ser Ala Phe Asn Lys Met Asp Lys Thr Ala
            660                 665                 670
Met Tyr Asn Ala Glu Lys Gly Phe Gly Phe Gly Leu Ser Leu Phe Ser
        675                 680                 685
Ser Arg Thr Leu Asn Tyr Glu His Met Asn Lys Glu Asn Lys Arg Gly
    690                 695                 700
Trp Tyr Thr Ser Asp Gly Met Phe Tyr Leu Tyr Asn Gly Asp Leu Ser
705                 710                 715                 720
His Tyr Ser Asp Gly Tyr Trp Pro Thr Val Asn Pro Tyr Lys Met Pro
                725                 730                 735
Gly Thr Thr Glu Thr Asp Ala Lys Arg Ala Asp Ser Asp Thr Gly Lys
            740                 745                 750
Val Leu Pro Ser Ala Phe Val Gly Thr Ser Lys Leu Asp Asp Ala Asn
        755                 760                 765
Ala Thr Ala Thr Met Asp Phe Thr Asn Trp Asn Gln Thr Leu Thr Ala
    770                 775                 780
His Lys Ser Trp Phe Met Leu Lys Asp Lys Ile Ala Phe Leu Gly Ser
785                 790                 795                 800
Asn Ile Gln Asn Thr Ser Thr Asp Thr Ala Ala Thr Thr Ile Asp Gln
                805                 810                 815
Arg Lys Leu Glu Ser Ser Asn Pro Tyr Lys Val Tyr Val Asn Asp Lys
            820                 825                 830
Glu Ala Ser Leu Thr Glu Gln Glu Lys Asp Tyr Pro Glu Thr Gln Ser
        835                 840                 845
Val Phe Leu Glu Ser Ser Asp Ser Lys Lys Asn Ile Gly Tyr Phe Phe
    850                 855                 860
Phe Lys Lys Ser Ser Ile Ser Met Ser Lys Ala Leu Gln Lys Gly Ala
865                 870                 875                 880
Trp Lys Asp Ile Asn Glu Gly Gln Ser Asp Lys Glu Val Glu Asn Glu
                885                 890                 895
Phe Leu Thr Ile Ser Gln Ala His Lys Gln Asn Gly Asp Ser Tyr Gly
            900                 905                 910
Tyr Met Leu Ile Pro Asn Val Asp Arg Ala Thr Phe Asn Gln Met Ile
        915                 920                 925
Lys Glu Leu Glu Ser Ser Leu Ile Glu Asn Asn Glu Thr Leu Gln Ser
    930                 935                 940
Val Tyr Asp Ala Lys Gln Gly Val Trp Gly Ile Val Lys Tyr Asp Asp
945                 950                 955                 960
Ser Val Ser Thr Ile Ser Asn Gln Phe Gln Val Leu Lys Arg Gly Val
                965                 970                 975
Tyr Thr Ile Arg Lys Glu Gly Asp Glu Tyr Lys Ile Ala Tyr Tyr Asn
            980                 985                 990
Pro Glu Thr Gln Glu Ser Ala Pro Asp Gln Glu Val Phe Lys Lys Leu
        995                 1000                1005
Glu Gln Ala Ala Gln Pro Gln Val Gln Asn Ser Lys Glu Lys Glu Lys
    1010                1015                1020
Ser Glu Glu Glu Lys Asn His Ser Asp Gln Lys Asn Leu Pro Gln Thr
1025                1030                1035                1040
Gly Glu Gly Gln Ser Ile Leu Ala Ser Leu Gly Phe Leu Leu Leu Gly
                1045                1050                1055
Ala Phe Tyr Leu Phe Arg Arg Gly Lys Asn Asn
            1060                1065
```

<210> 293
<211> 805
<212> PRT
<213> 化膿鏈球菌血清型M1

<220>
<223> 玻尿酸解離酶

<400> 293

```
Met Asn Thr Tyr Phe Cys Thr His His Lys Gln Leu Leu Leu Tyr Ser
 1               5                  10                  15
Asn Leu Phe Leu Ser Phe Ala Met Met Gly Gln Gly Thr Ala Ile Tyr
            20                  25                  30
Ala Asp Thr Leu Thr Ser Asn Ser Glu Pro Asn Asn Thr Tyr Phe Gln
        35                  40                  45
Thr Gln Thr Leu Thr Thr Thr Asp Ser Glu Lys Lys Val Val Gln Pro
    50                  55                  60
Gln Gln Lys Asp Tyr Tyr Thr Glu Leu Leu Asp Gln Trp Asn Ser Ile
65                  70                  75                  80
Ile Ala Gly Asn Asp Ala Tyr Asp Lys Thr Asn Pro Asp Met Val Thr
                85                  90                  95
Phe His Asn Lys Ala Glu Lys Asp Ala Gln Asn Ile Ile Lys Ser Tyr
            100                 105                 110
Gln Gly Pro Asp His Glu Asn Arg Thr Tyr Leu Trp Glu His Ala Lys
        115                 120                 125
Asp Tyr Ser Ala Ser Ala Asn Ile Thr Lys Thr Tyr Arg Asn Ile Glu
    130                 135                 140
Lys Ile Ala Lys Gln Ile Thr Asn Pro Glu Ser Cys Tyr Tyr Gln Asp
145                 150                 155                 160
Ser Lys Ala Ile Ala Ile Val Lys Asp Gly Met Ala Phe Met Tyr Glu
                165                 170                 175
His Ala Tyr Asn Leu Asp Arg Glu Asn His Gln Thr Thr Gly Lys Glu
            180                 185                 190
Asn Lys Glu Asn Trp Trp Val Tyr Glu Ile Gly Thr Pro Arg Ala Ile
        195                 200                 205
Asn Asn Thr Leu Ser Leu Met Tyr Pro Tyr Phe Thr Gln Glu Glu Ile
    210                 215                 220
Leu Lys Tyr Thr Ala Pro Ile Glu Lys Phe Val Pro Asp Pro Thr Arg
225                 230                 235                 240
Phe Arg Val Arg Ala Ala Asn Phe Ser Pro Phe Glu Ala Asn Ser Gly
                245                 250                 255
Asn Leu Ile Asp Met Gly Arg Val Lys Leu Ile Ser Gly Ile Leu Arg
            260                 265                 270
Lys Asp Asp Leu Glu Ile Ser Asp Thr Ile Lys Ala Ile Glu Lys Val
        275                 280                 285
Phe Thr Leu Val Asp Glu Gly Asn Gly Phe Tyr Gln Asp Gly Ser Leu
    290                 295                 300
Ile Asp His Val Val Thr Asn Ala Gln Ser Pro Leu Tyr Lys Lys Gly
305                 310                 315                 320
Ile Ala Tyr Thr Gly Ala Tyr Gly Asn Val Leu Ile Asp Gly Leu Ser
                325                 330                 335
Gln Leu Ile Pro Ile Ile Gln Lys Thr Lys Ser Pro Ile Lys Ala Asp
            340                 345                 350
Lys Met Ala Thr Ile Tyr His Trp Ile Asn His Ser Phe Phe Pro Ile
        355                 360                 365
Ile Val Arg Gly Glu Met Met Asp Met Thr Arg Gly Arg Ser Ile Ser
    370                 375                 380
Arg Phe Asn Ala Gln Ser His Val Ala Gly Ile Glu Ala Leu Arg Ala
385                 390                 395                 400
Ile Leu Arg Ile Ala Asp Met Ser Glu Glu Pro His Arg Leu Ala Leu
                405                 410                 415
Lys Thr Arg Ile Lys Thr Leu Val Thr Gln Gly Asn Ala Phe Tyr Asn
            420                 425                 430
Val Tyr Asp Asn Leu Lys Thr Tyr His Asp Ile Lys Leu Met Lys Glu
        435                 440                 445
Leu Leu Ser Asp Thr Ser Val Pro Val Gln Lys Leu Asp Ser Tyr Val
    450                 455                 460
Ala Ser Phe Asn Ser Met Asp Lys Leu Ala Leu Tyr Asn Asn Lys His
465                 470                 475                 480
```

```
Asp Phe Ala Phe Gly Leu Ser Met Phe Ser Asn Arg Thr Gln Asn Tyr
                485                 490                 495
Glu Ala Met Asn Asn Glu Asn Leu His Gly Trp Phe Thr Ser Asp Gly
            500                 505                 510
Met Phe Tyr Leu Tyr Asn Asn Asp Leu Gly His Tyr Ser Glu Asn Tyr
        515                 520                 525
Trp Ala Thr Val Asn Pro Tyr Arg Leu Pro Gly Thr Thr Glu Thr Glu
    530                 535                 540
Gln Lys Pro Leu Glu Gly Thr Pro Glu Asn Ile Lys Thr Asn Tyr Gln
545                 550                 555                 560
Gln Val Gly Met Thr Gly Leu Ser Asp Asp Ala Phe Val Ala Ser Lys
                565                 570                 575
Lys Leu Asn Asn Thr Ser Ala Leu Ala Ala Met Thr Phe Thr Asn Trp
            580                 585                 590
Asn Lys Ser Leu Thr Leu Asn Lys Gly Trp Phe Ile Leu Gly Asn Lys
        595                 600                 605
Ile Ile Phe Val Gly Ser Asn Ile Lys Asn Gln Ser Ser His Lys Ala
    610                 615                 620
Tyr Thr Thr Ile Glu Gln Arg Lys Glu Asn Gln Lys Tyr Pro Tyr Cys
625                 630                 635                 640
Ser Tyr Val Asn Asn Gln Pro Val Asp Leu Asn Asn Gln Leu Val Asp
                645                 650                 655
Phe Thr Asn Thr Lys Ser Ile Phe Leu Glu Ser Asp Asp Pro Ala Gln
            660                 665                 670
Asn Ile Gly Tyr Tyr Phe Phe Lys Pro Thr Thr Leu Ser Ile Ser Lys
        675                 680                 685
Ala Leu Gln Thr Gly Lys Trp Gln Asn Ile Lys Ala Asp Asp Lys Ser
    690                 695                 700
Pro Glu Ala Ile Lys Glu Val Ser Asn Thr Phe Ile Thr Ile Met Gln
705                 710                 715                 720
Asn His Thr Gln Asp Gly Asp Arg Tyr Ala Tyr Met Met Leu Pro Asn

                725                 730                 735
Met Thr Arg Gln Glu Phe Glu Thr Tyr Ile Ser Lys Leu Asp Ile Asp
            740                 745                 750
Leu Leu Glu Asn Asn Asp Lys Leu Ala Ala Val Tyr Asp His Asp Ser
        755                 760                 765
Gln Gln Met His Val Ile His Tyr Gly Lys Lys Ala Thr Met Phe Ser
    770                 775                 780
Asn His Asn Leu Ser His Gln Gly Phe Tyr Ser Phe Pro His Pro Val
785                 790                 795                 800
Arg Gln Asn Gln Gln
                805
```

<210> 294
<211> 780
<212> PRT
<213> 化膿鏈球菌血清型M2 (菌株MGAS10270)

<220>
<223> 玻尿酸解離酶

<400> 294

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

```
                85                  90                  95
Leu Asp Gln Trp Asn Ser Ile Ile Ala Gly Asn Asp Ala Tyr Asp Lys
            100                 105                 110
Thr Asn Pro Asp Met Val Thr Phe His Asn Lys Ala Glu Lys Asp Ala
        115                 120                 125

Gln Asn Ile Ile Lys Ser Tyr Gln Gly Pro Asp His Glu Asn Arg Thr
    130                 135                 140
Tyr Leu Trp Glu His Ala Lys Asp Tyr Ser Ala Ser Thr Asn Ile Thr
145                 150                 155                 160
Lys Thr Tyr Arg Asn Ile Glu Lys Ile Ala Lys Gln Ile Thr Asn Pro
                165                 170                 175
Glu Ser Cys Tyr Tyr Gln Asp Ser Lys Ala Ile Ala Ile Val Lys Asp
            180                 185                 190
Gly Met Ala Phe Met Tyr Glu His Ala Tyr Asn Leu Asn Arg Glu Asn
        195                 200                 205
His Gln Thr Thr Gly Lys Glu Asn Lys Glu Asn Trp Trp Val Tyr Glu
    210                 215                 220
Ile Gly Thr Pro Arg Ala Ile Asn Asn Thr Leu Ser Leu Met Tyr Pro
225                 230                 235                 240
Tyr Phe Thr Gln Glu Glu Ile Leu Lys Tyr Thr Ala Pro Ile Glu Lys
                245                 250                 255
Phe Val Pro Asp Pro Thr Arg Phe Arg Val Arg Ala Ala Asn Phe Ser
            260                 265                 270
Pro Phe Glu Ala Asn Ser Gly Asn Leu Ile Asp Met Gly Arg Val Lys

        275                 280                 285
Leu Ile Ser Gly Ile Leu Arg Lys Asp Asp Leu Glu Ile Ser Asp Thr
    290                 295                 300
Ile Lys Ala Ile Glu Lys Val Phe Thr Leu Val Asp Glu Gly Asn Gly
305                 310                 315                 320
Phe Tyr Gln Asp Gly Ser Leu Ile Asp His Val Val Thr Asn Thr Gln
                325                 330                 335
Ser Pro Leu Tyr Lys Lys Gly Ile Ala Tyr Thr Gly Ala Tyr Gly Asn
            340                 345                 350
Val Leu Ile Asp Gly Leu Ser Gln Leu Ile Pro Ile Ile Gln Lys Thr
        355                 360                 365
Lys Ser Pro Ile Glu Ala Asp Lys Met Ala Thr Ile Tyr His Trp Ile
    370                 375                 380
Asn His Ser Phe Phe Pro Ile Ile Val Arg Gly Glu Met Met Asp Met
385                 390                 395                 400
Thr Arg Gly Arg Ser Ile Ser Arg Phe Asn Ala Gln Ser His Val Ala
                405                 410                 415
Gly Ile Glu Ala Leu Arg Ala Ile Leu Arg Ile Ala Asp Met Ser Glu
            420                 425                 430
Glu Pro His Arg Leu Glu Leu Lys Thr Arg Ile Lys Thr Leu Val Thr
        435                 440                 445
Gln Gly Asn Ala Phe Tyr Asn Val Tyr Asp Asn Leu Lys Thr Tyr His
    450                 455                 460
Asp Ile Lys Leu Met Lys Glu Leu Leu Ser Asp Thr Ser Val Pro Val

465                 470                 475                 480
Gln Lys Leu Asp Ser Tyr Val Ala Ser Phe Asn Ser Met Asp Lys Leu
                485                 490                 495
Ala Leu Tyr Asn Asn Lys His Asp Phe Ala Phe Gly Leu Ser Met Phe
            500                 505                 510
Ser Asn Arg Thr Gln Asn Tyr Glu Ala Met Asn Asn Glu Asn Leu His
        515                 520                 525
Gly Trp Phe Thr Ser Asp Gly Met Phe Tyr Leu Tyr Asn Asn Asp Leu
    530                 535                 540
Gly His Tyr Ser Glu Asn Tyr Trp Ala Thr Val Asn Pro Tyr Arg Leu
545                 550                 555                 560
Pro Gly Thr Thr Glu Thr Glu Gln Lys Pro Leu Glu Gly Thr Pro Glu
                565                 570                 575
Asn Ile Lys Thr Asn Tyr Gln Gln Val Gly Met Thr Ser Leu Ser Asp
```

```
            580                 585                 590
Asp Ala Phe Val Ala Ser Lys Lys Leu Asn Asn Thr Ser Ala Leu Ala
        595                 600                 605
Ala Met Thr Phe Thr Asn Trp Asn Lys Ser Leu Thr Leu Asn Lys Gly
    610                 615                 620
Trp Phe Ile Leu Gly Asn Lys Ile Ile Phe Val Gly Ser Asn Ile Lys
625                 630                 635                 640
Asn Gln Ser Ser His Lys Ala Tyr Thr Thr Ile Glu Gln Arg Lys Glu
                645                 650                 655
Asn Gln Lys His Pro Tyr Cys Ser Tyr Val Asn Asn Gln Pro Val Asp
            660                 665                 670
Leu Asn Asn Gln Leu Val Asp Phe Thr Asn Thr Lys Ser Ile Phe Leu
        675                 680                 685
Glu Ser Asp Asp Pro Ala Gln Asn Ile Gly Tyr Tyr Phe Phe Lys Pro
    690                 695                 700
Arg Thr Leu Ser Ile Ser Lys Ala Leu Gln Thr Gly Lys Trp Gln Asn
705                 710                 715                 720
Ile Lys Ala Asp Asp Lys Ser Pro Glu Ala Ile Lys Glu Val Ser Asn
                725                 730                 735
Thr Phe Ile Thr Ile Met Gln Asn His Thr Gln Glu Gly Asp Arg Tyr
            740                 745                 750
Ala Tyr Met Met Leu Pro Asn Met Thr Arg Gln Glu Phe Glu Thr Tyr
        755                 760                 765
Ile Ser Lys Leu Asp Ile Asp Leu Leu Glu Asn Asn
    770                 775                 780
```

<210> 295
<211> 868
<212> PRT
<213> 化膿鏈球菌血清型M4 (菌株MGAS10750)

<220>
<223> 玻尿酸解離酶

<400> 295

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

225 230 235 240
Phe Arg Val Arg Ala Ala Asn Phe Pro Pro Phe Glu Ala Asn Ser Gly
245 250 255
Asn Leu Ile Asp Met Gly Arg Val Lys Leu Ile Ser Gly Ile Leu Arg
260 265 270
Lys Asp Asp Leu Glu Ile Ser Asp Thr Ile Lys Ala Ile Glu Lys Val
275 280 285
Phe Thr Leu Val Asp Glu Gly Asn Gly Phe Tyr Gln Asp Gly Ser Leu
290 295 300
Ile Asp His Val Val Thr Asn Ala Gln Ser Pro Leu Tyr Lys Lys Gly
305 310 315 320
Ile Ala Tyr Thr Gly Ala Tyr Gly Asn Val Leu Ile Asp Gly Leu Ser
325 330 335
Gln Leu Ile Pro Ile Ile Gln Lys Thr Lys Ser Pro Ile Glu Ala Asp
340 345 350
Lys Met Ala Thr Ile Tyr His Trp Ile Asn His Ser Phe Phe Pro Ile
355 360 365
Ile Val Arg Gly Glu Met Met Asp Met Thr Arg Gly Arg Ser Ile Ser
370 375 380
Arg Phe Asn Ala Gln Ser His Val Ala Gly Ile Glu Ala Leu Arg Ala
385 390 395 400
Ile Leu Arg Ile Ala Asp Met Ser Glu Glu Pro His Arg Leu Ala Leu
405 410 415
Lys Thr Arg Ile Lys Thr Leu Val Thr Gln Gly Asn Val Phe Tyr Asn
420 425 430
Val Tyr Asp Asn Leu Lys Thr Tyr His Asp Ile Lys Leu Met Lys Glu
435 440 445
Leu Leu Ser Asp Thr Ser Val Pro Val Gln Lys Leu Asp Ser Tyr Val
450 455 460
Ala Ser Phe Asn Ser Met Asp Lys Leu Ala Leu Tyr Asn Asn Lys His
465 470 475 480
Asp Phe Ala Phe Gly Leu Ser Met Phe Ser Asn Arg Thr Gln Asn Tyr
485 490 495
Glu Ala Met Asn Asn Glu Asn Leu His Gly Trp Phe Thr Ser Asp Gly
500 505 510
Met Phe Tyr Leu Tyr Asn Asn Asp Leu Gly His Tyr Ser Glu Asn Tyr
515 520 525
Trp Ala Thr Val Asn Pro Tyr Arg Leu Pro Gly Thr Thr Glu Thr Glu
530 535 540
Gln Lys Pro Leu Glu Gly Thr Pro Glu Asn Ile Lys Thr Asn Tyr Gln
545 550 555 560
Gln Val Gly Met Thr Ser Leu Ser Asp Asp Ala Phe Val Ala Ser Lys
565 570 575
Lys Leu Asn Asn Thr Ser Ala Leu Ala Ala Met Thr Phe Thr Asn Trp
580 585 590
Asn Lys Ser Leu Thr Leu Asn Lys Gly Trp Phe Ile Leu Gly Asn Lys
595 600 605
Ile Ile Phe Val Gly Ser Asn Ile Lys Asn Gln Ser Ser His Lys Ala
610 615 620
Tyr Thr Thr Ile Glu Gln Arg Lys Glu Asn Gln Lys His Pro Tyr Cys
625 630 635 640
Ser Tyr Val Asn Asn Gln Pro Val Asp Leu Asn Asn Gln Leu Val Asp
645 650 655
Phe Thr Asn Thr Lys Ser Ile Phe Leu Glu Ser Asp Asp Pro Ala Gln
660 665 670
Asn Ile Gly Tyr Tyr Phe Phe Lys Pro Thr Thr Leu Ser Ile Ser Lys
675 680 685
Ala Leu Gln Thr Gly Lys Trp Gln Asn Ile Lys Ala Asp Asp Lys Ser
690 695 700
Pro Glu Ala Ile Lys Glu Val Ser Asn Thr Phe Ile Thr Ile Met Gln
705 710 715 720
Asn His Thr Gln Asp Gly Asp Arg Tyr Ala Tyr Met Met Leu Pro Asn
725 730 735
Met Thr Arg Gln Glu Phe Glu Thr Tyr Ile Ser Lys Leu Asp Ile Asp
740 745 750

```
Leu Leu Glu Asn Asn Asp Lys Leu Ala Ala Val Tyr Asp His Asp Ser
        755                 760                 765
Gln Gln Met His Val Ile His Tyr Glu Lys Lys Ala Thr Thr Phe Ser
    770                 775                 780
Asn His Asn Leu Ser His Gln Gly Phe Tyr Ser Phe Pro His Pro Val
785                 790                 795                 800

Lys Gln Asn Gln Gln Gln Lys Leu Ala His Gln Gly Ile Ala Ala Lys
                805                 810                 815
Asn Asn Ala Leu Asn Ser His Lys Ile Pro His Lys Arg Gln Arg Arg
            820                 825                 830
Leu Pro Arg Thr Gly Tyr Gln Ser Ser Ser Leu Glu Phe Leu Gly Gly
        835                 840                 845
Ala Leu Val Ala Ser Phe Asn His Ile Thr Lys Pro Phe Arg Lys Lys
    850                 855                 860
Asp Leu Arg Ile
865
```

<210> 296
<211> 828
<212> PRT
<213> 化膿鏈球菌血清型M6

<220>
<223> 玻尿酸解離酶

<400> 296

```
Met Val Tyr Phe Tyr Leu Val Asp Gln Phe Thr Phe Ile Ile Ser Phe
 1               5                  10                  15
Leu Tyr Trp Arg Asn Leu Ser Val Asn Thr Tyr Phe Cys Thr His His
            20                  25                  30
Lys Gln Leu Leu Leu Tyr Ser Asn Leu Phe Leu Ser Phe Ala Met Met
        35                  40                  45
Gly Gln Gly Thr Ala Ile Tyr Ala Asp Thr Leu Thr Ser Asn Ser Glu
    50                  55                  60
Pro Asn Asn Thr Tyr Phe Gln Thr Gln Thr Leu Thr Thr Thr Asp Ser
65                  70                  75                  80
Glu Lys Lys Val Val Gln Pro Gln Gln Lys Asp Tyr Tyr Thr Glu Leu
                85                  90                  95
Leu Asp Gln Trp Asn Ser Ile Ile Ala Gly Asn Asp Ala Tyr Asp Lys
            100                 105                 110
Thr Asn Pro Asp Met Val Thr Phe His Asn Lys Ala Glu Lys Asp Ala
        115                 120                 125
Gln Asn Ile Ile Lys Ser Tyr Gln Gly Pro Asp His Glu Asn Arg Thr
    130                 135                 140
Tyr Leu Trp Glu His Ala Lys Asp Tyr Ser Ala Ser Thr Asn Ile Thr
145                 150                 155                 160
Lys Thr Tyr Arg Asn Ile Glu Lys Ile Ala Lys Gln Ile Thr Asn Pro
                165                 170                 175
Glu Ser Cys Tyr Tyr Gln Asp Ser Lys Ala Ile Ala Ile Val Lys Asp
            180                 185                 190
Gly Met Ala Phe Met Tyr Glu His Ala Tyr Asn Leu Asp Arg Glu Asn
        195                 200                 205
His Gln Thr Thr Gly Lys Glu Asn Lys Glu Asn Trp Trp Val Tyr Glu
    210                 215                 220
Ile Gly Thr Pro Arg Ala Ile Asn Asn Thr Leu Ser Leu Met Tyr Pro
225                 230                 235                 240
Tyr Phe Thr Gln Glu Glu Ile Leu Lys Tyr Thr Ala Pro Ile Glu Lys
                245                 250                 255
Phe Val Pro Asp Pro Thr Arg Phe Arg Val Arg Ala Ala Asn Phe Ser
            260                 265                 270
Pro Phe Glu Ala Asn Ser Gly Asn Leu Ile Asp Met Gly Arg Val Lys
        275                 280                 285
Leu Ile Ser Gly Ile Leu Arg Lys Asp Asp Leu Glu Ile Ser Asp Thr
```

```
    290                 295                 300
Ile Lys Ala Ile Glu Lys Val Phe Thr Leu Val Asp Glu Gly Asn Gly
305                 310                 315                 320
Phe Tyr Gln Asp Gly Ser Leu Ile Asp His Val Val Thr Asn Ala Gln
                325                 330                 335
Ser Pro Leu Tyr Lys Lys Gly Ile Ala Tyr Thr Gly Ala Tyr Gly Asn
            340                 345                 350
Val Leu Ile Asp Gly Leu Ser Gln Leu Ile Pro Ile Ile Gln Lys Thr
        355                 360                 365
Lys Ser Pro Ile Glu Ala Asp Lys Met Ala Thr Ile Tyr His Trp Ile
    370                 375                 380
Asn His Ser Phe Phe Pro Ile Ile Val Arg Gly Glu Met Met Asp Met
385                 390                 395                 400
Thr Arg Gly Arg Ser Ile Ser Arg Phe Asn Ala Gln Ser His Val Ala
                405                 410                 415
Gly Ile Glu Ala Leu Arg Ala Ile Leu Arg Ile Ala Asp Met Ser Glu
            420                 425                 430
Glu Pro His Arg Leu Ala Leu Lys Thr Arg Ile Lys Thr Leu Val Thr
        435                 440                 445
Gln Gly Asn Ala Phe Tyr Asn Val Tyr Asp Asn Leu Lys Thr Tyr His
    450                 455                 460
Asp Ile Lys Leu Met Lys Glu Leu Leu Ser Asp Thr Phe Val Pro Val
465                 470                 475                 480
Gln Lys Leu Asp Ser Tyr Val Ala Ser Phe Asn Ser Met Asp Lys Leu
                485                 490                 495
Ala Leu Tyr Asn Asn Lys His Asp Phe Ala Phe Gly Leu Ser Met Phe
            500                 505                 510
Ser Asn Arg Thr Gln Asn Tyr Glu Ala Met Asn Asn Glu Asn Leu His
        515                 520                 525
Gly Trp Phe Thr Ser Asp Gly Met Phe Tyr Leu Tyr Asn Asn Asp Leu
    530                 535                 540
Gly His Tyr Ser Glu Asn Tyr Trp Ala Thr Val Asn Pro Tyr Arg Leu
545                 550                 555                 560
Pro Gly Thr Thr Glu Thr Glu Gln Lys Pro Leu Glu Gly Thr Pro Glu
                565                 570                 575
Asn Ile Lys Thr Asp Tyr Gln Gln Val Gly Met Thr Ser Leu Ser Asp
            580                 585                 590
Asp Ala Phe Val Ala Ser Lys Lys Leu Asn Asn Thr Ser Ala Leu Ala
        595                 600                 605
Ala Met Thr Phe Thr Asn Trp Asn Lys Ser Leu Thr Leu Asn Lys Gly
    610                 615                 620
Trp Phe Ile Leu Gly Asn Lys Ile Ile Phe Val Gly Ser Asn Ile Lys
625                 630                 635                 640
Asn Gln Ser Ser His Lys Ala Tyr Thr Thr Ile Glu Gln Arg Lys Glu
                645                 650                 655
Asn Gln Lys His Pro Tyr Cys Ser Tyr Val Asn Asn Gln Pro Val Asp
            660                 665                 670
Leu Asn Asn Gln Leu Val Asp Phe Thr Asn Thr Lys Ser Ile Phe Leu
        675                 680                 685
Glu Ser Asp Asp Pro Ala Gln Asn Ile Gly Tyr Tyr Phe Phe Lys Pro
    690                 695                 700
Thr Thr Leu Ser Ile Ser Lys Ala Leu Gln Thr Gly Lys Trp Gln Asn
705                 710                 715                 720
Ile Lys Ala Asp Asp Lys Ser Pro Glu Ala Ile Lys Glu Val Ser Asn
                725                 730                 735
Thr Phe Ile Thr Ile Met Gln Asn His Thr Gln Asp Gly Asp Arg Tyr
            740                 745                 750
Ala Tyr Met Met Leu Pro Asn Met Thr Arg Gln Glu Phe Glu Thr Tyr
        755                 760                 765
Ile Ser Lys Leu Asp Ile Asp Leu Leu Glu Asn Asn Asp Lys Leu Ala
    770                 775                 780
Ala Val Tyr Asp His Asp Ser Gln Gln Met His Val Ile His Tyr Glu
785                 790                 795                 800
Lys Lys Ala Thr Met Phe Ser Asn His Asn Leu Ser His Gln Gly Phe
                805                 810                 815
```

```
Tyr Ser Phe Pro His Pro Val Lys Gln Asn Gln Gln
            820                 825
```

<210> 297
<211> 556
<212> PRT
<213> 化膿鏈球菌血清型M12 (菌株MGAS2096)

<220>
<223> 玻尿酸解離酶

<400> 297

```
Met Val Tyr Phe Tyr Leu Val Asn Gln Ser Thr Phe Ile Ile Ser Phe
 1               5                  10                  15
Leu Tyr Trp Arg Asn Leu Ser Val Asn Thr Tyr Phe Cys Thr His His
            20                  25                  30
Lys Gln Leu Leu Leu Tyr Ser Asn Leu Phe Leu Ser Phe Ala Met Met
        35                  40                  45
Gly Gln Gly Thr Ala Ile Tyr Ala Asp Thr Leu Thr Ser Asn Ser Glu
    50                  55                  60
Pro Asn Asn Thr Tyr Phe Gln Thr Gln Thr Leu Thr Thr Thr Asp Ser
65                  70                  75                  80
Glu Lys Lys Val Val Gln Pro Gln Gln Lys Asp Tyr Tyr Thr Glu Leu
                85                  90                  95
Leu Asp Gln Trp Asn Ser Ile Ile Ala Gly Asn Asp Ala Tyr Asp Lys
            100                 105                 110
Thr Asn Pro Asp Met Val Thr Phe His Asn Lys Ala Glu Lys Asp Ala
        115                 120                 125
Gln Asn Ile Ile Lys Ser Tyr Gln Gly Pro Asp His Glu Asn Arg Thr
    130                 135                 140
Tyr Leu Gly Asn Met Gln Arg Ile Ile Pro Leu Leu Leu Ile Ser Arg
145                 150                 155                 160
Lys Leu Thr Ala Ile Leu Lys Lys Ile Ser Lys Met Lys Ser Leu Met
                165                 170                 175
Glu Asp Ser Thr Ile Ser Thr Asn Gly Leu Thr Gln Gln Leu Lys Ile
            180                 185                 190
Tyr Asn Asp Met Asp Arg Val Thr Tyr His Asn Lys Gly Leu Asp Phe
        195                 200                 205
Ala Phe Gly Leu Ser Met Thr Ser Lys Asn Val Ala Arg Tyr Glu Ser
    210                 215                 220
Ile Asn Gly Glu Asn Leu Lys Gly Trp His Thr Gly Ala Gly Met Ser
225                 230                 235                 240
Tyr Leu Tyr Asn Ser Asp Val Lys His Tyr Arg Asp Asn Phe Trp Ala
                245                 250                 255
Thr Ala Asp Met Lys Arg Leu Ala Gly Thr Thr Thr Leu Asp Asn Glu
            260                 265                 270
Glu Pro Lys Ser Thr Asp Val Lys Lys Ser Ser Lys Thr Phe Val Gly
        275                 280                 285
Gly Thr Lys Phe Asp Asp Gln His Ala Ser Ile Gly Met Asp Phe Glu
    290                 295                 300
Asn Gln Asp Lys Thr Leu Thr Ala Lys Lys Ser Tyr Phe Ile Leu Asn
305                 310                 315                 320
Asp Lys Ile Val Phe Leu Gly Thr Gly Ile Lys Ser Thr Asp Ser Ser
                325                 330                 335
Lys Asn Pro Val Thr Thr Ile Glu Asn Arg Lys Ala Asn Asp Tyr Lys
            340                 345                 350
Leu Tyr Lys Asp Asp Thr Gln Thr Thr Asn Ser Asp Asn Gln Glu Thr
        355                 360                 365
Asn Ser Leu Phe Leu Glu Ser Thr Asn Ser Thr Gln Asn Asn Ile Gly
    370                 375                 380
Tyr His Phe Leu Asn Glu Ser Lys Ile Thr Val Lys Lys Glu Ser His
385                 390                 395                 400
Thr Gly Lys Trp Ser Asp Ile Asn Lys Ser Gln Lys Asp Ile Gln Lys
                405                 410                 415
```

```
Thr Asp Glu Tyr Tyr Glu Val Thr Gln Lys His Ser Asn Thr Asp Ser
            420                 425                 430
Lys Tyr Ala Tyr Val Leu Tyr Pro Gly Leu Ser Lys Asp Val Phe Lys
        435                 440                 445
Ser Lys Ala Ser Lys Val Thr Val Val Lys Gln Glu Asp Asp Phe His
    450                 455                 460
Val Val Lys Asp Asn Glu Ser Val Trp Ala Gly Ile Asn Tyr Ser Asp
465                 470                 475                 480
Ser Ala Lys Thr Phe Glu Ile Asn Asn Thr Lys Val Glu Val Lys Ala
                485                 490                 495
Lys Gly Met Phe Ile Leu Thr Lys Lys Asp Asp Asn Thr Tyr Glu Cys
            500                 505                 510
Ser Phe Tyr Asn Pro Glu Ser Thr Asn Ser Val Ser Asp Ile Glu Ser
        515                 520                 525
Lys Ile Ser Met Thr Gly Tyr Ser Ile Ile Asn Lys Asn Thr Ser Thr
    530                 535                 540
Ser Asn Glu Ser Gly Val Arg Phe Glu Leu Thr Lys
545                 550                 555
```

<210> 298
<211> 635
<212> PRT
<213> 化膿鏈球菌血清型M12 (菌株MGAS2096)

<220>
<223> 玻尿酸解離酶

<400> 298

```
Met Ala Phe Met Tyr Glu His Ala Tyr Asn Leu Asn Arg Glu Asn His
 1                5                  10                  15
Gln Thr Thr Gly Lys Glu Asn Lys Glu Asn Trp Trp Val Tyr Glu Ile
            20                  25                  30
Gly Thr Pro Arg Ala Ile Asn Asn Thr Leu Ser Leu Met Tyr Pro Tyr
        35                  40                  45
Phe Thr Gln Glu Glu Ile Leu Lys Tyr Thr Ala Pro Ile Glu Lys Phe
    50                  55                  60
Val Pro Asp Pro Thr Arg Phe Arg Val Arg Ala Ala Asn Phe Ser Pro
65                  70                  75                  80
Phe Glu Ala Ser Ser Gly Asn Leu Ile Asp Met Gly Arg Val Lys Leu
                85                  90                  95
Ile Ser Gly Ile Leu Arg Lys Asp Asp Leu Glu Ile Ser Asp Thr Ile
            100                 105                 110
Lys Ala Ile Glu Lys Val Phe Thr Leu Val Asp Glu Gly Asn Gly Phe
        115                 120                 125
Tyr Gln Asp Gly Ser Leu Ile Asp His Val Val Thr Asn Ala Gln Ser
    130                 135                 140
Pro Leu Tyr Lys Lys Gly Ile Ala Tyr Thr Gly Ala Tyr Gly Asn Val
145                 150                 155                 160
Leu Ile Asp Gly Leu Ser Gln Leu Ile Pro Ile Ile Gln Lys Thr Lys
                165                 170                 175
Ser Pro Ile Glu Ala Asp Lys Met Ala Thr Ile Tyr His Trp Ile Asn
            180                 185                 190
His Ser Phe Phe Pro Ile Ile Val Arg Gly Glu Met Met Asp Met Thr
        195                 200                 205
Arg Gly Arg Ser Ile Ser Arg Phe Asn Ala Gln Ser His Val Ala Gly
    210                 215                 220
Ile Glu Ala Leu Arg Ala Ile Leu Arg Ile Ala Asp Met Ser Glu Glu
225                 230                 235                 240
Pro His Arg Leu Ala Leu Lys Thr Arg Ile Lys Thr Leu Val Thr Gln
                245                 250                 255
Gly Asn Ala Phe Tyr Asn Val Tyr Asp Asn Leu Lys Thr Tyr His Asp
            260                 265                 270
Ile Lys Leu Met Lys Glu Leu Leu Ser Asp Thr Ser Val Pro Val Gln
        275                 280                 285
```

```
Lys Leu Asp Ser Tyr Val Ala Ser Phe Asn Ser Met Asp Lys Leu Ala
    290                 295                 300
Leu Tyr Asn Asn Lys His Asp Phe Ala Phe Gly Leu Ser Met Phe Ser
305                 310                 315                 320
Asn Arg Thr Gln Asn Tyr Glu Ala Met Asn Asn Glu Asn Leu His Gly
                325                 330                 335
Trp Phe Thr Ser Asp Gly Met Phe Tyr Leu Tyr Asn Asn Asp Leu Gly
            340                 345                 350
His Tyr Ser Glu Asn Tyr Trp Ala Thr Val Asn Pro Tyr Arg Leu Pro
        355                 360                 365
Gly Thr Thr Glu Thr Glu Gln Lys Pro Leu Glu Gly Thr Pro Glu Asn
    370                 375                 380
Ile Lys Thr Asn Tyr Gln Gln Val Gly Met Thr Ser Leu Ser Asp Asp
385                 390                 395                 400
Ala Phe Val Ala Ser Lys Lys Leu Asn Asn Thr Ser Ala Leu Ala Ala
                405                 410                 415
Met Thr Phe Thr Asn Trp Asn Lys Ser Leu Thr Leu Asn Lys Gly Trp
            420                 425                 430
Phe Ile Leu Gly Asn Lys Ile Ile Phe Val Gly Ser Asn Ile Lys Asn
        435                 440                 445
Gln Ser Ser His Lys Ala Tyr Thr Thr Ile Glu Gln Arg Lys Glu Asn
    450                 455                 460
Gln Lys His Pro Tyr Cys Ser Tyr Val Asn Asn Gln Pro Val Asp Leu
465                 470                 475                 480
Asn Asn Gln Leu Val Asp Phe Thr Asn Thr Lys Ser Ile Phe Leu Glu
                485                 490                 495
Ser Asp Asp Pro Ala Gln Asn Ile Gly Tyr Tyr Phe Phe Lys Pro Thr
            500                 505                 510
Thr Leu Ser Ile Ser Lys Ala Leu Gln Thr Gly Lys Trp Gln Asn Ile
        515                 520                 525
Lys Ala Asp Asp Lys Ser Pro Glu Ala Ile Lys Glu Val Ser Asn Thr
    530                 535                 540
Phe Ile Thr Ile Met Gln Asn His Thr Gln Asp Gly Asp Arg Tyr Ala
545                 550                 555                 560
Tyr Met Met Leu Pro Asn Met Thr Arg Gln Glu Phe Glu Thr Tyr Ile
                565                 570                 575
Ser Lys Leu Asp Ile Asp Leu Leu Glu Asn Asn Asp Lys Leu Ala Ala
            580                 585                 590
Val Tyr Asp His Asp Ser Gln Gln Met His Val Ile His Tyr Glu Lys
        595                 600                 605
Lys Ala Thr Met Phe Ser Asn His Asn Leu Ser His Gln Gly Phe Tyr
    610                 615                 620
Ser Phe Pro His Pro Val Lys Gln Asn Gln Gln
625                 630                 635


<210> 299
<211> 828
<212> PRT
<213> 化膿鏈球菌血清型M12 (菌株MGAS9429)

<220>
<223> 玻尿酸解離酶

<400> 299
Met Val Tyr Phe Tyr Leu Val Asn Gln Ser Thr Phe Ile Ile Ser Phe
 1               5                  10                  15
Leu Tyr Trp Arg Asn Leu Ser Val Asn Thr Tyr Phe Cys Thr His His
            20                  25                  30
Lys Gln Leu Leu Leu Tyr Ser Asn Leu Phe Leu Ser Phe Ala Met Met
        35                  40                  45
Gly Gln Gly Thr Ala Ile Tyr Ala Asp Thr Leu Thr Ser Asn Ser Glu
    50                  55                  60
Pro Asn Asn Thr Tyr Phe Gln Thr Gln Thr Leu Thr Thr Thr Asp Ser
65                  70                  75                  80
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```
Glu Lys Lys Val Val Gln Pro Gln Gln Lys Asp Tyr Tyr Thr Glu Leu
                85                  90                  95
Leu Asp Gln Trp Asn Ser Ile Ile Ala Gly Asn Asp Ala Tyr Val Lys
            100                 105                 110
Thr Asn Pro Asp Met Val Thr Phe His Asn Lys Ala Glu Lys Asp Ala
        115                 120                 125
Gln Asn Ile Ile Lys Ser Tyr Gln Gly Pro Asp His Glu Asn Arg Thr
    130                 135                 140
Tyr Leu Trp Glu His Ala Lys Asp Tyr Ser Ala Ser Thr Asn Ile Thr
145                 150                 155                 160
Lys Thr Tyr Arg Asn Ile Glu Lys Ile Ala Lys Gln Ile Thr Asn Pro
                165                 170                 175
Glu Ser Cys Tyr Tyr Gln Asp Ser Lys Ala Ile Ala Ile Val Lys Asp
            180                 185                 190
Gly Met Ala Phe Met Tyr Glu His Ala Tyr Asn Leu Asn Arg Glu Asn
        195                 200                 205
His Gln Thr Thr Gly Lys Glu Asn Lys Glu Asn Trp Trp Val Tyr Glu
    210                 215                 220
Ile Gly Thr Pro Arg Ala Ile Asn Asn Thr Leu Ser Leu Met Tyr Pro
225                 230                 235                 240
Tyr Phe Thr Gln Glu Glu Ile Leu Lys Tyr Thr Ala Pro Ile Glu Lys
                245                 250                 255
Phe Val Pro Asp Pro Thr Arg Phe Arg Val Arg Ala Ala Asn Phe Ser
            260                 265                 270
Pro Phe Glu Ala Ser Ser Gly Asn Leu Ile Asp Met Gly Arg Val Lys
        275                 280                 285
Leu Ile Ser Gly Ile Leu Arg Lys Asp Asp Leu Glu Ile Ser Asp Thr
    290                 295                 300
Ile Lys Ala Ile Glu Lys Val Phe Thr Leu Val Asp Glu Gly Asn Gly
305                 310                 315                 320
Phe Tyr Gln Asp Gly Ser Leu Ile Asp His Val Val Thr Asn Ala Gln
                325                 330                 335
Ser Pro Leu Tyr Lys Lys Gly Ile Ala Tyr Thr Gly Ala Tyr Gly Asn
            340                 345                 350
Val Leu Ile Asp Gly Leu Ser Gln Leu Ile Pro Ile Ile Gln Lys Thr
        355                 360                 365
Lys Ser Pro Ile Glu Ala Asp Lys Met Ala Thr Ile Tyr His Trp Ile
    370                 375                 380
Asn His Ser Phe Phe Pro Ile Ile Val Arg Gly Glu Met Met Asp Met
385                 390                 395                 400
Thr Arg Gly Arg Ser Ile Ser Arg Phe Asn Ala Gln Ser His Val Ala
                405                 410                 415
Gly Ile Glu Ala Leu Arg Ala Ile Leu Arg Ile Ala Asp Met Ser Glu
            420                 425                 430
Glu Pro His Arg Leu Ala Leu Lys Thr Arg Ile Lys Thr Leu Val Thr
        435                 440                 445
Gln Gly Asn Ala Phe Tyr Asn Val Tyr Asp Asn Leu Lys Thr Tyr His
    450                 455                 460
Asp Ile Lys Leu Met Lys Glu Leu Leu Ser Asp Thr Ser Val Pro Val
465                 470                 475                 480
Gln Lys Leu Asp Ser Tyr Val Ala Ser Phe Asn Ser Met Asp Lys Leu
                485                 490                 495
Ala Leu Tyr Asn Asn Lys His Asp Phe Ala Phe Gly Leu Ser Met Phe
            500                 505                 510
Ser Asn Arg Thr Gln Asn Tyr Glu Ala Met Asn Asn Glu Asn Leu His
        515                 520                 525
Gly Trp Phe Thr Ser Asp Gly Met Phe Tyr Leu Tyr Asn Asn Asp Leu
    530                 535                 540
Gly His Tyr Ser Glu Asn Tyr Trp Ala Thr Val Asn Pro Tyr Arg Leu
545                 550                 555                 560
Pro Gly Thr Thr Glu Thr Glu Gln Lys Pro Leu Glu Gly Thr Pro Glu
                565                 570                 575
Asn Ile Lys Thr Asn Tyr Gln Gln Val Gly Met Thr Ser Leu Ser Asp
            580                 585                 590
Asp Ala Phe Val Ala Ser Lys Lys Leu Asn Asn Thr Ser Ala Leu Ala
```

595 600 605
Ala Met Thr Phe Thr Asn Trp Asn Lys Ser Leu Thr Leu Asn Lys Gly
610 615 620
Trp Phe Ile Leu Gly Asn Lys Ile Ile Phe Val Gly Ser Asn Ile Lys
625 630 635 640
Asn Gln Ser Ser His Lys Ala Tyr Thr Thr Ile Glu Gln Arg Lys Glu
645 650 655
Asn Gln Lys His Pro Tyr Cys Ser Tyr Val Asn Asn Gln Pro Val Asp
660 665 670
Leu Asn Asn Gln Leu Val Asp Phe Thr Asn Thr Lys Ser Ile Phe Leu
675 680 685
Glu Ser Asp Asp Pro Ala Gln Asn Ile Gly Tyr Tyr Phe Phe Lys Pro
690 695 700
Thr Thr Leu Ser Ile Ser Lys Ala Leu Gln Thr Gly Lys Trp Gln Asn
705 710 715 720
Ile Lys Ala Asp Asp Lys Ser Pro Glu Ala Ile Lys Glu Val Ser Asn
725 730 735
Thr Phe Ile Thr Ile Met Gln Asn His Thr Gln Asp Gly Asp Arg Tyr
740 745 750
Ala Tyr Met Met Leu Pro Asn Met Thr Arg Gln Glu Phe Glu Thr Tyr
755 760 765
Ile Ser Lys Leu Asp Ile Asp Leu Leu Glu Asn Asn Asp Lys Leu Ala
770 775 780

Ala Val Tyr Asp His Asp Ser Gln Gln Met His Val Ile His Tyr Glu
785 790 795 800
Lys Lys Ala Thr Met Phe Ser Asn His Asn Leu Ser His Gln Gly Phe
805 810 815
Tyr Ser Phe Pro His Pro Val Lys Gln Asn Gln Gln
820 825

<210> 300
<211> 828
<212> PRT
<213> 化膿鏈球菌血清型M28

<220>
<223> 玻尿酸解離酶

<400> 300
Met Val Tyr Phe Tyr Leu Val Asn Gln Phe Thr Phe Ile Ile Ser Phe
1 5 10 15
Leu Tyr Arg Arg Asn Leu Ser Val Asn Thr Tyr Phe Cys Thr His His
20 25 30
Lys Gln Leu Leu Leu Tyr Ser Asn Leu Phe Leu Ser Phe Ala Met Met
35 40 45
Gly Gln Gly Thr Ala Ile Tyr Ala Asp Thr Leu Thr Ser Asn Ser Glu
50 55 60
Pro Asn Asn Thr Tyr Phe Gln Thr Gln Met Leu Thr Thr Thr Asp Ser
65 70 75 80
Glu Lys Lys Val Val Gln Pro Gln Gln Lys Asp Tyr Tyr Thr Glu Leu
85 90 95
Leu Asp Gln Trp Asn Ser Ile Ile Ala Gly Asn Asp Ala Tyr Asp Lys
100 105 110
Thr Asn Pro Asp Met Val Thr Phe His Asn Lys Ala Glu Lys Asp Ala
115 120 125
Gln Asn Ile Ile Lys Ser Tyr Gln Gly Pro Asp His Glu Asn Arg Thr
130 135 140
Tyr Leu Trp Glu His Ala Lys Asp Tyr Ser Ala Ser Ala Asn Ile Thr
145 150 155 160
Lys Thr Tyr Arg Asn Ile Glu Lys Ile Ala Lys Gln Ile Thr Asn Pro
165 170 175
Glu Ser Cys Tyr Tyr Gln Asp Ser Lys Ala Ile Ala Ile Val Lys Asp
180 185 190

```
Gly Met Ala Phe Met Tyr Glu His Ala Tyr Asn Leu Asp Arg Glu Asn
        195                 200                 205
His Gln Thr Thr Gly Lys Glu Asn Lys Glu Asn Trp Trp Val Tyr Glu
    210                 215                 220
Ile Gly Thr Pro Arg Ala Ile Asn Asn Thr Leu Ser Leu Met Tyr Pro
225                 230                 235                 240
Tyr Phe Thr Gln Glu Glu Ile Leu Lys Tyr Thr Ala Pro Ile Glu Lys
                245                 250                 255
Phe Val Pro Asp Pro Thr Arg Phe Arg Val Arg Ala Ala Asn Phe Ser
            260                 265                 270
Pro Phe Glu Ala Asn Ser Gly Asn Leu Ile Asp Met Gly Arg Val Lys
        275                 280                 285
Leu Ile Ser Gly Ile Leu Arg Lys Asp Asp Leu Glu Ile Ser Asp Thr
    290                 295                 300
Ile Lys Ala Ile Glu Lys Val Phe Thr Leu Val Asp Glu Gly Asn Gly
305                 310                 315                 320
Phe Tyr Gln Asp Gly Ser Leu Ile Asp His Val Val Thr Asn Ala Gln
                325                 330                 335
Ser Pro Leu Tyr Lys Lys Gly Ile Ala Tyr Thr Gly Ala Tyr Gly Asn
            340                 345                 350
Val Leu Ile Asp Gly Leu Ser Gln Leu Ile Pro Ile Ile Gln Lys Thr
        355                 360                 365
Lys Ser Ser Ile Glu Ala Asp Lys Met Ala Thr Ile Tyr His Trp Ile
    370                 375                 380
Asn His Ser Phe Phe Pro Ile Ile Val Arg Gly Glu Met Met Asp Met
385                 390                 395                 400
Thr Arg Gly Arg Ser Ile Ser Arg Phe Asn Ala Gln Ser His Val Ala
                405                 410                 415
Gly Ile Glu Ala Leu Arg Ala Ile Leu Arg Ile Ala Asp Met Ser Glu
            420                 425                 430
Glu Pro His Arg Leu Ala Leu Lys Thr Arg Ile Lys Thr Leu Val Thr
        435                 440                 445
Gln Gly Asn Ala Phe Tyr Asn Val Tyr Asp Asn Leu Lys Thr Tyr His
    450                 455                 460
Asp Ile Lys Leu Met Lys Glu Leu Leu Ser Asp Thr Ser Val Pro Val
465                 470                 475                 480
Gln Lys Leu Asp Ser Tyr Val Ala Ser Phe Asn Ser Met Asp Lys Leu
                485                 490                 495
Ala Leu Tyr Asn Asn Lys His Asp Phe Ala Phe Gly Leu Ser Met Phe
            500                 505                 510
Ser Asn Arg Thr Gln Asn Tyr Glu Ala Met Asn Asn Glu Asn Leu His
        515                 520                 525
Gly Trp Phe Thr Ser Asp Gly Met Phe Tyr Leu Tyr Asn Asn Asp Leu
    530                 535                 540
Gly His Tyr Ser Glu Asn Tyr Trp Ala Thr Val Asn Pro Tyr Arg Leu
545                 550                 555                 560
Pro Gly Thr Thr Glu Thr Glu Gln Lys Pro Leu Glu Gly Thr Pro Glu
                565                 570                 575
Asn Ile Lys Thr Asn Tyr Gln Gln Val Gly Met Thr Ser Leu Ser Asp
            580                 585                 590
Asp Ala Phe Val Ala Ser Lys Lys Leu Asn Asn Thr Ser Ala Leu Ala
        595                 600                 605
Ala Met Thr Phe Thr Asn Trp Asn Lys Ser Leu Thr Leu Asn Lys Gly
    610                 615                 620
Trp Phe Ile Leu Gly Asn Lys Ile Ile Phe Val Gly Ser Asn Ile Lys
625                 630                 635                 640
Asn Gln Ser Ser His Lys Ala Tyr Thr Thr Ile Glu Gln Arg Lys Glu
                645                 650                 655
Asn Gln Lys His Pro Tyr His Ala Tyr Val Asn Asn Gln Pro Val Asp
            660                 665                 670
Leu Asn Asn Gln Leu Val Asp Phe Thr Asn Thr Lys Ser Ile Phe Leu
        675                 680                 685
Glu Ser Asp Asp Ser Ala Gln Asn Ile Gly Tyr Tyr Phe Phe Lys Pro
    690                 695                 700
Thr Thr Leu Ser Ile Ser Lys Ala Leu Gln Thr Gly Lys Trp Gln Asn
```

705 710 715 720
Ile Lys Ala Asp Asp Lys Ser Pro Glu Ala Ile Lys Glu Val Ser Asn
725 730 735
Thr Phe Ile Thr Ile Met Gln Asn His Thr Gln Asp Gly Asp Arg Tyr
740 745 750
Ala Tyr Met Met Leu Pro Asn Met Thr Arg Gln Glu Phe Glu Thr Tyr
755 760 765
Ile Ser Lys Leu Asp Ile Asp Leu Leu Glu Asn Asn Asp Lys Leu Ala
770 775 780
Ala Val Tyr Asp His Asp Ser Gln Gln Met His Val Ile His Tyr Glu
785 790 795 800
Lys Lys Ala Thr Met Phe Ser Asn His Asn Leu Ser His Gln Gly Phe
805 810 815
Tyr Ser Phe Pro His Pro Val Lys Gln Asn Gln Gln
820 825

<210> 301
<211> 522
<212> PRT
<213> 豬鏈球菌（Streptococcus suis）

<220>
<223> 玻尿酸解離酶

<400> 301
Met Gly Phe Phe Ile Ser Gln Ser Lys Gln His Tyr Gly Ile Arg Lys
1 5 10 15
Tyr Lys Val Gly Val Cys Ser Ala Leu Ile Ala Leu Ser Ile Leu Gly
20 25 30
Thr Arg Val Ala Ala Asn Gln Leu Pro Ser Thr Glu Thr Ala Ser Pro
35 40 45
Gln Ser Ser Gln Leu Val Glu Thr Thr Pro Glu Thr Thr Glu Ala Val
50 55 60
Asn Leu Thr Thr Glu Ala Val Met Thr Ser Glu Val Ser Ser Glu Val
65 70 75 80
Ser Pro Val Thr Ser Thr Glu Thr Gln Pro Ser Ser Thr Ala Ala Glu
85 90 95
Thr Leu Ala Ser Pro Gln Ala Val Gln Ala Thr Lys Glu Glu Glu Lys
100 105 110
Asn Leu Val Ala Asn Gly Glu Phe Ala Ser Thr Thr Ala Ala Ser Gly
115 120 125
Asn Trp Ala Asp Pro Ala Ala Thr Asn Trp Glu Thr Trp Ile Pro Ala
130 135 140
Asn Val Lys Lys Glu Asn Gly Gln Val Arg Ile Asp Glu Gly Arg Leu
145 150 155 160
His Ile Ser Ser Thr Ala Ser Tyr Arg Val Ala Val His Gln Thr Val
165 170 175
Asp Val Asp Pro Asn Lys Arg Tyr Leu Phe Ser Tyr Asn Val Glu Thr
180 185 190
Lys Asp Leu Lys Gly Ser Gly Val Arg Val Arg Leu Arg Ser Leu Thr
195 200 205
Ala Glu Gly Lys Asp Leu Ser Pro Gln Glu Phe Ala Tyr Thr Pro Tyr
210 215 220
Lys Asn Gly Ser Gln Ala Glu His Ile Glu Gln Ile Leu Thr Val Ser
225 230 235 240
Pro Glu Thr Arg Lys Leu Lys Val Glu Leu Phe Phe Glu Asn Ser Val
245 250 255
Gly Gln Ala Trp Leu Asp Asn Ile Ser Leu Val Glu Tyr Val Glu Lys
260 265 270
Thr Pro Glu Thr Pro Glu Pro Ser Leu Glu Leu Val Gln Pro Glu Thr
275 280 285
Gly Gln Ile Ser Leu Ala Ser Asn Lys Val Tyr Leu Pro Val Arg Pro
290 295 300
Asp Leu Thr Tyr Arg Ile Ala Asp Ala Ala Val Ala Ile Val Glu Lys

```
305                 310                 315                 320
Asn Met Ile Arg Pro Leu Ala Ala Gly Lys Thr Gln Val Asp Val Tyr
                325                 330                 335
Asp Lys Asp Thr Lys Leu Ser Ser Phe Glu Leu Thr Val Thr Glu His
            340                 345                 350
Gln Ala Thr Val Phe Asp Thr Leu Arg Asn Asn Trp Glu Asp Ile Ser
        355                 360                 365
Leu Ala Asn Lys Arg Tyr Gln Ser Asn Asp Thr Gln Met Lys Ala Phe
    370                 375                 380
Leu Gly Arg Leu Asp Ala Gly Val Ala Ser Ser Leu Lys Lys Trp Val
385                 390                 395                 400
Glu Pro Thr Asn Gln Gly Lys Thr Ile Phe Asn Asp Ile Asp Phe Ser
                405                 410                 415
Lys Ser Ser His Leu Thr Thr Val Tyr Arg Arg Leu Glu Gln Met Ala
            420                 425                 430
Gln Val Val Glu Asn Pro Asp Ser Ala Tyr Tyr His Asp Arg Ser Leu
        435                 440                 445
Ile Asp Leu Val Arg Lys Gly Met Asn Trp Leu Tyr Thr Asn Val Tyr
    450                 455                 460
Asn Glu Asn Lys Ser Ile Asp Gly Asn Trp Trp Asp Tyr Glu Ile Gly
465                 470                 475                 480
Thr Pro Arg Ala Val Val Asn Thr Leu Ile Tyr Met His Pro Tyr Phe
                485                 490                 495
Ser Gln Glu Glu Ile Leu Thr Tyr Thr Lys Pro Ile Ser Lys Phe Val
            500                 505                 510
Pro Asp Pro Thr Thr Ile Ser Val Lys His
        515                 520
```

<210> 302
<211> 1164
<212> PRT
<213> 豬鏈球菌

<220>
<223> 玻尿酸解離酶

<400> 302

```
Met Gly Phe Phe Ile Ser Gln Ser Lys Gln His Tyr Gly Ile Arg Lys
 1                5                  10                  15
Tyr Lys Val Gly Val Cys Ser Ala Leu Ile Ala Leu Ser Ile Leu Gly
            20                  25                  30
Thr Arg Val Ala Ala Asn Gln Leu Pro Ser Thr Glu Thr Ala Ser Pro
        35                  40                  45
Gln Ser Ser Gln Leu Val Glu Thr Thr Pro Glu Thr Thr Glu Ala Val
    50                  55                  60
Met Thr Ser Glu Val Ser Ser Glu Val Ser Pro Val Thr Ser Thr Glu
65                  70                  75                  80
Thr Gln Pro Ser Ser Thr Thr Ala Glu Thr Leu Ala Ser Pro Gln Ala
                85                  90                  95

Val Gln Ala Thr Lys Glu Glu Lys Asn Leu Val Ala Asn Gly Glu Phe
            100                 105                 110
Ile Ser Thr Thr Ala Pro Ser Gly Asn Trp Lys Glu Leu Ala Ala Thr

        115                 120                 125
Asn Trp Glu Thr Trp Ile Pro Ala Asn Val Lys Lys Glu Asn Gly Gln
    130                 135                 140
Val Arg Ile Asp Glu Gly Arg Leu His Ile Ser Ser Thr Ala Ser Tyr
145                 150                 155                 160
Arg Val Ala Val His Gln Thr Val Asp Val Asp Pro Asn Lys Arg Tyr
                165                 170                 175
Leu Phe Ser Tyr Asp Val Glu Thr Lys Asp Leu Lys Gly Ser Gly Val
            180                 185                 190
```

```
Arg Val Arg Leu Arg Ser Leu Thr Ala Glu Gly Lys Asp Leu Ser Pro
        195                 200                 205
Gln Glu Phe Ala Tyr Thr Pro Tyr Lys Asn Gly Ser Gln Ala Glu His
    210                 215                 220
Ile Glu Gln Ile Leu Thr Val Ser Pro Glu Thr Arg Lys Leu Lys Val
225                 230                 235                 240
Glu Leu Phe Phe Glu Asn Ser Val Gly Gln Ala Trp Leu Asp Asn Ile
                245                 250                 255
Ser Leu Val Glu Tyr Val Glu Lys Thr Pro Glu Thr Pro Glu Gln Ser
            260                 265                 270
Pro Glu Leu Val Gln Pro Glu Thr Gly Gln Ile Ser Leu Ala Ser Asn
        275                 280                 285
Lys Val Tyr Leu Pro Val Arg Pro Asp Leu Thr Tyr Arg Ile Ala Asp
    290                 295                 300
Ala Ala Val Ala Thr Val Glu Lys Asn Met Ile Arg Pro Leu Ala Ala
305                 310                 315                 320
Gly Lys Thr Gln Val Asp Val Tyr Asp Lys Asp Thr Lys Leu Ser Ser
                325                 330                 335
Phe Glu Leu Ile Val Thr Glu His Gln Ala Thr Val Phe Asp Thr Leu
            340                 345                 350
Arg Asn Asn Trp Glu Asp Ile Ser Leu Ala Asn Lys Arg Tyr Gln Ser
        355                 360                 365
Asn Asp Ala Gln Met Lys Ala Phe Leu Gly Arg Leu Asp Ala Gly Val
    370                 375                 380
Ala Ser Ser Leu Glu Lys Trp Val Glu Pro Thr Glu Gln Ser Lys Thr
385                 390                 395                 400
Ile Phe Asn Asp Ile Asp Phe Ser Lys Ser Ser His Leu Thr Thr Val
                405                 410                 415
Tyr Arg Arg Leu Glu Gln Met Ala Gln Val Val Glu Asn Pro Asp Ser
            420                 425                 430
Ala Tyr Tyr His Asp Arg Ser Leu Ile Asp Leu Val Arg Lys Gly Met
        435                 440                 445
Asn Trp Leu Tyr Ala Asn Val Tyr Asn Glu Asn Lys Ser Ile Asp Gly
    450                 455                 460
Asn Trp Trp Asp Tyr Glu Ile Gly Thr Ser Arg Ala Val Val Asn Thr
465                 470                 475                 480
Leu Ile Tyr Met His Pro Tyr Phe Ser Gln Glu Glu Ile Leu Thr Tyr
                485                 490                 495
Thr Lys Pro Ile Ser Lys Phe Val Pro Asp Pro Thr Thr Ile Arg Lys
            500                 505                 510
Thr Leu Thr Asn Pro Val Pro Ala Val Gly Gly Asn Gln Thr Asp Leu
        515                 520                 525
Ser Lys Val Ala Ile Leu Glu Gly Ala Leu Arg Glu Asp Ala Asp Arg
    530                 535                 540
Val Arg Ala Gly Ala Gln Gly Leu Thr Thr Ile Met Lys Phe Val Asp
545                 550                 555                 560
Lys Gly Glu Gly Phe Tyr Arg Asp Gly Ser Phe Ile Asp His Thr Asn
                565                 570                 575
Val Ala Tyr Thr Gly Ala Tyr Gly Asn Val Leu Ile Glu Gly Phe Ser
            580                 585                 590
Gln Leu Leu Pro Val Ile Gln Pro Thr Glu Phe Ala Leu Lys Glu Glu
        595                 600                 605
Gln Thr Asn Ile Leu Tyr Glu Trp Ile Glu Lys Ala Phe Met Pro Ile
    610                 615                 620
Leu Val Arg Gly Glu Leu Met Asp Met Thr Arg Gly Arg Ser Ile Ser
625                 630                 635                 640
Arg Ala Thr Gly Glu Ser His Val Gln Ala Met Glu Ile Leu Arg Ser
                645                 650                 655
Leu Val Arg Ile Ala Glu Ser Ala Gln Pro Glu Gln Lys Thr Lys Leu
            660                 665                 670
Leu Ser Phe Val Lys Ala Gln Leu Thr Ser Asp Thr Phe Tyr Asp Ser
        675                 680                 685
Tyr Arg Ser Leu Lys Ser Tyr Lys Asp Ile Asp Leu Val Asn Lys Leu
    690                 695                 700
```

```
Leu Ala Asp Asn Gln Ile Pro Ala Glu Val Asp Lys Asp Tyr Ile Ala
705                 710                 715                 720
Ala Phe Asn Asn Met Asp Lys Phe Val Tyr Arg Ser Ala Gln Glu Gly
                725                 730                 735
Phe Thr Phe Ala Leu Ser Met Tyr Ser Ser Arg Thr Gln Asn Tyr Glu
            740                 745                 750
Asp Met Asn Asn Glu Asn Arg Lys Gly Trp Tyr Thr Ala Asp Gly Met
        755                 760                 765
Val Tyr Leu Tyr Asn Asp Asp Leu Ser His Tyr Ser Asn His Tyr Trp
    770                 775                 780
Ala Thr Val Asp Pro Tyr Arg Leu Pro Gly Thr Thr Thr Thr Lys Asp
785                 790                 795                 800
Lys Arg Glu Asp Gly Ser Gly Glu Val Thr Leu Ala Ser Asp Phe Val
                805                 810                 815
Gly Ala Ser Gln Leu Gly Asn Arg Leu Ala Thr Ile Ala Met Asp Phe
            820                 825                 830
Asn Asn Trp Asn Asn Ser Leu Thr Ala Arg Lys Ala Trp Ile Val Leu
        835                 840                 845
Gly Asn Lys Ile Val Phe Leu Gly Thr Asp Ile Gln His Gln Ser Ala
    850                 855                 860
Gln Gly Ala Glu Thr Thr Ile Glu Asn Arg Lys Leu Leu Thr Gly Glu
865                 870                 875                 880
Lys Tyr Ser Tyr Tyr Ile Asn Gly Gln Pro Val Asp Leu Ser Lys Glu
                885                 890                 895
Val Val Thr Asp Lys Thr Gln Ser Phe Tyr Met Thr Asn Gly Lys Asp
            900                 905                 910
Asn Gln Ser Ile Gly Tyr Val Phe Leu Asn Gln Leu Pro Thr His Ala
        915                 920                 925
Lys Leu Asp Gln Arg Thr Gly Lys Trp Ser Asp Ile Asn Tyr Asn Gln
    930                 935                 940
Ser Lys Glu Glu Val Ser Asn Ser Phe Val Ser Leu Trp His Glu His
945                 950                 955                 960
Ala Gln Thr Ser Ser Asn Tyr Ala Tyr Val Leu Val Pro Asn Gln Ser
                965                 970                 975
Met Glu Lys Val Asn Gln Ala Ala Ala Ser Val Lys Leu Leu His Gln
            980                 985                 990
Asp Arg Asp Leu Gln Val Val Tyr Asp Gln Glu Gln Asn Val Trp Gly
        995                 1000                1005
Val Val Lys Tyr Thr Asp Thr Ala Tyr Lys Leu Thr Asp Asp Ile Thr
    1010                1015                1020
Leu Thr Asp Ala Gly Leu Tyr Thr Ile Gln Lys Val Glu Gly Gly Tyr
1025                1030                1035                1040
Arg Ile Ala Phe Tyr Asn Pro Ser Thr Arg Thr Val Lys Asn Gly Ile
                1045                1050                1055
Glu Leu Thr Lys Ala Gly Ser Ser Leu Thr Val Glu Met Glu Pro Thr
            1060                1065                1070
Ala Ala Tyr Pro Ser Thr Val Trp Lys Val Thr Met Pro Glu Gly Ser
        1075                1080                1085
Asp Lys Gln Thr Gly Ser Val Glu Lys Thr Glu Lys Glu Glu Lys Gln
    1090                1095                1100
Leu Lys Glu Asn Gln Pro Ser Ser Glu Val Lys Gln Val Val His His
1105                1110                1115                1120
Ala Ala Glu Lys Thr Lys Pro Ser Lys Pro Arg Leu Pro Gln Thr Gly
                1125                1130                1135
Glu Glu Ala Ser Leu Gly Leu Gly Phe Leu Gly Leu Leu Thr Leu Gly
            1140                1145                1150
Ala Val Val Asp Phe Lys Cys Arg Arg Ser His Ser
        1155                1160
```

<210> 303
<211> 1164
<212> PRT
<213> 豬鏈球菌

<220>
<223> 玻尿酸解離酶

<400> 303

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

Ile Glu Gln Ile Leu Thr Val Ser Pro Glu Thr Arg Lys Leu Lys Val
225                 230                 235                 240
Glu Leu Phe Phe Glu Asn Ser Val Gly Gln Ala Trp Leu Asp Asn Ile
                245                 250                 255
Ser Leu Val Glu Tyr Val Glu Lys Thr Pro Glu Thr Pro Glu Gln Ser
            260                 265                 270
Pro Glu Leu Val Gln Pro Glu Thr Gly Gln Ile Ser Leu Ala Ser Asn
        275                 280                 285
Lys Val Tyr Leu Pro Val Arg Pro Asp Leu Thr Tyr Arg Ile Ala Asp
    290                 295                 300
Ala Ala Val Ala Thr Val Glu Lys Asn Met Ile Arg Pro Leu Ala Ala
305                 310                 315                 320
Gly Lys Thr Gln Val Asp Val Tyr Asp Lys Asp Thr Lys Leu Ser Ser
                325                 330                 335
Phe Glu Leu Ile Val Thr Glu His Gln Ala Thr Val Phe Asp Thr Leu
            340                 345                 350
Arg Asn Asn Trp Glu Asp Ile Ser Leu Ala Asn Lys Arg Tyr Gln Ser
        355                 360                 365
Asn Asp Ala Gln Met Lys Ala Phe Leu Gly Arg Leu Asp Ala Gly Val
    370                 375                 380
Ala Ser Ser Leu Glu Lys Trp Val Glu Pro Thr Glu Gln Ser Lys Thr
385                 390                 395                 400
Ile Phe Asn Asp Ile Asp Phe Ser Lys Ser Ser His Leu Thr Thr Val
                405                 410                 415
Tyr Arg Arg Leu Glu Gln Met Ala Gln Val Val Glu Asn Pro Asp Ser
            420                 425                 430
Ala Tyr Tyr His Asp Arg Ser Leu Ile Asp Leu Val Arg Lys Gly Met
        435                 440                 445
Asn Trp Leu Tyr Thr Asn Val Tyr Asn Glu Asn Lys Ser Ile Asp Gly
    450                 455                 460
Asn Trp Trp Asp Tyr Glu Ile Gly Thr Pro Arg Ala Val Val Asn Thr
465                 470                 475                 480
```

```
Leu Ile Tyr Met His Pro Tyr Phe Ser Gln Glu Glu Ile Leu Thr Tyr
                485                 490                 495
Thr Lys Pro Ile Ser Lys Phe Val Pro Asp Pro Thr Thr Ile Arg Lys
            500                 505                 510
Thr Leu Thr Asn Pro Val Pro Ala Val Gly Gly Asn Gln Thr Asp Leu
        515                 520                 525
Ser Lys Val Ala Ile Leu Glu Gly Ala Leu Arg Glu Asp Ala Asp Arg
    530                 535                 540
Val Arg Ala Gly Ala Gln Gly Leu Thr Thr Ile Met Lys Phe Val Asp
545                 550                 555                 560
Lys Gly Glu Gly Phe Tyr Arg Asp Gly Ser Phe Ile Asp His Thr Asn
                565                 570                 575
Val Ala Tyr Thr Gly Ala Tyr Gly Asn Val Leu Ile Glu Gly Phe Ser
            580                 585                 590
Gln Leu Leu Pro Val Ile Gln Pro Thr Glu Phe Ala Leu Lys Glu Glu
        595                 600                 605
Gln Thr Asn Ile Leu Tyr Glu Trp Ile Glu Lys Ala Phe Met Pro Ile
    610                 615                 620
Leu Val Arg Gly Glu Leu Met Asp Met Thr Arg Gly Arg Ser Ile Ser
625                 630                 635                 640
Arg Ala Thr Gly Glu Ser His Val Gln Ala Met Glu Ile Leu Arg Ser
                645                 650                 655
Leu Val Arg Ile Ala Glu Ser Ala Gln Pro Glu Gln Lys Thr Lys Leu
            660                 665                 670
Leu Ser Phe Val Lys Ala Gln Leu Thr Ser Asp Thr Phe Tyr Asp Ser
        675                 680                 685
Tyr Arg Ser Leu Lys Ser Tyr Lys Asp Ile Asp Leu Val Asn Lys Leu
    690                 695                 700
Leu Ala Asp Asn Gln Ile Pro Ala Glu Val Asp Lys Asp Tyr Ile Ala
705                 710                 715                 720
Ala Phe Asn Asn Met Asp Lys Phe Val Tyr Arg Ser Ala Gln Glu Gly
                725                 730                 735
Phe Thr Phe Ala Leu Ser Met Tyr Ser Ser Arg Thr Gln Asn Tyr Glu
            740                 745                 750
Asp Met Asn Asn Glu Asn Arg Lys Gly Trp Tyr Thr Ala Asp Gly Met
        755                 760                 765
Val Tyr Leu Tyr Asn Asp Asp Leu Ser His Tyr Ser Asn His Tyr Trp
    770                 775                 780
Ala Thr Val Asp Pro Tyr Arg Leu Pro Gly Thr Thr Thr Thr Lys Asp
785                 790                 795                 800
Lys Arg Glu Asp Gly Ser Gly Glu Val Thr Leu Ala Ser Asp Phe Val
                805                 810                 815
Gly Ala Ser Gln Leu Gly Asn Arg Leu Ala Thr Ile Ala Met Asp Phe
            820                 825                 830
Asn Asn Trp Asn Asn Ser Leu Thr Ala Arg Lys Ala Trp Ile Val Leu
        835                 840                 845
Gly Asn Lys Ile Val Phe Leu Gly Thr Asp Ile Gln His Gln Ser Ala
    850                 855                 860
Gln Gly Ala Glu Thr Thr Ile Glu Asn Arg Lys Leu Leu Thr Gly Glu
865                 870                 875                 880
Lys Tyr Ser Tyr Tyr Ile Asn Gly Gln Pro Val Asp Leu Ser Lys Glu
                885                 890                 895
Val Val Thr Asp Lys Thr Gln Ser Phe Tyr Met Thr Asn Gly Lys Asp
            900                 905                 910
Asn Gln Ser Ile Gly Tyr Val Phe Leu Asn Gln Leu Pro Thr His Ala
        915                 920                 925
Lys Leu Asp Gln Arg Thr Gly Lys Trp Ser Asp Ile Asn Tyr Asn Gln
    930                 935                 940
Ser Lys Glu Glu Val Ser Asn Ser Phe Val Ser Leu Trp His Glu His
945                 950                 955                 960
Ala Gln Thr Ser Ser Asn Tyr Ala Tyr Val Leu Val Pro Asn Gln Ser
                965                 970                 975
Met Glu Lys Val Asn Gln Ala Ala Ala Ser Val Lys Leu Leu His Gln
            980                 985                 990
```

Asp Arg Asp Leu Gln Val Val Tyr Asp Gln Glu Gln Asn Val Trp Gly
995 1000 1005
Val Val Lys Tyr Thr Asp Thr Ala Tyr Lys Leu Thr Asp Asp Ile Thr
1010 1015 1020
Leu Thr Asp Ala Gly Leu Tyr Thr Ile Gln Lys Val Glu Gly Gly Tyr
1025 1030 1035 1040
Arg Ile Ala Phe Tyr Asn Pro Ser Thr Arg Thr Val Lys Asn Gly Ile
1045 1050 1055
Glu Leu Thr Lys Ala Gly Ser Ser Leu Thr Val Glu Met Glu Pro Thr
1060 1065 1070
Ala Ala Tyr Pro Ser Thr Val Trp Lys Val Thr Met Pro Glu Gly Ser
1075 1080 1085
Asp Lys Gln Thr Gly Ser Val Glu Lys Thr Glu Lys Glu Glu Lys Gln
1090 1095 1100
Leu Lys Glu Asn Gln Pro Ser Ser Glu Val Lys Gln Val Val His His
1105 1110 1115 1120
Ala Ala Glu Lys Thr Lys Pro Ser Lys Pro Arg Leu Pro Gln Thr Gly
1125 1130 1135
Glu Glu Ala Ser Leu Gly Leu Gly Phe Leu Gly Leu Leu Thr Leu Gly
1140 1145 1150
Ala Val Val Asp Phe Lys Cys Arg Arg Ser His Ser
1155 1160

<210> 304
<211> 802
<212> PRT
<213> 費氏弧菌（Vibrio fischeri）（菌株ATCC 700601 / ES114）

<220>
<223> 玻尿酸解離酶

<400> 304
Met Tyr Met Ile Lys Lys His Arg Leu Asn Thr Ile Ala Leu Ser Met
1 5 10 15
Leu Phe Leu Phe Thr Gly Asn Ala Tyr Ala Ala Lys Asn Thr Gln Thr
20 25 30
Pro Gln Tyr Leu Pro Ser Asp Phe Glu Gln Val Arg Glu Asn Trp Ala
35 40 45
Glu Asn Tyr Leu Gly Asp Pro Ala Ile Thr Phe Asp Gln Thr Leu Lys
50 55 60
Asn Met Val Thr Ser Thr Asn Ser Ser Ala Gln Lys His Trp Asp Ser
65 70 75 80
Met Thr Pro Gln Pro Asn Ala Ser Gly Ile Trp Asp Asp Leu Pro Leu
85 90 95
Ile Asp Lys Asp Thr Thr Leu Gly Pro Asn Ile Arg Asn Ser Tyr Gln
100 105 110
Arg Leu Phe Thr Met Ala Lys Ala Tyr Arg Leu Arg Asp Gly Asn Leu
115 120 125
Glu Asn Asn Gln Leu Met Leu Asn Asp Ile Met Thr Ala Met Asn Tyr
130 135 140
Ile Asn Gln Asn Phe Tyr Phe Val Asn Gln Leu Glu Tyr Gly Asn Trp
145 150 155 160
Trp Gln Trp Glu Leu Ala Ile Pro Lys Asp Ile His Asn Ile Leu Val
165 170 175
Leu Leu Phe Asp Asp Ile Lys Asp Asn Tyr Gln Thr Ile Ile Thr Asn
180 185 190
His Leu Asn Ala Thr Arg Tyr Phe Thr Pro Asp Pro Thr His Leu Gly
195 200 205
Val Ser Pro Gly Ala Ala Glu Ser Thr Asn Pro Asn Tyr Arg Glu Ser
210 215 220
Thr Gly Gly Asn Arg Thr Asp Asn Ala Gln Val Val Leu Ile Arg Gly
225 230 235 240
Met Leu Glu Asn Asn Ser Glu Glu Ile Ser Gln Ala Ile Ala Ala Leu
245 250 255

```
Pro Ala Val Ile Glu Tyr Val Ser Glu Gly Asp Gly Tyr Tyr Thr Asp
            260                 265                 270
Gly Ser Phe Leu Gln His Ser Asp Ile Ala Tyr Asn Gly Thr Tyr Gly
        275                 280                 285
Asn Val Leu Leu Gly Gly Leu Gly Ile Gln Met Asn Ala Val Ala Gly
    290                 295                 300
Ser Pro Trp Ser Met Asp Asn Gln Thr Ile Ser Asn Val Tyr Asn Ile
305                 310                 315                 320
Ile Asn Gln Ser Tyr Glu Pro Leu Leu Tyr Lys Gly Ala Met Met Asp
                325                 330                 335
Met Val Asn Gly Arg Ser Ile Ser Arg Ser Ala Glu Gln Asn His Asp
            340                 345                 350
Val Gly Leu Asn Ile Val Asn Ser Met Leu Phe Tyr Thr Asn Gly Pro
        355                 360                 365
Asp Ser Asp Lys Asn Lys Gln Leu Ser Ser Leu Ile Lys Thr Gln Ile
    370                 375                 380
Thr Asp Asp Thr Tyr Gln Asn Phe Phe Asp Lys Ile Tyr Tyr Val Ser
385                 390                 395                 400
Thr Tyr Gln Ala Ala Gln His Ile Val Asn Asp Pro Thr Val Ser Leu
                405                 410                 415
Lys Asp Pro Leu Ile Gly Asn Phe Ser Tyr Pro Ser Met Asp Arg Ile
            420                 425                 430
Val His Arg Arg Thr Asp Trp Ala Phe Ala Leu Ala Met His Ser Tyr
        435                 440                 445
Arg Ile Gly Asn Tyr Glu Cys Met Asn Gly Glu Asn Leu Lys Gly Trp
    450                 455                 460
Phe Thr Gly Asp Gly Met Ile Tyr Leu Tyr Asn Asp Gln Leu Asp His
465                 470                 475                 480
Tyr Thr Gly Tyr Trp Pro Thr Val Asn Ala Ser Arg Met Pro Gly Thr
                485                 490                 495
Thr Val Asp Ser Gln Ile Met Ala Asp Cys Ser Gly Glu Arg Val Gly
            500                 505                 510
Gly Asn Val Asn Thr Asn Met Gln Trp Val Gly Ser Thr Ser Leu Asn
        515                 520                 525
Asn Tyr Gly Ile Ala Gly Met Gln Phe Tyr Asn Trp Ser Asp Thr Leu
    530                 535                 540
Ser Ala Tyr Lys Ser Trp Phe Met Phe Asp Asn Glu Val Val Met Leu
545                 550                 555                 560
Gly Ser Asn Ile Lys Asp Gln Ser Asn Ala Asn Asn Ile Thr Thr Ile
                565                 570                 575
Glu Asn Arg Lys Arg Leu Ala Glu Thr Lys Leu Phe Ile Asp Gly Thr
            580                 585                 590
Glu Gln Ala Ala Leu Pro Tyr Gln Gly Ala Pro Ala Thr Phe Ser Ile
        595                 600                 605
Arg Asn Lys Thr Leu Ala Asn Ser Asp Leu Ser Tyr Val Met Leu Thr
    610                 615                 620
Pro Lys Thr Ile Ser Ile Ser Gln Asn Asp Val Asp Gly Asn Trp Ser
625                 630                 635                 640
Asp Ile Gly Asn Ser Lys Gly Asp Val Ser Asp Ser Tyr Leu Gln Ala
                645                 650                 655
Thr Leu Thr Gln Val Asp Gln Ala Asp Tyr Gln Tyr Ala Leu Leu Pro
            660                 665                 670
Asn Gln Asn Asn Asp Thr Val Gln Asn Tyr Ala Gln His Pro Asp Val
        675                 680                 685
Thr Val Leu Arg Gln Asp Glu Gln Ala His Ala Val Gln Glu Asn Thr
    690                 695                 700
Leu Asn Ile Ile Ala Ala Asn Asn Trp Lys Asn Asn Pro Val Asn Ile
705                 710                 715                 720
Thr Asp Thr Ile Thr Leu Asn Ser Met Met Gly Phe Met Ile Lys Glu
                725                 730                 735
Glu Ser Ser Asn Thr Phe Thr Val Ala Val Ser Glu Pro Ile Gln Thr
            740                 745                 750
Ile Asp Ser Val Asn Phe Thr Phe Asp Lys Gln Gly Ile Val Ile Lys
        755                 760                 765
Glu Asp Ile Glu Asn Arg Val Val Leu Asn Gly Thr Thr Leu Thr Ile
```

```
    770                 775                 780
Asn Thr Ser Gly Leu Gln Gly Gln Ser Tyr Ser Phe Gln Val Thr Ile
785                 790                 795                 800
Gln Asp
```

<210> 305
<211> 517
<212> PRT
<213> 聚球藻屬（Synechococcus sp.）(菌株RCC307)

<220>
<223> 玻尿酸解離酶

<400> 305

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

```
Trp Ser Tyr His Asn Gly Gly His Trp Pro Ser Leu Leu Trp Pro Met
385                 390                 395                 400
Ala Ala Ala Val Leu Met His Gln Arg Leu Tyr Pro Asn Asp Asp Leu
                405                 410                 415
Leu Leu Leu Gly Gln Thr Arg Thr Met Leu Glu Glu Cys Tyr Trp Gln
            420                 425                 430
Gln Leu Asn Gln Leu Pro Arg Gln Gln Trp Ala Glu Tyr Phe Asp Gly
        435                 440                 445
Pro Thr Gly Thr Trp Val Gly Gln Gln Ala Arg Ile Asn Gln Thr Trp
    450                 455                 460
Thr Ile Val Gly Phe Leu Leu Leu His His Leu Met Arg Lys Ala Pro
465                 470                 475                 480
Gln Asp Val Lys Leu Leu Asp Leu Asp Asp Val Gly Pro Leu Arg Leu
                485                 490                 495
Ser Phe Gln Asp Gln His Glu Lys Ser Ser Thr Asp Glu Arg Lys Ser
            500                 505                 510
Phe Leu Lys Asn Tyr
        515
```

<210> 306
<211> 1021
<212> PRT
<213> 普通變形桿菌（Proteus vulgaris）

<220>
<223> 硫酸軟骨素-ABC內解離酶

<400> 306

```
Met Pro Ile Phe Arg Phe Thr Ala Leu Ala Met Thr Leu Gly Leu Leu
 1               5                  10                  15
Ser Ala Pro Tyr Asn Ala Met Ala Ala Thr Ser Asn Pro Ala Phe Asp
            20                  25                  30
Pro Lys Asn Leu Met Gln Ser Glu Ile Tyr His Phe Ala Gln Asn Asn
        35                  40                  45
Pro Leu Ala Asp Phe Ser Ser Asp Lys Asn Ser Ile Leu Thr Leu Ser
    50                  55                  60
Asp Lys Arg Ser Ile Met Gly Asn Gln Ser Leu Leu Trp Lys Trp Lys
65                  70                  75                  80
Gly Gly Ser Ser Phe Thr Leu His Lys Lys Leu Ile Val Pro Thr Asp
                85                  90                  95
Lys Glu Ala Ser Lys Ala Trp Gly Arg Ser Ser Thr Pro Val Phe Ser
            100                 105                 110
Phe Trp Leu Tyr Asn Glu Lys Pro Ile Asp Gly Tyr Leu Thr Ile Asp
        115                 120                 125
Phe Gly Glu Lys Leu Ile Ser Thr Ser Glu Ala Gln Ala Gly Phe Lys
    130                 135                 140
Val Lys Leu Asp Phe Thr Gly Trp Arg Ala Val Gly Val Ser Leu Asn
145                 150                 155                 160
Asn Asp Leu Glu Asn Arg Glu Met Thr Leu Asn Ala Thr Asn Thr Ser
                165                 170                 175
Ser Asp Gly Thr Gln Asp Ser Ile Gly Arg Ser Leu Gly Ala Lys Val
            180                 185                 190
Asp Ser Ile Arg Phe Lys Ala Pro Ser Asn Val Ser Gln Gly Glu Ile
        195                 200                 205
Tyr Ile Asp Arg Ile Met Phe Ser Val Asp Asp Ala Arg Tyr Gln Trp
    210                 215                 220
Ser Asp Tyr Gln Val Lys Thr Arg Leu Ser Glu Pro Glu Ile Gln Phe
225                 230                 235                 240
His Asn Val Lys Pro Gln Leu Pro Val Thr Pro Glu Asn Leu Ala Ala
                245                 250                 255
Ile Asp Leu Ile Arg Gln Arg Leu Ile Asn Glu Phe Val Gly Gly Glu
            260                 265                 270
Lys Glu Thr Asn Leu Ala Leu Glu Glu Asn Ile Ser Lys Leu Lys Ser
        275                 280                 285
```

```
Asp Phe Asp Ala Leu Asn Ile His Thr Leu Ala Asn Gly Gly Thr Gln
    290                 295                 300
Gly Arg His Leu Ile Thr Asp Lys Gln Ile Ile Ile Tyr Gln Pro Glu
305                 310                 315                 320
Asn Leu Asn Ser Gln Asp Lys Gln Leu Phe Asp Asn Tyr Val Ile Leu
                325                 330                 335
Gly Asn Tyr Thr Thr Leu Met Phe Asn Ile Ser Arg Ala Tyr Val Leu
            340                 345                 350
Glu Lys Asp Pro Thr Gln Lys Ala Gln Leu Lys Gln Met Tyr Leu Leu
        355                 360                 365
Met Thr Lys His Leu Leu Asp Gln Gly Phe Val Lys Gly Ser Ala Leu
    370                 375                 380
Val Thr Thr His His Trp Gly Tyr Ser Ser Arg Trp Trp Tyr Ile Ser
385                 390                 395                 400
Thr Leu Leu Met Ser Asp Ala Leu Lys Glu Ala Asn Leu Gln Thr Gln
                405                 410                 415
Val Tyr Asp Ser Leu Leu Trp Tyr Ser Arg Glu Phe Lys Ser Ser Phe
            420                 425                 430
Asp Met Lys Val Ser Ala Asp Ser Ser Asp Leu Asp Tyr Phe Asn Thr
        435                 440                 445
Leu Ser Arg Gln His Leu Ala Leu Leu Leu Leu Glu Pro Asp Asp Gln
    450                 455                 460
Lys Arg Ile Asn Leu Val Asn Thr Phe Ser His Tyr Ile Thr Gly Ala
465                 470                 475                 480
Leu Thr Gln Val Pro Pro Gly Gly Lys Asp Gly Leu Arg Pro Asp Gly
                485                 490                 495
Thr Ala Trp Arg His Glu Gly Asn Tyr Pro Gly Tyr Ser Phe Pro Ala
            500                 505                 510
Phe Lys Asn Ala Ser Gln Leu Ile Tyr Leu Leu Arg Asp Thr Pro Phe
        515                 520                 525
Ser Val Gly Glu Ser Gly Trp Asn Asn Leu Lys Lys Ala Met Val Ser
    530                 535                 540
Ala Trp Ile Tyr Ser Asn Pro Glu Val Gly Leu Pro Leu Ala Gly Arg
545                 550                 555                 560
His Pro Phe Asn Ser Pro Ser Leu Lys Ser Val Ala Gln Gly Tyr Tyr
                565                 570                 575
Trp Leu Ala Met Ser Ala Lys Ser Ser Pro Asp Lys Thr Leu Ala Ser
            580                 585                 590
Ile Tyr Leu Ala Ile Ser Asp Lys Thr Gln Asn Glu Ser Thr Ala Ile
        595                 600                 605
Phe Gly Glu Thr Ile Thr Pro Ala Ser Leu Pro Gln Gly Phe Tyr Ala
    610                 615                 620
Phe Asn Gly Gly Ala Phe Gly Ile His Arg Trp Gln Asp Lys Met Val
625                 630                 635                 640
Thr Leu Lys Ala Tyr Asn Thr Asn Val Trp Ser Ser Glu Ile Tyr Asn
                645                 650                 655
Lys Asp Asn Arg Tyr Gly Arg Tyr Gln Ser His Gly Val Ala Gln Ile
            660                 665                 670

Val Ser Asn Gly Ser Gln Leu Ser Gln Gly Tyr Gln Gln Glu Gly Trp
        675                 680                 685
Asp Trp Asn Arg Met Glu Gly Ala Thr Thr Ile His Leu Pro Leu Lys
    690                 695                 700
Asp Leu Asp Ser Pro Lys Pro His Thr Leu Met Gln Arg Gly Glu Arg
705                 710                 715                 720
Gly Phe Ser Gly Thr Ser Ser Leu Glu Gly Gln Tyr Gly Met Met Ala
                725                 730                 735
Phe Asn Leu Ile Tyr Pro Ala Asn Leu Glu Arg Phe Asp Pro Asn Phe
            740                 745                 750
Thr Ala Lys Lys Ser Val Leu Ala Ala Asp Asn His Leu Ile Phe Ile
        755                 760                 765
Gly Ser Asn Ile Asn Ser Ser Asp Lys Asn Lys Asn Val Glu Thr Thr
    770                 775                 780
```

```
Leu Phe Gln His Ala Ile Thr Pro Thr Leu Asn Thr Leu Trp Ile Asn
785                 790                 795                 800
Gly Gln Lys Ile Glu Asn Met Pro Tyr Gln Thr Thr Leu Gln Gln Gly
                805                 810                 815
Asp Trp Leu Ile Asp Ser Asn Gly Asn Gly Tyr Leu Ile Thr Gln Ala
            820                 825                 830
Glu Lys Val Asn Val Ser Arg Gln His Gln Val Ser Ala Glu Asn Lys
        835                 840                 845
Asn Arg Gln Pro Thr Glu Gly Asn Phe Ser Ser Ala Trp Ile Asp His
    850                 855                 860
Ser Thr Arg Pro Lys Asp Ala Ser Tyr Glu Tyr Met Val Phe Leu Asp
865                 870                 875                 880
Ala Thr Pro Glu Lys Met Gly Glu Met Ala Gln Lys Phe Arg Glu Asn
                885                 890                 895
Asn Gly Leu Tyr Gln Val Leu Arg Lys Asp Lys Asp Val His Ile Ile
            900                 905                 910
Leu Asp Lys Leu Ser Asn Val Thr Gly Tyr Ala Phe Tyr Gln Pro Ala
        915                 920                 925
Ser Ile Glu Asp Lys Trp Ile Lys Lys Val Asn Lys Pro Ala Ile Val
    930                 935                 940
Met Thr His Arg Gln Lys Asp Thr Leu Ile Val Ser Ala Val Thr Pro
945                 950                 955                 960
Asp Leu Asn Met Thr Arg Gln Lys Ala Ala Thr Pro Val Thr Ile Asn
                965                 970                 975
Val Thr Ile Asn Gly Lys Trp Gln Ser Ala Asp Lys Asn Ser Glu Val
            980                 985                 990
Lys Tyr Gln Val Ser Gly Asp Asn Thr Glu Leu Thr Phe Thr Ser Tyr
        995                 1000                1005
Phe Gly Ile Pro Gln Glu Ile Lys Leu Ser Pro Leu Pro
    1010                1015                1020
```

<210> 307
<211> 700
<212> PRT
<213> 解肝磷脂土地桿菌（Pedobacter heparinus）

<220>
<223> 軟骨素AC解離酶

<400> 307

```
Met Lys Lys Leu Phe Val Thr Cys Ile Val Phe Phe Ser Ile Leu Ser
 1               5                  10                  15
Pro Ala Leu Leu Ile Ala Gln Gln Thr Gly Thr Ala Glu Leu Ile Met
            20                  25                  30
Lys Arg Val Met Leu Asp Leu Lys Lys Pro Leu Arg Asn Met Asp Lys
        35                  40                  45
Val Ala Glu Lys Asn Leu Asn Thr Leu Gln Pro Asp Gly Ser Trp Lys
    50                  55                  60
Asp Val Pro Tyr Lys Asp Asp Ala Met Thr Asn Trp Leu Pro Asn Asn
65                  70                  75                  80
His Leu Leu Gln Leu Glu Thr Ile Ile Gln Ala Tyr Ile Glu Lys Asp
                85                  90                  95
Ser His Tyr Tyr Gly Asp Asp Lys Val Phe Asp Gln Ile Ser Lys Ala
            100                 105                 110
Phe Lys Tyr Trp Tyr Asp Ser Asp Pro Lys Ser Arg Asn Trp Trp His
        115                 120                 125
Asn Glu Ile Ala Thr Pro Gln Ala Leu Gly Glu Met Leu Ile Leu Met
    130                 135                 140
Arg Tyr Gly Lys Lys Pro Leu Asp Glu Ala Leu Val His Lys Leu Thr
145                 150                 155                 160
Glu Arg Met Lys Arg Gly Glu Pro Glu Lys Lys Thr Gly Ala Asn Lys
                165                 170                 175
Thr Asp Ile Ala Leu His Tyr Phe Tyr Arg Ala Leu Leu Thr Ser Asp
            180                 185                 190
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Glu Ala Leu Leu Ser Phe Ala Val Lys Glu Leu Phe Tyr Pro Val Gln
        195                 200                 205
Phe Val His Tyr Glu Glu Gly Leu Gln Tyr Asp Tyr Ser Tyr Leu Gln
    210                 215                 220
His Gly Pro Gln Leu Gln Ile Ser Ser Tyr Gly Ala Val Phe Ile Thr
225                 230                 235                 240
Gly Val Leu Lys Leu Ala Asn Tyr Val Arg Asp Thr Pro Tyr Ala Leu
                245                 250                 255
Ser Thr Glu Lys Leu Ala Ile Phe Ser Lys Tyr Tyr Arg Asp Ser Tyr
            260                 265                 270
Leu Lys Ala Ile Arg Gly Ser Tyr Met Asp Phe Asn Val Glu Gly Arg
        275                 280                 285
Gly Val Ser Arg Pro Asp Ile Leu Asn Lys Lys Ala Glu Lys Lys Arg
    290                 295                 300
Leu Leu Val Ala Lys Met Ile Asp Leu Lys His Thr Glu Glu Trp Ala
305                 310                 315                 320
Asp Ala Ile Ala Arg Thr Asp Ser Thr Val Ala Ala Gly Tyr Lys Ile
                325                 330                 335
Glu Pro Tyr His His Gln Phe Trp Asn Gly Asp Tyr Val Gln His Leu
            340                 345                 350
Arg Pro Ala Tyr Ser Phe Asn Val Arg Met Val Ser Lys Arg Thr Arg
        355                 360                 365
Arg Ser Glu Ser Gly Asn Lys Glu Asn Leu Leu Gly Arg Tyr Leu Ser
    370                 375                 380
Asp Gly Ala Thr Asn Ile Gln Leu Arg Gly Pro Glu Tyr Tyr Asn Ile
385                 390                 395                 400
Met Pro Val Trp Glu Trp Asp Lys Ile Pro Gly Ile Thr Ser Arg Asp
                405                 410                 415
Tyr Leu Thr Asp Arg Pro Leu Thr Lys Leu Trp Gly Glu Gln Gly Ser
            420                 425                 430
Asn Asp Phe Ala Gly Gly Val Ser Asp Gly Val Tyr Gly Ala Ser Ala
        435                 440                 445
Tyr Ala Leu Asp Tyr Asp Ser Leu Gln Ala Lys Lys Ala Trp Phe Phe
    450                 455                 460
Phe Asp Lys Glu Ile Val Cys Leu Gly Ala Gly Ile Asn Ser Asn Ala
465                 470                 475                 480
Pro Glu Asn Ile Thr Thr Thr Leu Asn Gln Ser Trp Leu Asn Gly Pro
                485                 490                 495
Val Ile Ser Thr Ala Gly Lys Thr Gly Arg Gly Lys Ile Thr Thr Phe
            500                 505                 510
Lys Ala Gln Gly Gln Phe Trp Leu Leu His Asp Ala Ile Gly Tyr Tyr
        515                 520                 525
Phe Pro Glu Gly Ala Asn Leu Ser Leu Ser Thr Gln Ser Gln Lys Gly
    530                 535                 540
Asn Trp Phe His Ile Asn Asn Ser His Ser Lys Asp Glu Val Ser Gly
545                 550                 555                 560
Asp Val Phe Lys Leu Trp Ile Asn His Gly Ala Arg Pro Glu Asn Ala
                565                 570                 575
Gln Tyr Ala Tyr Ile Val Leu Pro Gly Ile Asn Lys Pro Glu Glu Ile
            580                 585                 590
Lys Lys Tyr Asn Gly Thr Ala Pro Lys Val Leu Ala Asn Thr Asn Gln
        595                 600                 605
Leu Gln Ala Val Tyr His Gln Gln Leu Asp Met Val Gln Ala Ile Phe
    610                 615                 620
Tyr Thr Ala Gly Lys Leu Ser Val Ala Gly Ile Glu Ile Glu Thr Asp
625                 630                 635                 640
Lys Pro Cys Ala Val Leu Ile Lys His Ile Asn Gly Lys Gln Val Ile
                645                 650                 655
Trp Ala Ala Asp Pro Leu Gln Lys Glu Lys Thr Ala Val Leu Ser Ile
            660                 665                 670
Arg Asp Leu Lys Thr Gly Lys Thr Asn Arg Val Lys Ile Asp Phe Pro
        675                 680                 685
Gln Gln Glu Phe Ala Gly Ala Thr Val Glu Leu Lys
    690                 695                 700
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<210> 308
<211> 844
<212> PRT
<213> 食物穀菌（Victivallis vadensis）ATCC BAA-548

<220>
<223> 軟骨素AC解離酶

<400> 308

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Met His Arg Lys Ile Val Phe Pro Leu Phe Val Leu Leu Phe Thr Ala
 1               5                  10                  15
Phe Ala Ala Phe Ala Ala Ser Gln Pro Gln Trp Lys Trp Arg Gln Ser
            20                  25                  30
Lys Tyr Cys Arg Ile Thr Glu His Ala Gly Lys Lys Leu Leu Thr Val
        35                  40                  45
Ala Ile Pro Ala Asp Ala Pro Glu Ile Ser Arg Arg Asn Thr Ala Asp
    50                  55                  60
Thr Pro Val Gly Leu Thr Cys Phe Glu Gly Gln Pro Ile Glu Phe Ser
65                  70                  75                  80
Ile Arg Leu Arg Asn Ser Gly Ile Ser Arg Pro Asp Asn Leu His Asn
                85                  90                  95
Gly Ile Lys Phe Gln Leu Tyr Phe Arg Asp Gly Asn Gly Thr Glu Arg
            100                 105                 110
Trp Thr Gln Ala Glu Ile Pro His Glu Pro Phe Pro Trp Arg Arg Phe
        115                 120                 125
Arg Phe Ser Glu Arg Ile Pro Ala Asp Ala Thr Ser Gly Thr Leu Arg
    130                 135                 140
Leu Gly Leu Gln Gly Ser Ser Gly Asn Val Glu Phe Asp Leu Asp Ser
145                 150                 155                 160
Leu Gln Ile Arg Pro Leu Asp Pro Glu Leu Ser Pro Val Pro Pro Thr
                165                 170                 175
Pro Glu Gln Ile Arg Glu Cys Glu Leu Ile Glu Ser Arg Leu Arg Ala
            180                 185                 190
Gly Leu Pro Ala Gln Gln Pro Pro Pro Gly Pro Glu Val Lys Lys Leu
        195                 200                 205
Leu Glu Arg Gln Asn Gly Asp Gly Thr Phe Arg Asp Leu Asp Tyr Ser
    210                 215                 220
Ala Arg Asn Arg Ser Ile Trp Pro Ala Ala Arg His Leu Lys Arg Thr
225                 230                 235                 240
Phe Glu Leu Ala Leu Ala Arg Ala Thr Pro Gly His Ala Leu Tyr Arg
                245                 250                 255
Asp Pro Ala Ala Gly Glu Ala Val Arg Lys Ala Val Ala Trp Trp Ala
            260                 265                 270
Glu Arg Gln Pro Gln Asn Gly Asn Trp Trp Trp Asn Asp Met Tyr Val
        275                 280                 285
Pro Lys Ile Leu Gly Asn Ile Leu Leu Leu Ser Pro Glu Leu Phe Pro
    290                 295                 300
Asp Gly Pro Arg Arg Arg Ala Ala Leu Asn Val Cys Arg Gln Ala Cys
305                 310                 315                 320
Phe Leu Ser Arg Tyr Thr Gly Asn Asn Arg Val Phe Ile Ala Ala Asn
                325                 330                 335
Ile Phe Cys Arg Ala Leu Leu Glu Arg Asn Leu Pro Val Met Asp Arg
            340                 345                 350
Ala Ala Ala Val Leu Ser Glu Glu Ile Arg Phe Ala Pro Ala Glu His
        355                 360                 365
Lys Thr Ala Trp Ser Phe Gly Gly Ile Arg Ala Asp Gly Cys Tyr His
    370                 375                 380
Gln His Gly Pro Gln Ile Gln Phe Gly Asn Tyr Gly Gly Glu Phe Leu
385                 390                 395                 400
Ala Asn Ile Ala Tyr Trp Ser Asn Ile Leu Lys Glu Thr His Trp Glu
                405                 410                 415
Leu Ser Pro Glu Gln Trp Arg Ile Met Arg His Leu Thr Phe Asn Gly
            420                 425                 430
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Phe Gln Trp Val Leu Trp Arg Gly Arg Met Asp Leu Leu Ala Cys Gly
        435                 440                 445
Arg Gln Leu Gly Arg Asn Ala Ala Glu Thr Lys Gly Glu Arg Thr Leu
    450                 455                 460
Asn Ala Phe Ala Gln Leu Arg Asn Ala Asp Pro Gly Asp Arg Ala Pro
465                 470                 475                 480
Tyr Asp Ala Ala Leu Arg Arg Asn Arg Asp Gly Glu Asn Thr Leu Thr
                485                 490                 495
Gly Asn Arg His Phe Trp Asn Ser Asp Tyr Met Val His Arg Arg Pro
            500                 505                 510
Thr Trp Tyr Ala Ser Val Arg Met Asn Ser Val Arg Val Arg Pro Ile
        515                 520                 525
Glu Asp Asp Thr Asn Trp Asp Asn Ala Leu Gly Arg Tyr Phe Ser Asp
    530                 535                 540
Gly Ala Cys Leu Val Met Arg Ser Gly Arg Glu Tyr Glu Asn Ile Thr
545                 550                 555                 560
Ala Cys Trp Asp Trp Thr Arg Leu Pro Gly Thr Thr Leu Pro Lys Thr
                565                 570                 575
Pro Val Tyr Thr Gly Glu Asp Ala Arg Arg Phe Gly Leu Lys Ile Gly
            580                 585                 590
Gly Gly Asp Leu Pro Arg Trp Thr His Ser Arg Asn Trp Arg Gln Leu
        595                 600                 605
Gly Glu Thr Gly Phe Val Gly Gly Val Thr Asp Gly Glu Arg Gly Ala
    610                 615                 620
Ala Val Tyr Thr Gln Asp Leu Asp Gly Val Arg Ala Arg Lys Ala Trp
625                 630                 635                 640
Phe Phe Asp Arg Asp Ala Ile Tyr Cys Leu Gly Ser Gly Ile Thr Ser
                645                 650                 655
Thr Ser Pro Tyr Glu Val Ala Thr Thr Val Asn Ser Cys Leu Arg Asn
            660                 665                 670
Gly Glu Ile Gln Gln Gly Asp Gly Trp Phe Arg His Asp Gly Ile Gly
        675                 680                 685
Tyr Arg Gly Glu Asn Leu Lys Leu Thr Ala Gly Pro Arg Thr Gly Asp
    690                 695                 700
Trp Arg Tyr Val Glu Gly Gly Leu Thr Arg Pro Val Pro Glu Thr Lys
705                 710                 715                 720
Glu Leu Phe Thr Leu Thr Val Glu His Gly Val Lys Pro Arg Asn Ala
                725                 730                 735
Ser Tyr Ile Tyr Thr Ile Leu Pro Gly Ala Thr Pro Glu Glu Thr Ala
            740                 745                 750
Gly Thr Pro Pro Gly Arg Val Leu Arg Asn Thr Pro Glu Cys Gln Ala
        755                 760                 765
Val Glu Phe Ala Asp Gly Val Arg Ala Ala Ile Phe Tyr Glu Pro Gly
    770                 775                 780
Arg Leu Asp Asp Phe Glu Thr Asp Thr Pro Gly Val Phe Leu Ile Gly
785                 790                 795                 800
Lys Gly Thr Val His Ala Ala Asp Pro Thr Gly Arg His Ser Ser Phe
                805                 810                 815
Thr Leu Lys Leu Asn Gly Val Ser Arg Lys Val Pro Leu Pro Ala Gly
            820                 825                 830
Glu Phe Ala Gly Gln Ser Val Lys Ile Val Leu Lys
        835                 840
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I395593

公告本

發明專利說明書

（本說明書格式、順序，請勿任意更動，※記號部分請勿填寫）

※申請案號：98107084

※申請日：98、3、5　※IPC 分類：A61K 38/50 (2006.01)
A61K 38/47 (2006.01)
C12N 9/82 (2006.01)
C12N 9/50 (2006.01)
C12N 9/26 (2006.01)

一、發明名稱：（中文/英文）

可活化的基質降解酵素之活體內暫時性控制

IN VIVO TEMPORAL CONTROL OF ACTIVATABLE MATRIX-DEGRADING ENZYMES

二、中文發明摘要：

本發明提供用於控制基質降解酵素之活體內作用之持續時間的方法及組合。該等方法及組合容許在向細胞外基質（或「ECM」）投藥之後暫時性活體內活化基質降解酵素。具有受控作用持續時間之基質降解酵素可用於治療特徵在於一或多種 ECM 組份之沈積或積累增加的 ECM 介導之疾病或病症。

三、英文發明摘要：

Methods and combinations are provided for controlling the duration of action, *in vivo*, of matrix-degrading enzymes. The methods and combinations permit temporary in-vivo activation of matrix-degrading enzymes upon administration to the extra cellular matrix (or "ECM"). Matrix-degrading enzymes having a controlled duration of action can be used to treat ECM-mediated diseases or disorders characterized

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by increased deposition or accumulation of one or more ECM components.

四、指定代表圖：

(一)本案指定代表圖為：第（　無　）圖。

(二)本代表圖之元件符號簡單說明:

無

五、本案若有化學式時，請揭示最能顯示發明特徵的化學式：

無

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102年1月24日修正本

102年1月24日替換頁

七、申請專利範圍：

1.一種可活化的基質降解酵素（activatable matrix-degrading enzyme，AMDE）之用途，其係用於調配用於表皮下投藥以暫時地降解細胞外基質(ECM)之組份以治療ECM疾病或病狀之醫藥品，其中：

該AMDE係以當暴露於活化劑時足以降解與該疾病或病狀相關之ECM組份的量調配；

該AMDE為在該活化劑不存在之情況下在表皮下投藥後在ECM中無活性之基質降解酵素；且

該AMDE在ECM中在表皮下投藥後在暴露於該活化劑提供之活化條件後有限的時間內具有活性。

2.如申請專利範圍第1項之用途，其中該醫藥品係用於單劑量投藥，且含有為或約為10 μg至100 mg、50 μg至75 mg、100 μg至50 mg、250 μg至25 mg、500 μg至10 mg、1 mg至5 mg或2 mg至4 mg之量的AMDE。

3.如申請專利範圍第1項之用途，其中該酵素於中性pH值下實質上無活性。

4.如申請專利範圍第1項之用途，其是經調配用於皮下投藥、肌肉內投藥、病灶內投藥或皮內投藥。

5.如申請專利範圍第1項之用途，其中該活化劑係與該AMDE調配於同一組成物中或調配於分開的組成物中。

6.如申請專利範圍第1項之用途，其中該AMDE係選自組織蛋白酶（cathepsin）、鈣激活中性蛋白酶（calpain）及肝素酶（heparanase）。

7.如申請專利範圍第6項之用途，其中該AMDE為組織蛋白酶且該組織蛋白酶為半胱胺酸蛋白酶（cysteine protease）或天冬胺酸蛋白酶（aspartic protease）。

8.如申請專利範圍第7項之用途，其中該組織蛋白酶係選自組織蛋白酶S、組織蛋白酶K、組織蛋白酶L、組織蛋白酶B、組織蛋白酶C、組織蛋白酶H、組織蛋白酶F、組織蛋白酶O、組織蛋白酶R、組織蛋白酶V、組織蛋白酶W、組織蛋白酶D及組織蛋白酶E。

9.如申請專利範圍第8項之用途，其中該組織蛋白酶為組織蛋白酶L。

10.如申請專利範圍第7項之用途，其中該組織蛋白酶具有選自SEQ ID NO: 57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93及96中之任一者的胺基酸序列，或為SEQ ID NO: 57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93及96中之任一者的對偶基因或物種變異體或其他變異體。

11.如申請專利範圍第1項之用途，其中該活化條件係選自pH值、離子強度、溫度及金屬離子。

12.如申請專利範圍第11項之用途，其中該AMDE需要超過一種用於活性之活化條件。

13.如申請專利範圍第11項之用途，其中該活化條件為pH值。

14.如申請專利範圍第13項之用途，其中該活化條件為酸性pH值。

15.如申請專利範圍第14項之用途，其中：

該AMDE於中性pH值下無活性；

該活化劑提供酸性pH值活化條件以活化該酵素；且

該AMDE於pH 5.5下具活性。

16.一種組織蛋白酶L之用途，其係用於調配用於在外層皮膚之下的表皮下投藥以治療膠原蛋白介導之疾病或病狀之醫藥品，其中：

該膠原蛋白介導之疾病或病狀與膠原蛋白中富含之累積的纖維組織相關；且

該組織蛋白酶L係於酸性緩衝液中調配，該酸性緩衝液提供用於投藥之酸性pH值活化條件，藉此該組織蛋白酶L在表皮下投藥後有限的時間內具有活性以降解皮膚之纖維中的ECM之膠原蛋白組份。

17.如申請專利範圍第14或16項之用途，其中該pH值為在或約在3至6.5、或3.5至6、或3至5.5、或3至4.5、或4至6、或4至5.5、或4.5至5、或5至6之範圍內的酸性pH值。

18.如申請專利範圍第17項之用途，其中該pH值約為或為3、3.5、4、4.5、5、5.5、6或6.5。

19.如申請專利範圍第14項之用途，其中活化劑作為緩衝溶液於該pH值下提供酸性pH值活化條件。

20.如申請專利範圍第16或19項之用途，其中該緩衝液含有選自2-(N-嗎啉基)乙烷磺酸(MES)、乙酸、檸檬酸、檸檬酸磷酸鹽及組胺酸之酸。

21.如申請專利範圍第16或19項之用途，其中該緩衝液之離子強度經選擇以使得該AMDE於中性pH值下在預定時間內具活性。

22.如申請專利範圍第21項之用途，其中該預定時間為或約為1分鐘、2分鐘、3分鐘、4分鐘、5分鐘、6分鐘、7分鐘、8分鐘、9分鐘、10分鐘、20分鐘、30分鐘、40分鐘、50分鐘、1小時、2小時、3小時或4小時。

23.如申請專利範圍第15項之用途，其中該AMDE為溶酶體酵素。

24.如申請專利範圍第15項之用途，其中該AMDE為組織蛋白酶或肝素酶。

25.如申請專利範圍第24項之用途，其中該AMDE為組織蛋白酶且該組織蛋白酶為半胱胺酸蛋白酶或天冬胺酸蛋白酶。

26.如申請專利範圍第25項之用途，其中該組織蛋白酶係選自組織蛋白酶B、組織蛋白酶F、組織蛋白酶H、組織蛋白酶K、組織蛋白酶L、組織蛋白酶V及組織蛋白酶D。

27.如申請專利範圍第26項之用途，其中該組織蛋白酶具有選自SEQ ID NO: 65、71、183、68、60、1、189及90中之任一者的胺基酸序列，或為SEQ ID NO: 65、71、183、68、60、1、189及90中之任一者的對偶基因或物種變異體或其他變異體。

28.如申請專利範圍第26項之用途，其中該組織蛋白酶為組織蛋白酶L。

29.如申請專利範圍第16或28項之用途，其中該組織蛋白酶L酵素為呈單鏈形式。

30.如申請專利範圍第16或28項之用途，其中該組織蛋白酶L酵素為呈雙鏈形式。

31.如申請專利範圍第16或28項之用途，其中該組織蛋白酶L酵素包含：

具有如SEQ ID NO:1胺基酸1-175所述之胺基酸序列或與胺基酸1-175之序列展示至少90%序列一致性之序列的重鏈；及

具有如SEQ ID NO:1胺基酸179-220所述之胺基酸序列或與胺基酸179-220之序列展示至少90%序列一致性之序列的輕鏈。

32.如申請專利範圍第16或28項之用途，其中該組織蛋白酶L具有如SEQ ID NO:1所述之胺基酸序列或為其對偶基因、物種變異體或其他變異體。

33.如申請專利範圍第1項之用途，其中該AMDE為呈單鏈或雙鏈形式之成熟蛋白質。

34.如申請專利範圍第11項之用途，其中：

該AMDE經修飾以具溫度敏感性，藉此該AMDE在低於37℃之溫度下具有活性，該活化劑提供了低於37℃之溫度下之活化條件；

該AMDE於37℃下無活性。

35.如申請專利範圍第11項之用途，其中該活化條件為溫度且該溫度為或約為20℃、21℃、22℃、23℃、24℃、25℃、

26℃、27℃、28℃、29℃或 30℃。

36.如申請專利範圍第 34 項之用途，其中該 AMDE 係選自胰腺彈性蛋白酶、彈性蛋白酶-2A、彈性蛋白酶-2B、嗜中性白血球彈性蛋白酶、蛋白酶-3、內源性血管彈性蛋白酶、組織蛋白酶 G、肥大細胞凝乳酶、肥大細胞類胰蛋白酶(tryptase)、纖溶酶(plasmin)、凝血酶、顆粒酶(granzyme) B、組織蛋白酶 S、組織蛋白酶 K、組織蛋白酶 L、組織蛋白酶 B、組織蛋白酶 C、組織蛋白酶 H、組織蛋白酶 F、組織蛋白酶 O、組織蛋白酶 R、組織蛋白酶 V、組織蛋白酶 W、鈣激活中性蛋白酶 1、鈣激活中性蛋白酶 2、豆蛋白酶(legumain)、組織蛋白酶 Z、組織蛋白酶 D、組織蛋白酶 E、MMP-1、MMP-8、MMP-13 及 MMP-18、MMP-2、MMP-9、MMP-3、MMP-10、MMP-11、MMP-7、MMP-26、MMP-12、MMP-14、MMP-15、MMP-16 及 MMP-17、MMP-19、MMP-20、ADAMTS-1、ADAMTS-2、ADAMTS-3、ADAMTS-4、ADAMTS-5、ADAMTS-14 及肝素酶或其對偶基因或物種變異體或其他變異體。

37.如申請專利範圍第 34 項之用途，其中該活化劑為冷緩衝液。

38.如申請專利範圍第 34 項之用途，其中該活化劑與該 AMDE 提供於同一組成物中或提供於分開的組成物中。

39.如申請專利範圍第 11 項之用途，其中該活化條件為金屬離子且該金屬離子為 Ca^{2+}。

40.如申請專利範圍第 1 項之用途，其中該一或多種

ECM組份係選自膠原蛋白、彈性蛋白、纖維結合蛋白(fibronectin)或蛋白聚糖。

41.如申請專利範圍第16或40項之用途，其中該ECM組份為膠原蛋白且該膠原蛋白係選自I型、II型、III型或IV型膠原蛋白。

42.如申請專利範圍第16或40項之用途，其中該膠原蛋白為I型膠原蛋白。

43.如申請專利範圍第1項之用途，其中該ECM之疾病或病狀為膠原蛋白介導之疾病或病狀。

44.如申請專利範圍第16或43項之用途，其中該膠原蛋白介導之疾病或病狀係選自脂肪團、杜普宜特朗氏病(Dupuytren's disease)、帕榮雷氏病(Peyronie's disease)、萊德豪斯纖維化(Ledderhose fibrosis)、關節僵硬、現有瘢痕、硬皮病、淋巴水腫及膠原性結腸炎。

45.如申請專利範圍第44項之用途，其中該膠原蛋白介導之疾病或病狀為關節僵硬，該關節僵硬為凍肩。

46.如申請專利範圍第44項之用途，其中該膠原蛋白介導之疾病或病狀為選自手術黏連、瘢痕瘤、肥厚性瘢痕及凹陷性瘢痕之現有瘢痕。

47.一種醫藥組成物，其包含經調配用於表皮下投藥以用於暫時地降解細胞外基質(ECM)之組份以治療ECM之疾病或病狀的可活化的基質降解酵素(AMDE)，其中：

該AMDE係以當暴露於活化劑時足以降解與該疾病或病狀相關之ECM組份的量調配；

該 AMDE 為在該活化劑不存在之情況下在表皮下投藥後在 ECM 中無活性之基質降解酵素；且

該 AMDE 在 ECM 中在表皮下投藥後在暴露於該活化劑提供之活化條件後有限的時間內具有活性。

48.如申請專利範圍第 47 項之組成物，其中該組成物係用於單劑量投藥，且含有為或約為 10 μg 至 100 mg、50 μg 至 75 mg、100 μg 至 50 mg、250 μg 至 25 mg、500 μg 至 10 mg、1 mg 至 5 mg 或 2 mg 至 4 mg 之量的 AMDE。

49.如申請專利範圍第 47 項之組成物，其中該酵素於中性 pH 值下實質上無活性。

50.如申請專利範圍第 47 項之組成物，其經調配用於皮下投藥、肌肉內投藥、病灶內投藥或皮內投藥。

51.如申請專利範圍第 47 項之組成物，其中該活化劑係與該 AMDE 調配於同一組成物中或調配於分開的組成物中。

52.如申請專利範圍第 47 項之組成物，其中該 AMDE 係選自組織蛋白酶、鈣激活中性蛋白酶及肝素酶。

53.如申請專利範圍第 52 項之組成物，其中該 AMDE 為組織蛋白酶且該組織蛋白酶為半胱胺酸蛋白酶或天冬胺酸蛋白酶。

54.如申請專利範圍第 53 項之組成物，其中該組織蛋白酶係選自組織蛋白酶 S、組織蛋白酶 K、組織蛋白酶 L、組織蛋白酶 B、組織蛋白酶 C、組織蛋白酶 H、組織蛋白酶 F、組織蛋白酶 O、組織蛋白酶 R、組織蛋白酶 V、組織蛋白酶

W、組織蛋白酶 D 及組織蛋白酶 E。

55.如申請專利範圍第 54 項之組成物，其中該組織蛋白酶為組織蛋白酶 L。

56.如申請專利範圍第 53 項之組成物，其中該組織蛋白酶具有選自 SEQ ID NO: 57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93 及 96 中之任一者的胺基酸序列，或為 SEQ ID NO: 57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93 及 96 中之任一者的對偶基因或物種變異體或其他變異體。

57.如申請專利範圍第 47 項之組成物，其中該活化條件係選自 pH 值、離子強度、溫度及金屬離子。

58.如申請專利範圍第 57 項之組成物，其中該 AMDE 需要超過一種用於活性之活化條件。

59.如申請專利範圍第 57 項之組成物，其中該活化條件為 pH 值。

60.如申請專利範圍第 59 項之組成物，其中該活化條件為酸性 pH 值。

61.如申請專利範圍第 60 項醫藥組成物，其中：

該 AMDE 於中性 pH 值下無活性；

該活化劑提供酸性 pH 值活化條件以活化該酵素；且

該 AMDE 於 pH 5.5 下具活性。

62.一種醫藥組成物，其包含經調配用於在外層皮膚之下的表皮下投藥以治療膠原蛋白介導之疾病或病狀的組織蛋白酶 L，其中：

該膠原蛋白介導之疾病或病狀與膠原蛋白中富含的累積之纖維組織相關；且

該組織蛋白酶L係於酸性緩衝液中調配，該酸性緩衝液提供用於投藥之酸性pH值活化條件，藉此該組織蛋白酶L在表皮下投藥後有限的時間內具有活性以降解皮膚之纖維中的ECM之膠原蛋白組份。

63.如申請專利範圍第60或62項之組成物，其中該pH值為在或約在3至6.5、或3.5至6、或3至5.5、或3至4.5、或4至6、或4至5.5、或4.5至5、或5至6之範圍內的酸性pH值。

64.如申請專利範圍第63項之組成物，其中該pH值約為或為3、3.5、4、4.5、5、5.5、6或6.5。

65.如申請專利範圍第60項之組成物，其中活化劑作為緩衝溶液於該pH值下提供酸性pH值活化條件。

66.如申請專利範圍第62或65項之組成物，其中該緩衝液含有選自2-(N-嗎啉基)乙烷磺酸（MES）、乙酸、檸檬酸、檸檬酸磷酸鹽及組胺酸之酸。

67.如申請專利範圍第62或65項之組成物，其中該緩衝液之離子強度經選擇以使得該AMDE於中性pH值下在預定時間內具活性。

68.如申請專利範圍第67項之組成物，其中該預定時間為或約為1分鐘、2分鐘、3分鐘、4分鐘、5分鐘、6分鐘、7分鐘、8分鐘、9分鐘、10分鐘、20分鐘、30分鐘、40分鐘、50分鐘、1小時、2小時、3小時或4小時。

69.如申請專利範圍第 61 項之組成物，其中該 AMDE 為溶酶體酵素。

70.如申請專利範圍第 61 項之組成物，其中該 AMDE 為組織蛋白酶或肝素酶。

71.如申請專利範圍第 70 項之組成物，其中該 AMDE 為組織蛋白酶且該組織蛋白酶為半胱胺酸蛋白酶或天冬胺酸蛋白酶。

72.如申請專利範圍第 71 項之組成物，其中該組織蛋白酶係選自組織蛋白酶 B、組織蛋白酶 F、組織蛋白酶 H、組織蛋白酶 K、組織蛋白酶 L、組織蛋白酶 V 及組織蛋白酶 D。

73.如申請專利範圍第 72 項之組成物，其中該組織蛋白酶具有選自 SEQ ID NO: 65、71、183、68、60、1、189 及 90 中之任一者的胺基酸序列，或為 SEQ ID NO: 65、71、183、68、60、1、189 及 90 中之任一者的對偶基因或物種變異體或其他變異體。

74.如申請專利範圍第 72 項之組成物，其中該組織蛋白酶為組織蛋白酶 L。

75.如申請專利範圍第 47 項之組成物，其中該 AMDE 為呈單鏈或雙鏈形式之成熟蛋白質。

76.如申請專利範圍第 62 或 74 項之組成物，其中該組織蛋白酶 L 酵素包含：

具有如 SEQ ID NO:1 胺基酸 1-175 所述之胺基酸序列或與胺基酸 1-175 之序列展示至少 90%序列一致性之序列的重鏈；及

具有如 SEQ ID NO:1 胺基酸 179-220 所述之胺基酸序列或與胺基酸 179-220 之序列展示至少 90%序列一致性之序列的輕鏈。

77.如申請專利範圍第 62 或 74 項中之醫藥組成物，其中該組織蛋白酶 L 具有如 SEQ ID NO:1 所述之胺基酸序列或為其對偶基因、物種變異體或其他變異體。

78.如申請專利範圍第 57 項之醫藥組成物，其中：

該 AMDE 經修飾以具溫度敏感性，藉此該 AMDE 在低於 37℃之溫度下具有活性，該活化劑提供了低於 37℃之溫度下之活化條件；且

該 AMDE 於 37℃下無活性。

79.如申請專利範圍第 78 項之醫藥組成物，其中該活化條件為溫度且該溫度為或約為 20℃、21℃、22℃、23℃、24℃、25℃、26℃、27℃、28℃、29℃或 30℃。

80.如申請專利範圍第 78 項之醫藥組成物，其中該 AMDE 係選自胰腺彈性蛋白酶、彈性蛋白酶-2A、彈性蛋白酶-2B、嗜中性白血球彈性蛋白酶、蛋白酶-3、內源性血管彈性蛋白酶、組織蛋白酶 G、肥大細胞凝乳酶、肥大細胞類胰蛋白酶、纖溶酶、凝血酶、顆粒酶 B、組織蛋白酶 S、組織蛋白酶 K、組織蛋白酶 L、組織蛋白酶 B、組織蛋白酶 C、組織蛋白酶 H、組織蛋白酶 F、組織蛋白酶 O、組織蛋白酶 R、組織蛋白酶 V、組織蛋白酶 W、鈣激活中性蛋白酶 1、鈣激活中性蛋白酶 2、豆蛋白酶、組織蛋白酶 Z、組織蛋白酶 D、組織蛋白酶 E、MMP-1、MMP-8、MMP-13 及 MMP-18、

MMP-2、MMP-9、MMP-3、MMP-10、MMP-11、MMP-7、MMP-26、MMP-12、MMP-14、MMP-15、MMP-16 及 MMP-17、MMP-19、MMP-20、ADAMTS-1、ADAMTS-2、ADAMTS-3、ADAMTS-4、ADAMTS-5、ADAMTS-14 及肝素酶或其對偶基因或物種變異體或其他變異體。

81.如申請專利範圍第 78 項之醫藥組成物，其中該活化劑為冷緩衝液。

82.如申請專利範圍第 78 項之醫藥組成物，其中該活化劑與該 AMDE 提供於同一組成物中或提供於分開的組成物中。

83.如申請專利範圍第 57 項之組成物，其中該活化條件為金屬離子且該金屬離子為 Ca^{2+}。

84.如申請專利範圍第 47 項之醫藥組成物，其中該一或多種 ECM 組份係選自膠原蛋白、彈性蛋白、纖維結合蛋白或蛋白聚糖。

85.如申請專利範圍第 84 項之醫藥組成物，其中該 ECM 組份為膠原蛋白且該膠原蛋白係選自 I 型、II 型、III 型或 IV 型膠原蛋白。

86.如申請專利範圍第 47 項之醫藥組成物，其中該 ECM 之疾病或病狀為膠原蛋白介導之疾病或病狀。

87.如申請專利範圍第 62 或 86 項之醫藥組成物，其中該膠原蛋白介導之疾病或病狀係選自脂肪團、杜普宜特朗氏病、帕榮雷氏病、萊德豪斯纖維化、關節僵硬、現有瘢痕、硬皮病、淋巴水腫及膠原性結腸炎。

88.如申請專利範圍第 87 項之醫藥組成物，其中該膠原蛋白介導之疾病或病狀為關節僵硬，該關節僵硬為凍肩。

89.如申請專利範圍第 87 項之醫藥組成物，其中該膠原蛋白介導之疾病或病狀為選自手術黏連、瘢痕瘤、肥厚性瘢痕及凹陷性瘢痕之現有瘢痕。

90.一種組合，其包含：

可活化的基質降解酵素(AMDE)，其中該 AMDE 為在活化劑不存在之情況下在表皮下投藥後在 ECM 中無活性之基質降解酵素；

活化劑，其提供 AMDE 之活化條件使得當 AMDE 暴露於該活化劑時為具有活性的；及

一或多種選自其他生物製劑(biologic)、小分子化合物、分散劑、麻醉劑及血管收縮劑之其他藥劑。

91.如申請專利範圍第 90 項之組合，其中該活化劑提供選自 pH 值、金屬離子、溫度及離子強度之活化條件。

92.如申請專利範圍第 90 項之組合，其中該 AMDE 係選自胰腺彈性蛋白酶、彈性蛋白酶-2A、彈性蛋白酶-2B、嗜中性白血球彈性蛋白酶、蛋白酶-3、內源性血管彈性蛋白酶、組織蛋白酶 G、肥大細胞凝乳酶、肥大細胞類胰蛋白酶、纖溶酶、凝血酶、顆粒酶 B、組織蛋白酶 S、組織蛋白酶 K、組織蛋白酶 L、組織蛋白酶 B、組織蛋白酶 C、組織蛋白酶 H、組織蛋白酶 F、組織蛋白酶 O、組織蛋白酶 R、組織蛋白酶 V、組織蛋白酶 W、鈣激活中性蛋白酶 1、鈣激活中性蛋白酶 2、豆蛋白酶、組織蛋白酶 Z、組織蛋白酶 D、組織

蛋白酶 E、MMP-1、MMP-8、MMP-13 及 MMP-18、MMP-2、MMP-9、MMP-3、MMP-10、MMP-11、MMP-7、MMP-26、MMP-12、MMP-14、MMP-15、MMP-16 及 MMP-17、MMP-19、MMP-20、ADAMTS-1、ADAMTS-2、ADAMTS-3、ADAMTS-4、ADAMTS-5、ADAMTS-14 及肝素酶或其對偶基因或物種變異體或其他變異體。

93.如申請專利範圍第 90 項之組合，其中該組合中之 AMDE 係用於單劑量投藥，且含有約 10 μg 至 100 mg、50 μg 至 75 mg、100 μg 至 50 mg、250 μg 至 25 mg、500 μg 至 10 mg、1 mg 至 5 mg 或 2 mg 至 4 mg 之量的 AMDE。

94.如申請專利範圍第 90 項之組合，其中該其他藥劑為分散劑，該分散劑為玻尿酸酶。

95.如申請專利範圍第 94 項之組合，其中該玻尿酸酶經糖基化。

96.如申請專利範圍第 94 項之組合，其中該玻尿酸酶為 PH20 或其截短形式。

97.如申請專利範圍第 96 項之組合，其中該 PH20 係選自羊類、牛類或人類 PH20。

98.如申請專利範圍第 94 項之組合，其中該玻尿酸酶為可溶性的。

99.如申請專利範圍第 98 項之組合，其中該玻尿酸酶具有 SEQ ID NO:226-231 中所闡明之胺基酸序列，或為其對偶基因或物種變異體或其他變異體。

100.如申請專利範圍第 94 項之組合，其中該玻尿酸酶

為以稱為 rHuPH20 之組成物形式提供的可溶性玻尿酸酶。

101.如申請專利範圍第 94 項之組合，其中該組合中之玻尿酸酶係用於單劑量投藥，且含有為或約為 10 單位至 500,000 單位、100 單位至 100,000 單位、500 單位至 50,000 單位、1000 單位至 10,000 單位、5000 單位至 7500 單位、5000 單位至 50,000 單位或 1000 單位至 10,000 單位之量的玻尿酸酶。

102.如申請專利範圍第 90 項之組合，其中該其他藥劑為麻醉劑，該麻醉劑為利多卡因(lidocaine)。

103.如申請專利範圍第 102 項之組合，其中該組合中之利多卡因係用於單劑量投藥且含有為或約為 10 mg 至 1000 mg、100 mg 至 500 mg、200 mg 至 400 mg、20 mg 至 60 mg 或 30 mg 至 50 mg 之量的利多卡因。

104.如申請專利範圍第 90 項之組合，其中該其他藥劑為血管收縮劑，該血管收縮劑為 α 腎上腺素能受體促效劑。

105.如申請專利範圍第 104 項之組合，其中該 α 腎上腺素能受體促效劑係選自可巴君（levonordefrin）、腎上腺素（ephinephrine）及去甲腎上腺素（norepinephrine）。

106.如申請專利範圍第 104 項之組合，其中該 α 腎上腺素能受體促效劑為實現血管收縮之量的腎上腺素。

107.如申請專利範圍第 106 項之組合，其中該組合中之腎上腺素係用於單劑量投藥，且含有為或約為 10 μg 至 5 mg、50 μg 至 1 mg、50 μg 至 500 μg、50 μg 至 250 μg、100 μg 至 500 μg、200 μg 至 400 μg、1 mg 至 5 mg 或 2 mg 至 4

mg之量的腎上腺素。

108.如申請專利範圍第90項之組合，其係用於治療ECM之疾病或病狀。

109.如申請專利範圍第108項之組合，其中該AMDE為組織蛋白酶L且該ECM之疾病或病狀為脂肪團。

110.一種醫藥組成物，其包含用於治療ECM介導的疾病或病狀之量的之組織蛋白酶L，其中：

該組成物經調配用於單劑量投藥；且

該組成物調配於具有活化該組織蛋白酶L之pH值之酸性緩衝液中。

111.如申請專利範圍第110項之組成物，其中該組成物中之組織蛋白酶L的量為或約為10 μg至100 mg、50 μg至75 mg、100 μg至50 mg、250 μg至25 mg、500 μg至10 mg、1 mg至5 mg或2 mg至4 mg。

112.如申請專利範圍第110項之組成物，其進一步包含利多卡因、腎上腺素及玻尿酸酶中之一或多者。

113.一種組合，其包含組織蛋白酶L與玻尿酸酶。

114.如申請專利範圍第113項之組合，其中該玻尿酸酶為稱為rHuPH20之組成物。

115.如申請專利範圍第113項之組合，其中該組織蛋白酶L及該玻尿酸酶處於分開的組成物中或處於單一組成物中。

116.如申請專利範圍第113項之組合，其進一步包含活化該組織蛋白酶L之酸性緩衝液。

117.如申請專利範圍第113項之組合，其中該組織蛋白酶L及該玻尿酸酶處於調配為醫藥組成物之單一組成物中。

118.一種套組，其包含如申請專利範圍第90或113項之組合，及視情況投藥說明書。

119.一種容器，其包含兩個隔室，其中：

第一隔室含有治療有效量之可活化的基質降解酵素（AMDE），其中：

該AMDE為在該活化劑不存在之情況下在表皮下投藥後在ECM中無活性之基質降解酵素；且

該量係用於單一劑量或複數個劑量且當暴露於活化劑時單一劑量有效治療ECM之疾病或病狀；且

第二隔室含有活化劑，其中該活化劑提供該酵素活性所需之活化條件。

120.如申請專利範圍第119項之容器，其中該酵素於pH 5.5下實質上具活性。

121.如申請專利範圍第119項之容器，其中該酵素於中性pH值下實質上無活性。

122.如申請專利範圍第119項之容器，其進一步包含混合隔室。

123.如申請專利範圍第119項之容器，其為管或瓶。

124.如申請專利範圍第119項之容器，其為注射器。

125.如申請專利範圍第124項之容器，其中該注射器進一步包含注射用針。

126.如申請專利範圍第119項之容器，其中：

該活化劑提供選自pH值、金屬離子或離子強度之活化條件，且

該活化劑以液體溶液或懸浮液形式提供。

127.如申請專利範圍第126項之容器，其中該液體溶液為緩衝液。

128.如申請專利範圍第126項之容器，其中該活化條件為酸性之pH值。

129.如申請專利範圍第128項之容器，其中該pH值在或約在3至6.5、或3.5至6、或3至5.5、或3至4.5、或4至6、或4至5.5、或4.5至5、或5至6之範圍內。

130.如申請專利範圍第128項之容器，其中該pH值約為或為3、3.5、4、4.5、5、5.5、6或6.5。

131.如申請專利範圍第127項之容器，其中該活化劑為酸性緩衝溶液。

132.如申請專利範圍第131項之容器，其中該緩衝液含有選自2-(N-嗎啉基)乙烷磺酸（MES）、乙酸、檸檬酸、檸檬酸磷酸鹽及組胺酸之酸。

133.如申請專利範圍第132項之容器，其中該緩衝液之離子強度經選擇以使得該AMDE在投藥之後在預定時間內具活性。

134.如申請專利範圍第126項之容器，其中該活化條件為金屬離子且該金屬離子為Ca^{2+}。

135.如申請專利範圍第119項之容器，其中該AMDE係選自胰腺彈性蛋白酶、彈性蛋白酶-2A、彈性蛋白酶-2B、

嗜中性白血球彈性蛋白酶、蛋白酶-3、內源性血管彈性蛋白酶、組織蛋白酶G、肥大細胞凝乳酶、肥大細胞類胰蛋白酶、纖溶酶、凝血酶、顆粒酶B、組織蛋白酶S、組織蛋白酶K、組織蛋白酶L、組織蛋白酶B、組織蛋白酶C、組織蛋白酶H、組織蛋白酶F、組織蛋白酶O、組織蛋白酶R、組織蛋白酶V、組織蛋白酶W、鈣激活中性蛋白酶1、鈣激活中性蛋白酶2、豆蛋白酶、組織蛋白酶Z、組織蛋白酶D、組織蛋白酶E、MMP-1、MMP-8、MMP-13、MMP-18、MMP-2、MMP-9、MMP-3、MMP-10、MMP-11、MMP-7、MMP-26、MMP-12、MMP-14、MMP-15、MMP-16及MMP-17、MMP-19、MMP-20、ADAMTS-1、ADAMTS-2、ADAMTS-3、ADAMTS-4、ADAMTS-5、ADAMTS-14及肝素酶或其對偶基因或物種變異體或其他變異體。

136.如申請專利範圍第119項之容器，其中該AMDE係選自組織蛋白酶、鈣激活中性蛋白酶及肝素酶。

137.如申請專利範圍第119項之容器，其中該AMDE為溶酶體酵素。

138.如申請專利範圍第119項之容器，其中該AMDE為呈單鏈或雙鏈形式之成熟蛋白質。

139.如申請專利範圍第136項之容器，其中該AMDE為組織蛋白酶且該組織蛋白酶為半胱胺酸蛋白酶或天冬胺酸蛋白酶。

140.如申請專利範圍第139項之容器，其中該組織蛋白酶係選自組織蛋白酶S、組織蛋白酶K、組織蛋白酶L、組

織蛋白酶B、組織蛋白酶C、組織蛋白酶H、組織蛋白酶F、組織蛋白酶O、組織蛋白酶R、組織蛋白酶V、組織蛋白酶W、組織蛋白酶D及組織蛋白酶E。

141.如申請專利範圍第140項之容器，其中該組織蛋白酶具有選自SEQ ID NO: 57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93及96中之任一者的胺基酸序列，或為SEQ ID NO: 57、60、1、65、180、68、71、74、77、183、186、189、80、195、90、93及96中之任一者的對偶基因或物種變異體或其他變異體。

142.如申請專利範圍第119項之容器，其中該AMDE及活化劑係以用於多劑量投藥之量提供。

143.如申請專利範圍第119項之容器，其中該AMDE及活化劑係以單一單位劑量提供。

144.如申請專利範圍第143項之容器，其中該容器中之AMDE為或約為10 μg至100 mg、50 μg至75 mg、100 μg至50 mg、250 μg至25 mg、500 μg至10 mg、1 mg至5 mg或2 mg至4 mg。

145.如申請專利範圍第119項之容器，其中該容器中之液體的總體積為或約為1-100 ml、1-50 ml、10-50 ml、10-30 ml、1-20 ml或1-10 ml。

146.如申請專利範圍第119項之容器，其中該AMDE處於溶液或懸浮液中。

147.如申請專利範圍第119項之容器，其中該AMDE經凍乾。

148.一種容器，其包含兩個隔室，其中：

第一隔室含有治療有效量之組織蛋白酶 L，其中該量有效治療細胞外基質（ECM）之疾病或病狀；且

第二隔室含有酸性緩衝液，其為活化該組織蛋白酶 L 之酸性緩衝液。

149.如申請專利範圍第 148 項之容器，其中該酸性緩衝液之 pH 值具有為或約為 4.5 至 6 之範圍。

150.如申請專利範圍第 148 項之容器，其中該酸性緩衝液之 pH 值為或約為 4.5、5、5.5 或 6。

151.如申請專利範圍第 148 項之容器，其中該緩衝液含有選自 2-(N-嗎啉基)乙烷磺酸（MES）、乙酸、檸檬酸、檸檬酸磷酸鹽及組胺酸之酸。

152.如申請專利範圍第 151 項之容器，其中該緩衝液之離子強度經選擇以使得該 AMDE 在投藥之後在預定時間內具活性。

153.如申請專利範圍第 148 項之容器，其中該組織蛋白酶 L 具有 SEQ ID NO:1 中所闡明之胺基酸序列，或為 SEQ ID NO:1 的對偶基因或物種變異體或其他變異體。

154.如申請專利範圍第 148 項之容器，其中該組織蛋白酶 L 經凍乾。

155.如申請專利範圍第 148 項之容器，其中該容器中之組織蛋白酶 L 係用於單劑量投藥，且含有為或約為 10 μg 至 100 mg、50 μg 至 75 mg、100 μg 至 50 mg、250 μg 至 25 mg、500 μg 至 10 mg、1 mg 至 5 mg 或 2 mg 至 4 mg 之量的

組織蛋白酶 L。

156.如申請專利範圍第 148 項之容器，其中該容器中之總體積為或約為 1-100 ml、1-50 ml、10-50 ml、10-30 ml、1-20 ml 或 1-10 ml。

157.如申請專利範圍第 148 項之容器，其中該 ECM 之疾病或病狀為選自脂肪團、杜普宜特朗氏病、帕榮雷氏病、萊德豪斯纖維化、關節僵硬、現有瘢痕、硬皮病、淋巴水腫及膠原性結腸炎之膠原蛋白介導之疾病或病狀。

158.如申請專利範圍第 148 項之容器，其中該 ECM 之疾病或病狀為脂肪團。

159.一種組合，其包含：

如申請專利範圍第 148 項之容器；及

一或多個其他容器，其含有選自生物製劑、小分子化合物、分散劑、麻醉劑及血管收縮劑之另一藥理學有效藥劑及其組合。

160.如申請專利範圍第 159 項之組合，其中該醫藥有效藥劑為分散劑，該分散劑為玻尿酸酶。

161.如申請專利範圍第 160 項之組合，其中該玻尿酸酶為 PH20。

162.如申請專利範圍第 160 項之組合，其中該玻尿酸酶為可溶性的。

163.如申請專利範圍第 162 項之組合，其中該玻尿酸酶具有 SEQ ID NO:226-231 中所闡明之胺基酸序列，或為其對偶基因或物種變異體或其他變異體。

164.如申請專利範圍第 160 項之組合，其中該玻尿酸酶經糖基化。

165.如申請專利範圍第 160 項之組合，其中該容器中之玻尿酸酶係用於單劑量投藥，且含有為或約為 10 單位至 500,000 單位、100 單位至 100,000 單位、500 單位至 50,000 單位、1000 單位至 10,000 單位、5000 單位至 7500 單位、5000 單位至 50,000 單位或 1000 單位至 10,000 單位之量的玻尿酸酶。

166.如申請專利範圍第 159 項之組合，其中該醫藥有效藥劑為麻醉劑，該麻醉劑為利多卡因，且該容器中之利多卡因係用於單劑量投藥，且含有為或約為 10 mg 至 1000 mg、100 mg 至 500 mg、200 mg 至 400 mg、20 mg 至 60 mg 或 30 mg 至 50 mg 之量的利多卡因。

167.如申請專利範圍第 159 項之組合，其中該醫藥有效藥劑為血管收縮劑，該血管收縮劑為 α 腎上腺素能受體促效劑。

168.如申請專利範圍第 167 項之組合，其中該 α 腎上腺素能受體促效劑係選自可巴君、腎上腺素及去甲腎上腺素。

169.如申請專利範圍第 168 項之組合，其中該 α 腎上腺素能受體促效劑為實現血管收縮之量的腎上腺素。

170.如申請專利範圍第 169 項之組合，其中該容器中之腎上腺素係用於單劑量投藥，且該腎上腺素之量為或約為 10 μg 至 5 mg、50 μg 至 1 mg、50 μg 至 500μg、50 μg 至 250μg、100 μg 至 500μg、200 μg 至 400 μg、1 mg 至 5 mg

或 2 mg 至 4 mg。

171.如申請專利範圍第 159 項之組合，其中該藥理學有效藥劑提供於分開的容器中。

172.如申請專利範圍第 159 項之組合，其中：

該其他容器包含至少兩種藥理學有效藥劑；且

該等藥劑以彼此分開之分開的組成物形式提供。

173.如申請專利範圍第 159 項之組合，其中該等藥理學有效藥劑以同一組成物被提供於同一容器中。

174.如申請專利範圍第 159 項之組合，其中該其他容器含有玻尿酸酶、利多卡因及腎上腺素。

175.如申請專利範圍第 159 項之組合，其中該其他容器為注射器。

176.如申請專利範圍第 159 項之組合，其中該其他容器中之總體積為或約為 1-100 ml、1-50 ml、10-50 ml、10-30 ml、1-20 ml 或 1-10 ml。

177.一種套組，其包含如申請專利範圍第 119 項之容器、投藥裝置及視情況投藥說明書。

178.一種套組，其包含如申請專利範圍第 159 項之組合、投藥裝置及視情況投藥說明書。

八、圖式：

無