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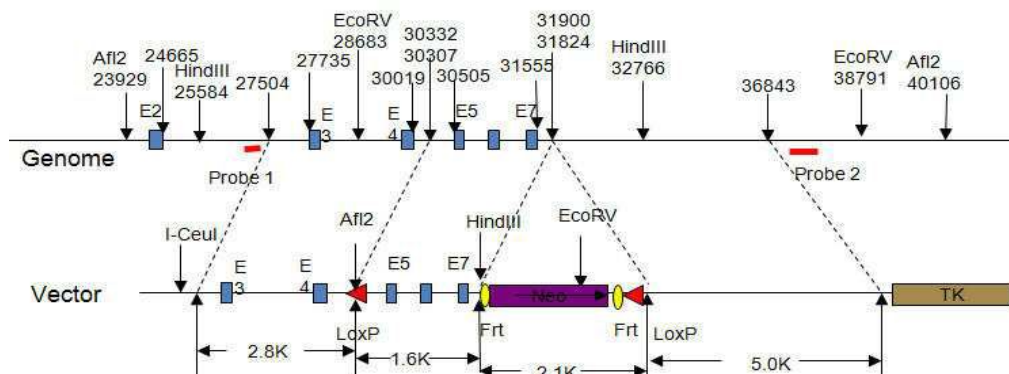　　**양부현**

전체 청구항 수 : 총 9 항

(54) 발명의 명칭 **뇌하수체 종양과 관련된 유전자 및 그의 용도**

(57) 요 약

본 발명은 성장호르몬 과다분비 질환 진단 키트 및 성장호르몬 과다분비 질환의 예방 또는 치료용 물질의 스크리닝 방법에 관한 것이다.

본 발명은 유전자 또는 단백질 마커를 사용함으로써 성장호르몬 분비성 뇌하수체 종양 및 말단비대증을 비롯한 성장호르몬 과다분비 질환의 신뢰도 있는 조기진단 또는 발병 위험성 예측에 유용하게 이용될 수 있다.

대 표 도 - 도1

명 세 서

청구범위

청구항 1

서열목록 제72서열 내지 제142서열로 구성된 군으로부터 선택되는 아미노산 서열로 이루어진 폴리펩타이드에 특이적으로 결합하는 항체 또는 앱타머를 포함하는 성장호르몬 과다분비 질환 진단 키트.

청구항 2

제 1 항에 있어서, 상기 서열목록 제72서열 내지 제131서열로 구성된 군으로부터 선택되는 아미노산 서열로 이루어진 폴리펩타이드는 뇌하수체 종양 조직에서 고발현되고, 상기 서열목록 제132서열 내지 제142서열로 구성된 군으로부터 선택되는 아미노산 서열로 이루어진 폴리펩타이드는 성장호르몬 과다분비 조직에서 저발현되는 것을 특징으로 하는 성장호르몬 과다분비 질환 진단 키트.

청구항 3

제 1 항에 있어서, 상기 아미노산 서열은 서열목록 제74서열, 제81 내지 제83서열, 제95서열, 제96서열, 제98서열, 제109서열, 제113서열 및 제115서열로 구성된 군으로부터 선택되는 것을 특징으로 하는 성장호르몬 과다분비 질환 진단 키트.

청구항 4

서열목록 제1서열 내지 제71서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열에 특이적으로 결합하는 프라이머 또는 프로브를 포함하는 성장호르몬 과다분비 질환 진단 키트.

청구항 5

제 4 항에 있어서, 상기 서열목록 제1서열 내지 제60서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열은 성장호르몬 과다분비 조직에서 고발현되고, 상기 서열목록 제61서열 내지 제71서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열은 성장호르몬 과다분비 조직에서 저발현 되는 것을 특징으로 하는 성장호르몬 과다분비 질환 진단 키트.

청구항 6

제 4 항에 있어서, 상기 뉴클레오타이드 서열은 서열목록 제3서열, 제10서열 내지 제12서열, 제24서열, 제25서열, 제27서열, 제38서열, 제42서열 및 제44서열로 구성된 군으로부터 선택되는 것을 특징으로 하는 성장호르몬 과다분비 질환 진단 키트.

청구항 7

제 1 항 내지 제 6 항 중 어느 한 항에 있어서, 상기 성장호르몬 과다분비 질환은 성장호르몬 분비성 뇌하수체 종양 또는 말단비대증인 것을 특징으로 하는 뇌하수체 종양 진단 키트.

청구항 8

다음의 단계를 포함하는 성장호르몬 과다분비 질환의 예방 또는 치료용 물질의 스크리닝 방법:

(a) 서열목록 제1서열 내지 제71서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열을 포함하는 세포에 분석하고자 하는 시료를 접촉시키는 단계; 및

(b) 상기 뉴클레오타이드 서열의 발현량을 측정하는 단계, 상기 뉴클레오타이드 서열 중에서 서열목록 제1서열 내지 제60서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열의 발현이 억제되거나 또는 서열목록 제61서열 내지 제71서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열의 발현이 증가되는 경우에는 상기 시료는 성장호르몬 과다분비 질환의 예방 또는 치료용 물질로 판정된다.

청구항 9

제 8 항에 있어서, 상기 성장호르몬 과다분비 질환은 성장호르몬 분비성 뇌하수체 종양 또는 발단 비대증인 것을 특징으로 하는 스크리닝 방법.

발명의 설명

기 술 분 야

[0001] 본 발명은 뇌하수체 종양 특이적인 발현양상을 보이는 유전자 및 이를 이용한 뇌하수체 종양의 진단방법에 관한 것이다.

배 경 기 술

[0002] 뇌하수체 종양은 간뇌의 시상하부 아래쪽에 위치하여 다양한 호르몬을 분비하는 내분비 기관인 뇌하수체(Pituitary gland)에 발생하는 종양으로, 한 가지 이상의 호르몬을 과다하게 분비하는 기능성 뇌하수체 종양(functioning pituitary adenoma) 및 호르몬 분비에 영향을 미침이 없이 종양 자체에 의해서만 증상을 일으키는 비기능성 뇌하수체 종양(non-functioning pituitary adenoma)으로 나뉜다. 기능성 뇌하수체 종양은 호르몬 장기의 활성화로 인한 다양한 내분비 대사 질환 합병증을 유발한다.

[0003] 뇌하수체 종양의 진단은 환자의 손, 발 및 얼굴 등의 외형상의 특징과 임상증상이 진단에 큰 부분을 차지하며, 성장호르몬 및 IGF-1(인슐린양 성장인자-1)의 측정을 통해서도 진단되어 왔다. 성장 호르몬 자체와 인슐린양 성장인자-1은 연령에 따라 감소하며, 정상인에서의 성장호르몬은 박동성 분비와 일중 변동을 보이면서 수면, 운동, 스트레스 등에 의해 자극되므로, 무작위적인 성장호르몬의 측정으로는 신뢰도 높은 진단을 할 수 없다. 또한 뇌하수체 종양의 크기와 양상을 확인하고 적절한 치료 계획을 수립하기 위해서 뇌하수체의 자기공명영상이나 전산화 단층 촬영이 이용된다.

[0004] 뇌하수체 종양의 위험요인으로 시상하부 원인설과 뇌하수체 원인설이 있다. 전자는 시상하부의 기능 이상으로 지속적인 호르몬의 이상 분비로 인해 뇌하수체에 종양이 발생한다는 설이고, 후자는 시상하부와는 관계없이 뇌하수체 세포가 종양세포로 전환된다는 설이다. 뇌하수체 선종이 분자생물학적으로 단일 세포에서 유래된 사실과 종양을 절제하기만 하면 완치된다는 점을 근거로 종양세포 전환설이 더 인정받고 있으나, 아직 정확한 원인은 밝혀지지 않았으며, 이의 초기 진행기작에 대한 포괄적인 이해는 아직까지 이루어지지 않고 있다. 따라서 증상이 뚜렷하지 않은 초기 환자를 진단하거나 발병 전 대상체의 유전적 위험성을 예측하기 위한 신뢰도 있는 유전자 마커의 개발이 요구되고 있다.

[0005] 본 명세서 전체에 걸쳐 다수의 논문 및 특허문헌이 참조되고 그 인용이 표시되어 있다. 인용된 논문 및 특허문헌의 개시 내용은 그 전체로서 본 명세서에 참조로 삽입되어 본 발명이 속하는 기술 분야의 수준 및 본 발명의 내용이 보다 명확하게 설명된다.

발명의 내용

해결하려는 과제

[0006] 본 발명자들은 기능성 뇌하수체 종양을 비롯, 성장호르몬 과다분비와 관련된 다양한 질환의 발병 기작을 연구하기 위한 성장호르몬 분비성 뇌하수체 종양 특이적인 안정적 동물모델을 확립하고, 아울러 이를 통하여 성장호르몬 과다분비 질환에 대한 신뢰도 있는 유전자/단백질 마커를 발굴하고자 개발하고자 예의 연구 노력하였다. 그 결과, *Aip* 유전자의 특정 엑손 부위를 타겟팅하는 Lox-Cre 시스템을 이용할 경우 성장자극세포(somatotroph) 특이적으로 *Aip* 유전자가 결실된 동물모델을 수득할 수 있다는 사실을 발견하고, 상기 동물모델과 대조군 간의 유전자 발현 프로파일 비교분석을 통하여 서열목록 제96서열 내지 제190서열로 구성된 군으로부터 선택되는 아미노산 서열로 이루어진 폴리펩타이드 또는 이들을 코딩하는 뉴클레오타이드 서열이 성장호르몬 과다분비 질환의 유용한 진단 마커가 될 수 있음을 발견함으로써, 본 발명을 완성하게 되었다.

[0007] 따라서 본 발명의 목적은 성장호르몬 과다분비 질환 진단 키트를 제공하는 데 있다.

[0008] 본 발명의 다른 목적은 성장호르몬 과다분비 질환의 예방 또는 치료용 물질의 스크리닝 방법을 제공하는 데 있다.

[0009] 본 발명의 다른 목적 및 이점은 하기의 발명의 상세한 설명, 청구범위 및 도면에 의해 보다 명확하게 된다.

과제의 해결 수단

[0010] 본 발명의 일 양태에 따르면, 본 발명은 서열목록 제72서열 내지 제142서열로 구성된 군으로부터 선택되는 아미노산 서열로 이루어진 폴리펩타이드에 특이적으로 결합하는 항체 또는 앱타머를 포함하는 성장호르몬 과다분비 질환 진단 키트를 제공한다.

[0011] 본 발명자들은 기능성 뇌하수체 종양을 비롯, 성장호르몬 과다분비와 관련된 다양한 질환의 발병 기작을 연구하기 위한 성장호르몬 분비성 뇌하수체 종양 특이적인 안정적 동물모델을 확립하고, 아울러 이를 통하여 성장호르몬 과다분비 질환에 대한 신뢰도 있는 유전자/단백질 마커를 발굴하고자 개발하고자 예의 연구 노력하였다. 그 결과, *Aip* 유전자의 특정 엑손 부위를 타겟팅하는 Lox-Cre 시스템을 이용할 경우 성장자극세포(somatotroph) 특이적으로 *Aip* 유전자가 결실된 동물모델을 수득할 수 있다는 사실을 발견하고, 상기 동물모델과 대조군 간의 유전자 발현 프로파일 비교분석을 통하여 서열목록 제72서열 내지 제142서열로 구성된 군으로부터 선택되는 아미노산 서열로 이루어진 폴리펩타이드 또는 이들을 코딩하는 뉴클레오타이드 서열이 성장호르몬 과다분비 질환의 유용한 진단 마커가 될 수 있음을 발견하였다.

[0012] *Aip* 유전자는 세포 내 다양한 방향족 탄수화물(aryl hydrocarbon) 수용체와 상호작용하는 단백질을 코딩하는 유전자로서, 세포의 성장, 증식 및 분열과정을 조절한다. *Aip*의 소실 또는 기능 이상은 뇌하수체 종양을 유발함이 보고되었으므로, 본 발명의 유전자 전달체로 형질전환된 동물을 성장 호르몬(growth hormone, GH) 프로모터 하에서 Cre-재조합 효소를 발현하는 형질전환 동물과 교배할 경우, 성장자극세포(somatotroph) 특이적으로 *Aip* 유전자가 결실된 동물을 수득할 수 있다. 이러한 동물 모델은 다양한 형태의 뇌하수체 종양 중 성장 호르몬 분비성 뇌하수체 종양만이 특이적으로 발생하므로, 성장호르몬 과다분비와 관련된 질환에 대한 인 비보 연구용 모델로서 유용하게 이용될 수 있다.

[0013] 본 발명에 따르면, 본 발명의 동물모델은 성장자극세포 특이적으로 *Aip* 유전자의 특정 엑손이 결실됨으로 인해 과량의 성장호르몬을 분비하여, 비정상적인 성장호르몬 분비를 직접 또는 간접적인 원인으로 하는 다양한 질환에서 특이적으로 고발현 또는 저발현되는 유전자를 스크리닝하기 위한 동물모델로 적용될 수 있다.

[0014] 본 명세서에서 용어 "성장호르몬 과다분비 질환"은 성장 호르몬(growth hormone, GH)의 과다 분비 및 이로 인한 조직의 비정상적인 성장을 수반하는 모든 질환을 의미한다.

[0015] 본 명세서에서, 용어 "진단"은 특정 질병 또는 질환에 대한 한 객체의 감수성(susceptibility)을 판정하는 것, 한 객체가 특정 질병 또는 질환을 현재 가지고 있는 지 여부를 판정하는 것, 특정 질병 또는 질환에 걸린 한 객

체의 예후(prognosis)를 판정하는 것, 또는 테라메트릭스(therametrics)(예컨대, 치료 효능에 대한 정보를 제공하기 위하여 객체의 상태를 모니터링 하는 것)을 포함한다.   본 발명에 따르면, 본 발명의 폴리펩타이드를 마커로 하여, 이의 발현량이 정상인에 비하여 유의하게 높거나(양성 마커) 낮다(음성마커)는 사실이 통상적인 면역분석 방법 등을 통해 확인되면 성장호르몬 과다분비 질환의 발병 위험도가 높은 것으로 판단된다.

[0016]   본 명세서에서 용어 "폴리펩타이드"는 펩타이드 결합에 의해 아미노산 잔기들이 서로 결합되어 형성된 선형의 분자를 의미한다.

[0017]   본 발명의 폴리펩타이드는 서열목록 제72서열 내지 제142서열로 구성된 군으로부터 선택되는 아미노산 서열에 대하여 실질적인 동일성(substantial identity)을 나타내는 아미노산 서열도 포함하는 것으로 해석된다. 상기의 실질적인 동일성은, 상기한 본 발명의 아미노산 서열과 임의의 다른 서열을 최대한 대응되도록 얼라인하고, 당업계에서 통상적으로 이용되는 알고리즘을 이용하여 얼라인된 서열을 분석한 경우에, 최소 80%의 상동성, 보다 바람직하게는 최소 90%의 상동성, 가장 바람직하게는 최소 95%의 상동성을 나타내는 아미노산 서열을 의미한다.

[0018]   또한, 본 발명의 폴리펩타이드는 서열목록 제72서열 내지 제142서열로 구성된 군으로부터 선택되는 아니모산 서열의 천연형 아미노산 서열 뿐만 아니라 이의 아미노산 서열 변이체가 또한 본 발명의 범위에 포함된다.   아미노산의 변이체란 본 발명의 천연 아미노산 서열과 하나 이상의 아미노산 잔기가 결실, 삽입, 비보전적 또는 보전적 치환 또는 이들의 조합에 의하여 상이한 서열을 가지는 단백질을 의미한다. 분자의 활성을 전체적으로 변경시키지 않는 단백질 및 펩파이드에서의 아미노산 교환은 당해 분야에 공지되어 있다(H.Neurath, R.L.Hill, The Proteins, Academic Press, New York, 1979).   가장 통상적으로 일어나는 교환은 아미노산 잔기 Ala/Ser, Val/Ile, Asp/Glu, Thr/Ser, Ala/Gly, Ala/Thr, Ser/Asn, Ala/Val, Ser/Gly, Tyr/Phe, Ala/Pro, Lys/Arg, Asp/Asn, Leu/Ile, Leu/Val, Ala/Glu 및 Asp/Gly 간의 교환이다.   경우에 따라서는 본 발명의 폴리펩타이드는 인산화(phosphorylation), 황화(sulfation), 아크릴화(acrylation), 당화(glycosylation), 메틸화 (methylation) 또는 파네실화(farnesylation) 등으로 수식(modification)될 수도 있다.

[0019]   본 발명에 따르면, 본 발명의 폴리펩타이드를 항원-항체 반응을 이용한 면역분석(immunoassay) 방법에 따라 검출하여 성장호르몬 과다분비 질환을 진단하는 데 이용될 수 있다.   이러한 면역분석은 종래에 개발된 다양한 면역분석(immunoassay) 또는 면역염색(immunostaining) 프로토콜에 따라 실시될 수 있다.   예를 들어, 본 발명의 방법이 방사능면역분석 방법에 따라 실시되는 경우, 방사능동위원소(예컨대, C^{14}, I^{125}, P^{32} 및 S^{35})로 표지된 항체가 본 발명의 폴리펩타이드를 검출하는 데 이용될 수 있다.

[0020]   본 발명에서 이용되는 항체는 폴리클로날 또는 모노클로날 항체이며, 바람직하게는 모노클로날 항체이다.   본 발명의 폴리펩타이드에 대한 항체는 당업계에서 통상적으로 실시되는 방법들, 예를 들어, 융합 방법(Kohler and Milstein, European Journal of Immunology, 6:511-519(1976)), 재조합 DNA 방법(미국 특허 제4,816,567호) 또는 파아지 항체 라이브러리 방법(Clackson et al, Nature, 352:624-628(1991) 및 Marks et al, J. Mol. Biol., 222:58, 1-597(1991))에 의해 제조될 수 있다.   항체 제조에 대한 일반적인 과정은 Harlow, E. and Lane, D., Using Antibodies: A Laboratory Manual, Cold Spring Harbor Press, New York, 1999; Zola, H., Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc., Boca Raton, Florida, 1984; 및 Coligan , CURRENT PROTOCOLS IN IMMUNOLOGY, Wiley/Greene, NY, 1991에 상세하게 기재되어 있다.   예를 들어, 단일클론 항체를 생산하는 하이브리도마 세포의 제조는 불사멸화 세포주를 항체-생산 림프구와 융합시켜 이루어지며, 이 과정에 필요한 기술은 당업자에게 잘 알려져 있으며 용이하게 실시할 수 있다.   폴리클로날 항체는 본 발명의 폴리펩타이드 항원을 적합한 동물에게 주사하고, 이 동물로부터 항혈청을 수집한 다음, 공지의 친화성(affinity) 기술을 이용하여 항혈청으로부터 항체를 분리하여 얻을 수 있다.

[0021]   상술한 면역분석 과정에 의한 최종적인 시그널의 세기를 분석함으로써, 관절염을 진단할 수 있다.   즉, 인간의 시료에서 본 발명의 폴리펩타이드에 대한 시그널이 정상 시료 보다 강하거나(양성마커) 또는 약하게(음성마커) 나오는 경우에는 성장호르몬 과다분비 질환의 발병 위험도가 높은 것으로 진단된다.

[0022]   본 발명의 키트는 항체 대신에 본 발명의 폴리펩타이드 마커에 특이적으로 결합하는 앱타머를 이용할 수 있다.   본 명세서에서 용어 "앱타머"는 단일 줄기의(single-stranded) 핵산(RNA 또는 DNA) 분자 또는 펩타이드 분자로서 특정 표적물질에 높은 친화력과 특이성으로 결합하여 작용을 나타내는 것을 의미한다.   앱타머의 일반적인 내용은 Bock LC et al., Nature 355(6360):5646(1992); Hoppe-Seyler F, Butz K "Peptide aptamers: powerful new tools for molecular medicine". J Mol Med. 78(8):42630(2000);Cohen BA, Colas P, Brent R . "An artificial cell-cycle inhibitor isolated from a combinatorial library". Proc Natl Acad Sci USA.

95(24):142727(1998)에 상세하게 개시되어 있다.

[0023] 본 발명의 구체적인 구현예에 따르면, 상기 서열목록 제72서열 내지 제131서열로 구성된 군으로부터 선택되는 아미노산 서열로 이루어진 폴리펩타이드는 성장호르몬 과다분비 조직에서 고발현 되고, 상기 서열목록 제132서열 내지 제142서열로 구성된 군으로부터 선택되는 아미노산 서열로 이루어진 폴리펩타이드는 성장호르몬 과다분비 조직에서 저발현된다.

[0024] 본 명세서에서 용어 "고발현"은 본 발명의 뉴클레오타이드 또는 폴리펩타이드의 발현량이 정상인에 비하여 유의하게 높은 경우를 의미하며, 바람직하게는 본 발명의 뉴클레오타이드 또는 폴리펩타이드의 발현량이 정상인의 150% 이상인 경우를 의미한다.

[0025] 본 명세서에서 용어 "저발현"은 본 발명의 뉴클레오타이드 또는 폴리펩타이드의 발현량이 정상인에 비하여 유의하게 낮은 경우를 의미하며, 바람직하게는 본 발명의 뉴클레오타이드 또는 폴리펩타이드의 발현량이 정상인의 5-65%인 경우를 의미한다.

[0026] 본 발명의 보다 구체적인 구현예에 따르면, 상기 아미노산 서열은 서열목록 제74서열, 제81 내지 제83서열, 제95서열, 제96서열, 제98서열, 제109서열, 제113서열 및 제115서열로 구성된 군으로부터 선택된다.

[0027] 본 발명의 다른 양태에 따르면, 본 발명은 서열목록 제1서열 내지 제71서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열에 특이적으로 결합하는 프라이머 또는 프로브를 포함하는 성장호르몬 과다분비 질환 진단 키트를 제공한다.

[0028] 본 명세서에서, 용어 "뉴클레오타이드"는 단일가닥 또는 이중가닥 형태로 존재하는 디옥시리보뉴클레오타이드 또는 리보뉴클레오타이드이며, 다르게 특별하게 언급되어 있지 않은 한 자연의 뉴클레오타이드의 유사체를 포함한다(Scheit, *Nucleotide Analogs*, John Wiley, New York(1980); Uhlman 및 Peyman, *Chemical Reviews*, 90:543-584(1990)).

[0029] 본 발명의 뉴클레오타이드 서열은 첨부한 서열목록에 기재된 뉴클레오타이드 서열에 한정되지 않는다는 것은 당업자에게 명확하다.

[0030] 뉴클레오타이드에서의 변이는 단백질에서 변화를 가져오지 않는 것도 있다. 이러한 핵산은 기능적으로 균등한 코돈 또는 동일한 아미노산을 코딩하는 코돈 (예를 들어, 코돈의 축퇴성에 의해, 아르기닌 또는 세린에 대한 코돈은 여섯 개이다), 또는 생물학적으로 균등한 아미노산을 코딩하는 코돈을 포함하는 핵산분자를 포함한다.

[0031] 상술한 생물학적 균등 활성을 갖는 변이를 고려한다면, 본 발명에서 이용되는 핵산 분자는 서열목록에 기재된 서열과 실질적인 동일성(substantial identity)을 나타내는 서열도 포함하는 것으로 해석된다. 상기의 실질적인 동일성은, 상기한 본 발명의 서열과 임의의 다른 서열을 최대한 대응되도록 얼라인하고, 당업계에서 통상적으로 이용되는 알고리즘을 이용하여 얼라인된 서열을 분석한 경우에, 최소 60%의 상동성, 보다 바람직하게는 70%의 상동성, 보다 더 바람직하게는 80%의 상동성, 가장 바람직하게는 90%의 상동성을 나타내는 서열을 의미한다.

[0032] 서열비교를 위한 얼라인먼트 방법은 당업계에 공지되어 있다. 얼라인먼트에 대한 다양한 방법 및 알고리즘은 Smith and Waterman, *Adv. Appl. Math.* 2:482(1981); Needleman and Wunsch, *J. Mol. Bio. 48:443(1970);* Pearson and Lipman, *Methods in Mol. Biol.* 24: 307-31(1988); Higgins and Sharp, *Gene* 73:237-44(1988); Higgins and Sharp, *CABIOS* 5:151-3(1989); Corpet et al., *Nuc. Acids Res.* 16:10881-90(1988); Huang et al., *Comp. Appl. BioSci.* 8:155-65(1992) and Pearson et al., *Meth. Mol. Biol.* 24:307-31(1994)에 개시되어 있다. NCBI Basic Local Alignment Search Tool(BLAST)(Altschul et al., *J. Mol. Biol.* 215:403-10(1990))은 NBCI(National Center for Biological Information) 등에서 접근 가능하며, 인터넷 상에서 blastp, blasm, blastx, tblastn and tblastx와 같은 서열 분석 프로그램과 연동되어 이용할 수 있다. BLSAT는 http://www.ncbi.nlm.nih.gov/BLAST/에서 접속 가능하다. 이 프로그램을 이용한 서열 상동성 비교 방법은 http://www.ncbi.nlm.nih.gov/BLAST/blast_help.html에서 확인할 수 있다.

[0033] 본 명세서에서 사용되는 용어 "프라이머"는 올리고뉴클레오타이드를 의미하는 것으로, 핵산쇄(주형)에 상보적인 프라이머 연장 산물의 합성이 유도되는 조건, 즉, 뉴클레오타이드와 DNA 중합효소와 같은 중합제의 존재, 그리고 적합한 온도와 pH의 조건에서 합성의 개시점으로 작용할 수 있다. 바람직하게는, 프라이머는 디옥시리보뉴클레오타이드이며 단일쇄이다. 본 발명에서 이용되는 프라이머는 자연(naturally occurring) dNMP(즉, dAMP,

dGMP, dCMP 및 dTMP), 변형 뉴클레오타이드 또는 비-자연 뉴클레오타이드를 포함할 수 있다. 또한, 프라이머는 리보뉴클레오타이드도 포함할 수 있다.

[0034] 본 발명의 프라이머는 타겟 핵산에 어닐링 되어 주형-의존성 핵산 중합효소에 의해 타겟 핵산에 상보적인 서열을 형성하는 연장 프라이머(extension primer)일 수 있으며, 이는 고정화 프로브가 어닐링 되어 있는 위치까지 연장되어 프로브가 어닐링 되어 있는 부위를 차지한다.

[0035] 본 발명에서 이용되는 연장 프라이머는 타겟 핵산의 제1위치에 상보적인 혼성화 뉴클레오타이드 서열을 포함한다. 용어 "상보적"은 소정의 어닐링 또는 혼성화 조건하에서 프라이머 또는 프로브가 타겟 핵산 서열에 선택적으로 혼성화할 정도로 충분히 상보적인 것을 의미하며, 실질적으로 상보적(substantially complementary) 및 완전히 상보적(perfectly complementary)인 것을 모두 포괄하는 의미를 가지며, 바람직하게는 완전히 상보적인 것을 의미한다. 본 명세서에서, 프라이머 서열과 관련하여 사용되는 용어, "실질적으로 상보적인 서열"은 완전히 일치되는 서열뿐만 아니라, 특정 서열에 어닐링하여 프라이머 역할을 할 수 있는 범위 내에서, 비교대상의 서열과 부분적으로 불일치되는 서열도 포함되는 의미이다.

[0036] 프라이머는, 중합제의 존재 하에서 연장 산물의 합성을 프라이밍시킬 수 있을 정도로 충분히 길어야 한다. 프라이머의 적합한 길이는 다수의 요소, 예컨대, 온도, 응용분야 및 프라이머의 소스(source)에 따라 결정되지만 전형적으로 15-30 뉴클레오타이드이다. 짧은 프라이머 분자는 주형과 충분히 안정된 혼성 복합체를 형성하기 위하여 일반적으로 보다 낮은 온도를 요구한다. 용어 "어닐링" 또는 "프라이밍"은 주형 핵산에 올리고디옥시뉴클레오타이드 또는 핵산이 병치(apposition)되는 것을 의미하며, 상기 병치는 중합효소가 뉴클레오타이드를 중합시켜 주형 핵산 또는 그의 일부분에 상보적인 핵산 분자를 형성하게 한다.

[0037] 프라이머의 서열은 주형의 일부 서열과 완전하게 상보적인 서열을 가질 필요는 없으며, 주형과 혼성화 되어 프라이머 고유의 작용을 할 수 있는 범위 내에서의 충분한 상보성을 가지면 충분하다. 따라서 본 발명에서의 프라이머는 주형인 상술한 뉴클레오티드 서열에 완벽하게 상보적인 서열을 가질 필요는 없으며, 이 유전자 서열에 혼성화되어 프라이머 작용을 할 수 있는 범위 내에서 충분한 상보성을 가지면 충분하다. 이러한 프라이머의 디자인은 상술한 뉴클레오티드 서열을 참조하여 당업자에 의해 용이하게 실시할 수 있으며, 예컨대, 프라이머 디자인용 프로그램(예: PRIMER 3 프로그램)을 이용하여 할 수 있다.

[0038] 본 명세서에서, 용어 "핵산 분자"는 DNA(gDNA 및 cDNA) 그리고 RNA 분자를 포괄적으로 포함하는 의미를 가지며, 핵산 분자에서 기본 구성 단위인 뉴클레오타이드는 자연의 뉴클레오타이드뿐만 아니라, 당 또는 염기 부위가 변형된 유사체 (analogue)도 포함한다(Scheit, Nucleotide Analogs, John Wiley, New York(1980); Uhlman 및 Peyman, Chemical Reviews, 90:543-584(1990)).

[0039] 본 발명의 키트에서 출발물질이 gDNA인 경우, gDNA의 분리는 당업계에 공지된 통상의 방법에 따라 실시될 수 있다(참조: Rogers & Bendich (1994)).

[0040] 출발물질이 mRNA인 경우에는, 당업계에 공지된 통상의 방법에 총 RNA를 분리하여 실시된다(참조: Sambrook, J. et al., Molecular Cloning. A Laboratory Manual, 3rd ed. Cold Spring Harbor Press(2001); Tesniere, C. et al., Plant Mol. Biol. Rep., 9:242(1991); Ausubel, F.M. et al., Current Protocols in Molecular Biology, John Willey & Sons(1987); 및 Chomczynski, P. et al., Anal. Biochem. 162:156(1987)). 분리된 총 RNA는 역전사효소를 이용하여 cDNA로 합성된다. 상기 총 RNA는 인간(예컨대, 비만 또는 당뇨 환자)으로부터 분리된 것이기 때문에, mRNA의 말단에는 폴리-A 테일을 갖고 있으며, 이러한 서열 특성을 이용한 올리고 dT 프라이머 및 역전사 효소를 이용하여 cDNA을 용이하게 합성할 수 있다(참조: PNAS USA, 85:8998(1988); Libert F, et al., Science, 244:569(1989); 및 Sambrook, J. et al., Molecular Cloning. A Laboratory Manual, 3rd ed. Cold Spring Harbor Press(2001)).

[0041] 본 발명의 키트에 있어서, 상기 특정 서열을 규명하는 것은 당업계에 공지된 다양한 방법을 응용하여 실시될 수 있다. 예를 들어, 본 발명에 응용될 수 있는 기술은, 형광 인 시투 혼성화 (FISH), 직접적 DNA 서열결정, PFGE 분석, 서던 블롯 분석, 단일-가닥 컨퍼메이션 분석(SSCA, Orita et al., PNAS, USA 86:2776(1989)), RNase 보호 분석(Finkelstein et al., Genomics, 7:167(1990)), 닷트 블롯 분석, 변성 구배 젤 전기영동(DGGE, Wartell et al., Nucl.Acids Res., 18:2699(1990)), 뉴클레오타이드 미스매치를 인식하는 단백질(예: E. coli 의 mutS 단백질)을 이용하는 방법(Modrich, Ann. Rev. Genet., 25:229-253(1991)) 및 대립형-특이 PCR을 포함하나, 이에 한정되는 것은 아니다.

[0042] 다른 기술들은 일반적으로 본 발명의 뉴클레오타이드 서열에 상보적인 프로브 또는 프라이머를 이용한다.

[0043] 예를 들어, RNase 보호 분석에서, 본 발명의 뉴클레오타이드를 포함하는 서열에 상보적인 리보프로브가 이용된 다. 상기 리보프로브와 인간으로부터 분리한 DNA 또는 mRNA를 혼성화시키고, 이어 미스매치를 검출할 수 있는 RNase A 효소로 절단한다. 만일, 미스매치가 있어 RNase A가 인식을 한 경우에는, 보다 작은 밴드가 관찰된다.

[0044] 혼성화 시그널을 이용하는 분석에서, 본 발명의 뉴클레오타이드를 포함하는 서열에 상보적인 프로브가 이용된다. 이러한 기술에서, 프로브와 타깃 서열의 혼성화 시그널을 검출하여 직접적으로 질환의 위험도를 결정 한다.

[0045] 본 명세서에서, 용어 "프로브"는 특정 뉴클레오타이드 서열에 혼성화될 수 있는 디옥시리보뉴클레오타이드 및 리보뉴클레오타이드를 포함하는 자연 또는 변형되는 모노머 또는 결합을 갖는 선형의 올리고머를 의미한다.

[0046] 바람직하게는, 프로브는 혼성화에서의 최대 효율을 위하여 단일가닥이다. 프로브는 바람직하게는 디옥시리보뉴 클레오타이드이다.

[0047] 본 발명에 이용되는 프로브로서, 상기 뉴클레오타이드를 포함하는 서열에 완전하게(perfectly) 상보적인 서열이 이용될 수 있으나, 특이적 혼성화를 방해하지 않는 범위 내에서 실질적으로(substantially) 상보적인 서열이 이 용될 수도 있다. 바람직하게는, 본 발명에 이용되는 프로브는 본 발명의 뉴클레오타이드를 포함하는 서열에 혼 성화될 수 있는 서열을 포함한다. 보다 바람직하게는, 상기 프로브의 3'-말단 또는 5'-말단은 상기 뉴클레오 타이드에 상보적인 염기를 갖는다. 일반적으로, 혼성화에 의해 형성되는 듀플렉스(duplex)의 안정성은 말단의 서열의 일치에 의해 결정되는 경향이 있기 때문에, 3'-말단 또는 5'-말단에 상기 뉴클레오타이드 염기에 상보 적인 염기를 갖는 프로브에서 말단 부분이 혼성화되지 않으면, 이러한 듀플렉스는 엄격한 조건에서 해체될 수 있다.

[0048] 혼성화에 적합한 조건은 Joseph Sambrook, et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.(2001) 및 Haymes, B. D., et al., Nucleic Acid Hybridization, A Practical Approach, IRL Press, Washington, D.C. (1985)에 개시된 사항을 참조하여 결정할 수 있다. 혼성화에 이용되는 엄격한 조건(stringent condition)은 온도, 이온세기(완충액 농도) 및 유기 용매 와 같은 화합물의 존재 등을 조절하여 결정될 수 있다. 이러한 엄격한 조건은 혼성화되는 서열에 의존하여 다르 게 결정될 수 있다.

[0049] 본 발명의 보다 구체적인 구현예에 따르면, 상기 서열목록 제1서열 내지 제60서열로 구성된 군으로부터 선택되 는 뉴클레오타이드 서열은 성장호르몬 과다분비 조직에서 고발현되고, 상기 서열목록 제61서열 내지 제71서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열은 성장호르몬 과다분비 조직에서 저발현된다.

[0050] 본 발명의 보다 구체적인 구현예에 따르면, 상기 뉴클레오타이드 서열은 서열목록 제3서열, 제10서열 내지 제12 서열, 제24서열, 제25서열, 제27서열, 제38서열, 제42서열 및 제44서열로 구성된 군으로부터 선택된다.

[0051] 본 발명의 구체적인 구현예에 따르면, 본 발명에 의해 진단될 수 있는 성장호르몬 과다분비 질환은 성장호르몬 분비성 뇌하수체 종양 또는 말단 비대증이다.

[0052] 본 발명에서 용어 "분비성 뇌하수체 종양"은 내분비 기관인 뇌하수체(Pituitary gland)에서 한 가지 이상의 호 르몬을 과다하게 분비하는 종양을 의미한다. 따라서, 본 명세서에서 용어 "분비성 뇌하수체 종양"은 "기능성 뇌하수체 종양(functioning pituitary adenoma)"과 동일한 의미로 사용된다.

[0053] 본 발명에서 용어 "성장호르몬 분비성 뇌하수체 종양"은 분비성(기능성) 뇌하수체 종양 중 성장 호르몬을 과다 하게 분비하는 종양을 의미한다.

[0054] 본 발명에서 용어 "말단 비대증(acromegaly)"은 뇌하수체에서 과량의 성장호르몬이 생산, 분비되어 손, 발 또 는 얼굴 등의 신체의 말단이 과도한 성장에 의하여 비대해지는 증상을 말한다. 말단 비대증은 신체 말단의 비 대 뿐 아니라 과다발한, 다모증, 두통, 기억력감퇴, 체중증가, 관절병증, 고혈압, 불임, 유루증, 심장비대, 당 뇨병 및 지각이상 등의 증상을 보이기도 한다. 본 발명의 동물모델은 성장자극세포(somatotroph) 특이적으로 Aip 유전자의 특정 엑손이 결실됨으로 인해 과량의 성장호르몬을 분비하는 것을 그 특징으로 하므로, 뇌하수체 종양에 의한 과량의 성장호르몬 분비를 주 원인으로 하는 말단 비대증의 특이적인 유전자 발현 프로파일을 반영 한다.

[0055] 본 발명의 또 다른 구현예에 따르면, 본 발명은 다음의 단계를 포함하는 성장호르몬 과다분비 질환의 예방 또는 치료용 물질의 스크리닝 방법을 제공한다:

[0056] (a) 서열목록 제1서열 내지 제71서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열을 포함하는 세포에 분석하고자 하는 시료를 접촉시키는 단계; 및

[0057] (b) 상기 뉴클레오타이드 서열의 발현량을 측정하는 단계, 상기 뉴클레오타이드 서열 중에서 서열목록 제1서열 내지 제60서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열의 발현이 억제되거나 또는 서열목록 제61서열 내지 제71서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열의 발현이 증가되는 경우에는 상기 시료는 성장호르몬 과다분비 질환의 예방 또는 치료용 물질로 판정된다.

[0058] 본 발명의 방법에 따르면, 우선 본 발명의 뉴클레오타이드 서열을 포함하는 세포에 분석하고자 하는 시료를 접촉시킨다. 바람직하게는, 본 발명의 뉴클레오타이드 서열을 포함하는 상기 세포는 뇌하수체 조직 내 세포이며, 보다 바람직하게는 성장자극세포(somatotroph)이다. 본 발명의 스크리닝 방법을 언급하면서 사용되는 용어 "시료"는 본 발명의 뉴클레오타이드 서열의 발현량에 영향을 미치는지 여부를 검사하기 위하여 스크리닝에서 이용되는 미지의 물질을 의미한다. 상기 시료는 화학 물질, 뉴클레오타이드, 안티센스-RNA, siRNA(small interferenceRNA) 및 천연물 추출물을 포함하나, 이에 한정되는 것은 아니다. 이어, 시료가 처리된 세포에서 본 발명의 뉴클레오티드 서열의 발현량을 측정한다. 발현량의 측정은 상기 기재한 바와 같으며, 측정 결과, 서열목록 제1서열 내지 제60서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열의 발현이 억제되거나 또는 서열목록 제61서열 내지 제71서열로 구성된 군으로부터 선택되는 뉴클레오타이드 서열의 발현이 증가되는 경우에는 상기 시료는 성장호르몬 과다분비 질환의 치료제 조성물로 판정될수 있다.

[0059] 본 발명의 구체적인 구현예에 따르면, 상기 성장호르몬 과다분비 질환은 성장호르몬 분비성 뇌하수체 종양 또는 말단비대증이다.

발명의 효과

[0060] 본 발명의 특징 및 이점을 요약하면 다음과 같다:

[0061] (a) 본 발명은 성장호르몬 과다분비 질환 진단 키트 및 성장호르몬 과다분비 질환의 예방 또는 치료용 물질의 스크리닝 방법을 제공한다.

[0062] (b) 본 발명은 유전자 또는 단백질 마커를 사용함으로써 성장호르몬 분비성 뇌하수체 종양 및 말단비대증을 비롯한 성장호르몬 과다분비 질환의 신뢰도 있는 조기진단 또는 발병 위험성 예측에 유용하게 이용될 수 있다.

도면의 간단한 설명

[0063] 도 1은 sAIPKO(somatotroph specific aryl hydrocarbon receptor interacting protein knock out mouse) 제작을 위한 Lox-Cre 시스템에 사용될 AIP floxed 벡터의 모식도를 보여주는 그림이다. 마우스 Aip 유전자에 존재하는 7개의 엑손 중에서 5번, 6번 및 7번 엑손에 flox를 삽입한 AIP floxed 모델을 제작하였다.

도 2a는 Lox-Cre 시스템을 이용하여 본 발명의 동물 모델을 제작하는 과정을 도식화한 그림이다. Aip 유전자의 5, 6, 7번 엑손의 양 끝에 flox를 삽입한 floxed 모델을 제작한 후 GH Cre-마우스와 교배함으로써 GH(성장호르몬)를 분비하는 성장자극세포에 특이적으로 Aip 유전자의 5, 6, 7번 엑손이 녹-아웃된 sAIPKO 동물 모델을 수득하였다. 도 2b는 sAIPKO 마우스에서 종양이 발생하고, 정상 마우스에 비하여 뇌하수체 크기가 증가한 (Hyperplasia) 결과를 보여주는 그림이다. 도 2c는 정상 수컷 마우스, sAIPKO 수컷 마우스, 정상 암컷 마우스 및 sAIPKO 수컷 마우스 각각의 뇌하수체의 크기 증가를 정량화하여 각 주령마다 분석한 결과를 보여준다.

도 3a는 레티쿨린(reticulin) 특수 염색을 통해 sAIPKO 동물 모델에서 뇌하수체가 과대해지고 종양이 발생함을 보여주는 그림이다. 도 3b는 각 선포(acinar) 단위당 세포 수 및 면적의 측정을 통해 레티쿨린 염색결과를 정량화한 결과를 보여준다. 선포(acinar) 단위당 세포 수 및 면적은 증가한 반면 단위 면적당 세포 수는 같으므로 비대화(Hypertrophy)가 아닌 과증식(Hyperplasia)임을 알 수 있다. 도 3b는 레티쿨린 염색 결과를 정량화한 결과를 나타내는 그래프로서, 각 선포(acinar) 단위당 세포 수 및 면적이 증가하였으나, 단위 면적당 세포 수는 같으므로 Hypertrophy가 아닌 Hyperplasia임을 알 수 있다. 도 3c는 종양 발생율을 분석한 결과를 나타

낸 그림으로, 24주령부터 종양이 발생하여 30주령부터는 약 90% 이상에서 종양이 발생하는 것을 확인할 수 있다.

도 4a는 H & E 염색을 통해 호산성 세포집단으로 구성된 종양이 발생함을 확인한 결과를 나타낸 그림이다. 도 4b는 면역염색을 통해 발생된 종양이 뇌하수체에서 분비되는 호르몬들 중 성장호르몬에만 양성 반응을 보이는 종양임을 보여주는 그림이다. 도 4c는 혈청학적 검사를 통해 성장호르몬의 분비가 18주령부터 증가된 상태임을 보여주는 그림이다.

도 5는 9.4 T MRI를 수행하여 살아있는 상태에서도 종양이 발생함을 확인한 결과이다. sAIPKO 동물모델에서 뇌하수체의 크기 증가 및 종양 발생이 MRI로도 확인되었다.

도 6a는 sAIPKO 동물 모델이 성장호르몬 과분비에 의해 개체의 크기가 증가하였음을 육안 소견으로 확인한 결과이다. sAIPKO 동물 모델은 체중(도 6b) 및 정둔장 길이(crown-rump length)(도 6c)도 증가하였다.

도 7은 성장 호르몬 과분비에 의한 당뇨병 발병을 확인한 결과를 보여주는 그림이다. 도 7a는 무작위적인 혈당 변화를 관찰한 결과이며, 도 7b는 인슐린을 Kg 당 0.1 U를 복강주사한 후 2시간에 걸쳐 혈당을 측정한 결과로서, sAIPKO 동물 모델에서 동일한 인슐린에도 혈당 감소 효과가 떨어져 있음을 확인할 수 있다. 도 7c는 상기 도 7b의 실험에서 초기 15분 동안 감소한 혈당 정도를 결과이며, 도 7d는 상기 도 7b의 실험에서 2시간에 걸친 혈당 변화 정도의 AUC 값을 비교한 결과이다.

도 8a는 지놈 DNA를 $Af12$로 절단 후 5'^{32}P-표지를 이용하여 서던 블롯팅을 수행한 결과를 나타낸 그림이다. 대조군(wild type)은 16.2kb에서, 타겟 대립 유전자는 6.5 kb에서 밴드가 확인되었다. 도 8b는 $Aip^{lox/lox}$마우스의 지노타입 PCR을 시행한 아가로스 젤 전기영동 결과를 나타낸 그림이다. 2, 3, 4번째 레인은 각각 대조군(wild type; $Aip^{+/+}$마우스), 이형접합체($Aip^{lox/+}$마우스), 그리고 동형접합체($Aip^{lox/lox}$마우스)를 의미한다.

도 9는 sAIPKO 동물 모델 뇌하수체 종양을 각각 p27, CDK(Cyclin dependent kinase) 4, 에스트로겐 수용체 (ER)-α(도 9a)로 염색한 면역 형광 염색 결과를 나타낸 그림이다. p27의 경우 대조군 마우스의 뇌하수체에서는 주로 핵에서 발현함을 확인할 수 있으며, 과증식 단계의 sAIPKO 동물에서는 세포질에서 주로 발현하고, 종양 단계에서는 핵과 세포질 모두에서 발현이 소실됨을 확인할 수 있다. CDK4의 경우 대조군 마우스의 뇌하수체에서는 핵과 세포질 모두 고르게 분포하고 있음을 확인할 수 있으며 과증식 단계의 sAIPKO 동물에서는 전반적인 발현양이 증가하고, 종양 단계에서는 핵막 주위에서만 발현함을 확인할 수 있다. ER-α의 경우 대조군 마우스와 비교해서 sAIPKO 마우스의 과증식 단계와 종양 단계 모두에서 발현이 증가함을 확인할 수 있다.

도 10은 각각 GH3 세포에 AIP siRNA 100 nM를 48시간 처리한 뒤 AIP 발현량을 PCR을 통해 확인한 결과(도 10a) 및 이에 따른 p27, CDK4 및 ER-α유전자 발현 변화를 실시간 PCR을 통해 확인한 결과(도 10b)를 보여주는 그림이다.

발명을 실시하기 위한 구체적인 내용

[0064] 이하, 실시예를 통하여 본 발명을 더욱 상세히 설명하고자 한다. 이들 실시예는 오로지 본 발명을 보다 구체적으로 설명하기 위한 것으로, 본 발명의 요지에 따라 본 발명의 범위가 이들 실시예에 의해 제한되지 않는다는 것은 당업계에서 통상의 지식을 가진 자에 있어서 자명할 것이다.

[0065] **실시예**

[0066] **실험 방법**

[0067] $Aip^{loxp/loxp}$ 마우스의 제작

[0068] 배아줄기세포에서 상동 재조합으로 마우스 Aip 좌위를 타겟팅하기 위하여, 197-kb 박테리아 인공 염색체(RPCI-23, invitrogen)로부터 C57BL/6 마우스Aip 유전자를 분리하였다. 상기 염색체를 $Af12$로 절단하고, Aip의 3-7번 엑손 및 3' UTR을 포함하는 서브클론을 동정하였다.

[0069] 3-7번 엑손을 포함하는 지놈 절편을 분리하여 Frt-플랭킹된 역방향 PGK (phosphoglycerate kinase)-네오마이신

카세트의 업스트림과 pVBFRTCK01 (VegaBiolab, USA) 내에 존재하는 말단 loxP 사이트를 클로닝하였다. 두 번째 loxP 사이트를 4번 인트론에 삽입하였다. 3'UTR을 포함하는 5.0-kb 절편을 3-7번 엑손을 이미 포함하는 플라스미드 내 티미딘 카이네이즈 저항성 카세트의 업스트림 위치에 클로닝하여 타게팅 컨스트럭트 pVBFRTCK-AIP를 제작하였다. 양쪽 상동성 암(homologous arm)의 방향을 나타내기 위하여 제한효소 절단 분석을 수행하였다. 엑손 및 타게팅 벡터(loxP, Frt, Neo)의 중요 인자를 시퀀싱하였다. pVBFRTCK-AIP를 C57BL/6 마우스 배아줄기세포 내로 전기영동하여 정확하게 타게팅된 클론들을 서던 블롯팅을 통해 동정하였다. 배아줄기세포 지놈 DNA를 *Af12*로 절단하고 6.5-kb 타겟 및 16.2-kb 야생형 밴드를 나타내기 위한 프로브 1 또는 12.1-kb 타겟 및 16.2-kb 야생형 밴드를 나타내기 위한 프로브 2로 표지하였다. 정확하게 타게팅된 클론들을 알비노 C57BL/6J 배반포에 주입하여 키메라를 생성시켰다. 수컷 키메라들은 인간 ACTB 프로모터(B6;Cg-Tg(ACTFLPe)9205Dym/J, Jackson labs) 하에서 FLP1 재조합 효소 유전자를 발현하는 반접합체 암컷 마우스와 교배하여 PGK-네오마이신 카세트를 제거함과 동시에 생식계열 돌연변이를 수득하였다. 네오마이신 카세트의 제거는 남은 하나의 loxP 사이트 인접 프라이머를 이용한 PCR을 통해 확인하였다. 수득한 자손에 대해 트랜스 *FLP1* 유전자의 존재여부를 PCR을 통해 스크리닝하였다. 트랜스 유전자를 가지는 생식계열 돌연변이는 $Flp^{tg/+}; Aip^{lox/+}$로 표시하였다. *Af12*로 절단하고 5'^{32}P-표지된올리고뉴클레오타이드로 프로브한 테일 DNA의 서던 블롯팅을 수행하여 생식계열 전달이 이루어졌는지를 확인하고자 하였다(도 8a). $Flp^{tg/+}; Aip^{lox/+}$ 마우스의 교차교배를 수행하여 $Aip^{lox/lox}$ 마우스를 수득하였다. 이들 마우스의 유전적 배경은 C57BL/6J이다. 교배를 통해 *FLP1* 트랜스 유전자를 가지는 동물들은 이후의 교배에 사용되었다.

[0070]

[0071] $rGHp-Cre^{tg/+}; Aip^{lox/lox}$ 마우스의 제작

[0072] 뇌하수체 성장자극세포에서 Cre-재조합 효소를 발현하는 마우스는 Luque 등 (Luque RM 148 2007)에 의해 개발된 바 있다. 이들 마우스에서, 랫트 GH 유전자(r*GHp*)의 개시코던 310 bp 5'이 뇌하수체 성장자극세포 타게팅에 사용되었고, 수득한 트랜스 유전자는 발현 시 뇌하수체 전엽에서 성장자극세포에 의해 유도된 세포의 loxP-변형 대립인자의 선택적 Cre-매개 재조합이 가능하게 하였다. $rGHp-Cre^{tg/+}$ 암컷 마우스와 수컷 $Aip^{lox/lox}$ 마우스를 교배함으로써 $GHp-Cre^{tg/+}; Aip^{lox/+}$ 마우스를 수득하였다. $rGHp-Cre^{tg/+}; Aip^{lox/+}$ 마우스의 교차 교배를 통해 $rGHp-Cre^{tg/+}; Aip^{lox/lox}$ 성장자극세포 내 *Aip* 유전자의 동형 붕괴(homozygous disruption)를 유도하였다.

[0073]

[0074] *sAIPKO 동물 모델 뇌하수체 종양의 면역 형광 염색*

[0075] 대조군에 비해 뇌하수체의 과증식(hyperplasia)이 생긴 sAIPKO 동물 모델에서는 p27 발현양이 증가하고 종양이 생긴 sAIPKO 동물 모델에서는 p27 발현이 사라짐을 확인할 수 있었다. CDK4 의 경우 과증식에서 발현양이 증가하며 종양이 생긴 뇌하수체에서는 핵주위(perinuclear)에 분포함을 확인하였다(도 9a).

[0076]

[0077] *sAIPKO 동물 모델의 RNA 시퀀싱 분석*

[0078] 대조군 마우스의 정상 뇌하수체와 sAIPKO 마우스의 과증식(hyperplasia) 뇌하수체, sAIPKO 마우스의 뇌하수체 종양을 RNA 시퀀싱을 시행하였다.

[0079] 30주령의 대조군 마우스로부터 뇌하수체 조직을 절개하였으며, 과증식성 또는 선종성 sAIPKO 마우스(18주령)를 이용하여 RNA 시퀀싱을 수행하였다. 마우스를 희생시키기 전에 MRI 촬영을 하여 확장되거나 선종화된 뇌하수체 종양의 형태 변화를 확인하였다. RNA 라이브러리를 구축하기 위하여, 양질의 무-DNA RNA에 대한 poly A 분별을 NEBNext Poly(A) mRNA Magnetic Isolation Module (NEB, USA) 및 표준 키트 프로토콜을 이용하여 수행하였다. 다음으로, NEBNext Ultra RNA library Prep Kit(NEB, USA)을 이용하여 cDNA 라이브러리를 구축하였다. 요약하면, 미리 정제한 mRNA로부터 절편화 및 무작위 프라이밍을 하고 제 1 및 제 2 스트랜드를 제작하였다. 이후 젤 전기영동으로 원하는 길이를 선택하여 정제된 산물의 말단 평활화(end-repair)하고, dA 꼬리를 붙인 후 어답터 라이게이션을 하였다. 라이브러리 강화를 위해 각 조건에 따른 PCR 증폭을 수행하였다. 최종 라이브러리의 특성은 Agilnet 220 TapeStation System(Santa Clara, CA)을 이용하여 분석하였다. Illumina Hiseq 2500 시스템 상에서 150bp 길이에 대한 페어드 엔드(paired-end) 시퀀싱을 수행하였다. 샘플 당 평균 3천2백

만(2천2백9십만-사천백팔십만) 염기쌍이 기록되었다. 시퀸싱된 리드(read)는 Tophat v2.0.10(45)를 통해 mm10 표준 유전자로 매핑하였다. Cufflinks v2.1.1을 이용하여 Ensemble 유전자 모델(17)의 전사체의 양을 계산하였다. 시차 분석(differential analysis)에서 분산 방법을 위한 블라인드 옵션(blind option)을 이용하였다. 유전자 수준에서 3개 그룹(대조군, 과증식군 및 종양군) 간의 발현 차이를 계산하기 위하여 CuffDiff v2.1.1를 사용하였다. 발현의 차이는 DESeq를 이용하여 라이브러리 표준화 및 분산 평가를 위한 built-in 과정을 적용함으로써 정량화하였다. 수치를 도출하기 위해 R 패키지 CummerBund (http://compbio.mit.edu/cummeRbund/)를 사용하였다. p-값을 계산하기 위하여, 시험은 베타 음이항식에 의한 명확한 샘플링에 기초하여 수행하였다. 다중 검정에 대한 Benjamini-Hochberg 정정을 통해 P 값을 정정하였다. 대조군과 비교하여 hyperplastic 또는 선종성 조직에서 2배 이상 증가한 유전자를 GePS 소프트웨어(Genomatix Software GmbH, Munich, Germany)를 이용하여 추가 분석하였다. 통계학적으로 유의한 결과를 보이는 유전자 목록은 하기의 표 1 및 2에 표시하였다.

표 1

[0080]　　　　　　　　　　　　정상→ 과증식 →종양으로 진행함에 따라 발현량이 2배 이상 증가하는 유전자

서열목록	유전자	대조군	과증식군	종양군
1	1810058N05Rik	2.49387	5.11082	12.58991496
2	4833413E03Rik	0.273062	1.2243	2.629417576
3	C3	1.8098	4.27441	18.28382773
4	Cabp1	9.5042	21.1309	62.5604137
5	Cartpt	1.76774	10.4303	40.02459476
6	Capn8	0.475871	3.89767	9.543572849
7	Cd79b	7.22857	16.7396	35.55119176
8	Col7a1	1.92588	6.51727	14.81489262
9	Cox6a2	0.533894	2.28334	6.280508339
10	Cpn1	0.0728919	1.59435	4.151554406
11	Crisp1	1.31883	17.718	73.26060189
12	Crisp3	0.218853	3.08955	58.47775734
13	Crlf1	7.18144	15.2944	55.39240924
14	Cryba4	2.39915	9.89661	38.57495008
15	Dlk1	1906.76	3950.38	10364.15225
16	Ggt1	0.562932	1.27439	2.863913085
17	Gm13594	0.656811	1.52996	5.164833918
18	H2afj	32.6205	81.3335	184.2077179
19	Hdc	9.93572	22.0138	57.0624877
20	Hist1h3f	1.36389	3.56722	7.46807716
21	Hs3st2	0.278224	2.32327	5.325484711
22	Hist1h4i	16.0181	23.9918	63.54739876
23	Mettl11b	0.658858	1.82537	4.15865575
24	Mgarp	0.794196	3.55217	19.32790376
25	Mmp7	1.04427	7.10807	54.91156311
26	Nrgn	1.54992	4.32832	9.833150054
27	Penk	6.70186	23.3162	223.8297033
28	Plac8	1.83277	4.05404	9.62993167
29	Ptprcap	0.450322	1.00752	2.535654677
30	Ramp3	5.35206	25.3214	59.8197297
31	Reep6	2.27718	5.95894	16.54712224
32	Rhof	3.26705	8.39749	18.63127037
33	Sdcbp2	0.850964	2.00619	6.093804839
34	Slc10a4	5.88834	12.0629	26.76440068
35	Tmem210	0.86568	1.94984	6.49950524
36	Thbs2	0.977242	2.11167	5.360591335
37	Ube2c	0.677518	1.87271	5.180030413
38	Vgf	3.80182	40.5008	103.3534079
39	Abhd14a	5.90694	5.49752	38.35833863

40	Bpifa1	8.02376	10.5471	62.06709277
41	Col5a3	0.841769	0.97466	5.416871308
42	Dnmt3l	0	4.17241	4.94149
43	Fos	42.9132	22.0428	111.632364
44	Hcn1	0	1.17561	1.24653
45	Kcnk10	2.58906	16.3064	15.14262092
46	Nr4a1	27.4494	121.545	65.76905924
47	Rtp1	1.19137	9.13635	4.876349522
48	Wfdc2	30.6351	35.7095	145.065098
49	Fut2	5.76917	17.4742	14.23637451
50	Id3	24.6203	14.8559	79.24854895
51	Rpl29	52.3623	87.6911	973.6255084
52	Wnt10a	16.9565	49.4568	92.85260498
53	1600012P17Rik, Pappa2	10.2091	30.8621	24.73478318
54	Arhgap36	12.0484	51.25	31.10359143
55	Cebpd	36.7606	93.5054	133.1650947
56	Csn3	0	1.45159	4.90401
57	Fcrlb	0	0	4.81864
58	Hapln4	3.38126	15.064	14.55748671
59	Nell2	12.5469	57.7029	108.2923721
60	Slc1a7	2.6652	22.3205	12.13741832

표 2

[0081] 정상→ 과증식 →종양으로 진행함에 따라 발현량이 2배 이상 감소하는 유전자

서열목록	유전자	대조군	과증식군	종양군
61	Acss3	3.53855	1.74047	0.472298882
62	Baz1a, Gm20403	2.99613	1.37372	0.310004064
63	Col4a3	4.39024	1.66309	0.69130517
64	Fam169a	5.12822	2.4207	0.583498107
65	Gabrb2	3.08555	1.4606	0.743718564
66	Gnrhr	43.2932	20.9549	8.137691461
67	Osbpl3	6.53092	2.56618	1.04744784
68	Pla2r1	4.1749	2.0495	0.801380054
69	Slc1a3	10.4346	4.46148	1.963638944
70	Uty	8.42335	7.50991	1.566563007
71	Agtr1a	39.7627	13.5824	14.17180717

[0082] *RNA 시퀀싱 결과의 확인*

[0083] 인 비트로에서 AIP 넉 다운에 의한 효과 확인을 위해 siRNA 형질전환 실험을 진행하였으며, AIP에 대한 siRNA는 Thermo Fisher Scientific Bioscience Inc, Lafayette, CO에서 구입하였다(282827).

[0084] GH3 세포에 100 nM 48시간 처리하여 AIP가 감소하는 것을 웨스턴 블롯팅과 PCR을 통해 확인하였으며(도 10a), GH3 세포에서 AIP가 감소함에 따라 p27, CDK4 및 ER-α 유전자 발현 변화가 과증식 및 종양 발생의 경우와 같은 양상을 보임을 실시간 PCR을 통해 확인하였다(도 10b).

[0085] 이상으로 본 발명의 특정한 부분을 상세히 기술하였는 바, 당업계의 통상의 지식을 가진 자에게 있어서 이러한 구체적인 기술은 단지 바람직한 구현예일 뿐이며, 이에 본 발명의 범위가 제한되는 것이 아닌 점은 명백하다. 따라서, 본 발명의 실질적인 범위는 첨부된 청구항과 그의 등가물에 의하여 정의된다고 할 것이다.

도면

도면1
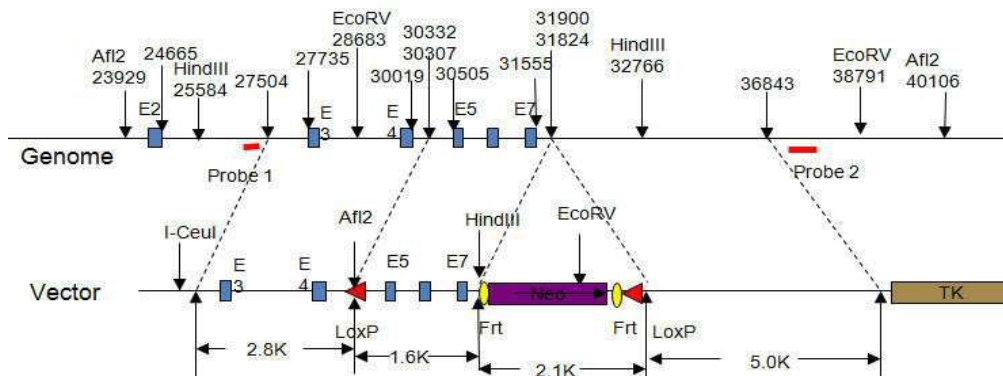
도면2a
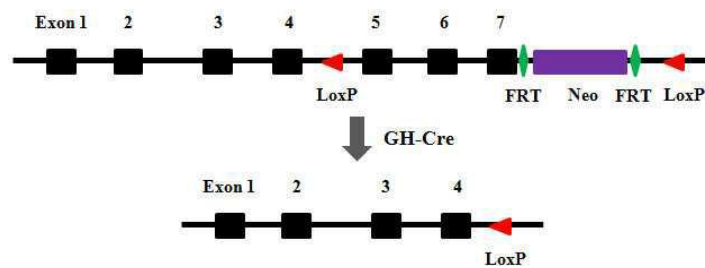
도면2b
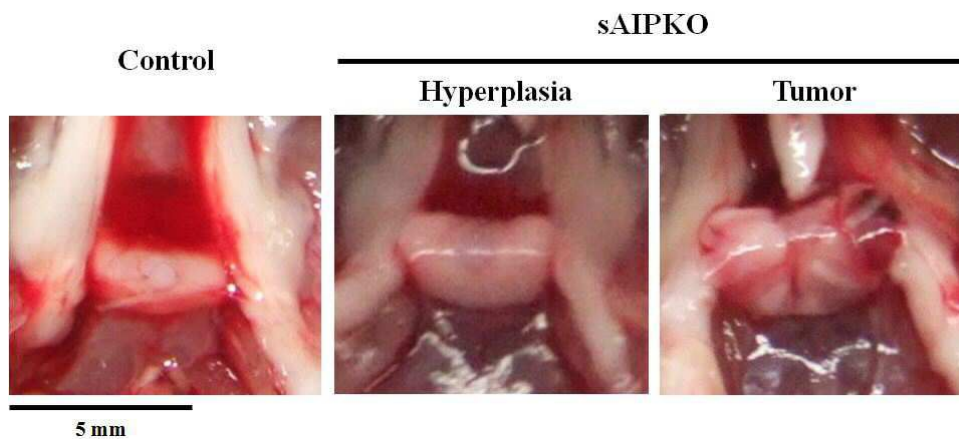
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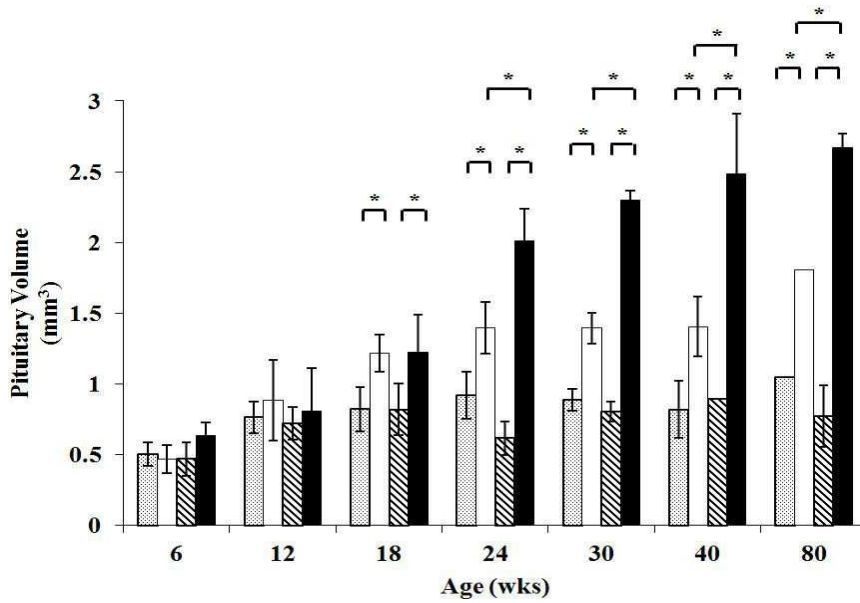
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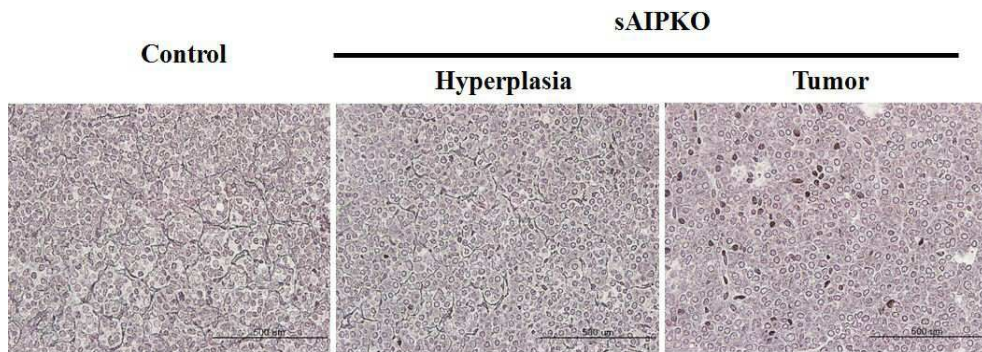
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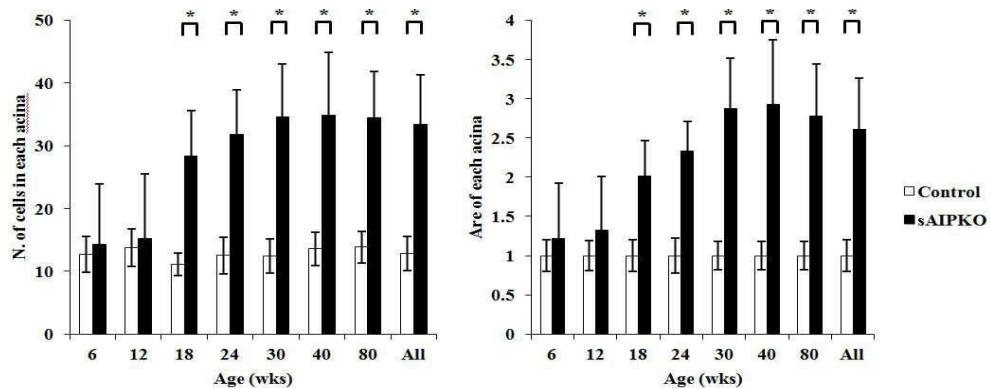
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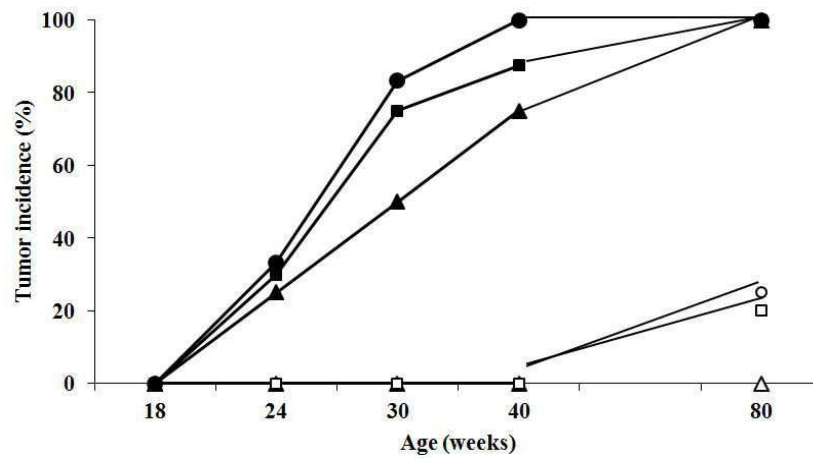
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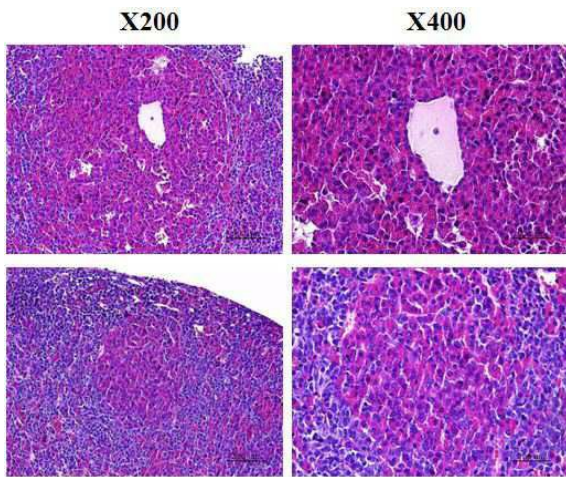
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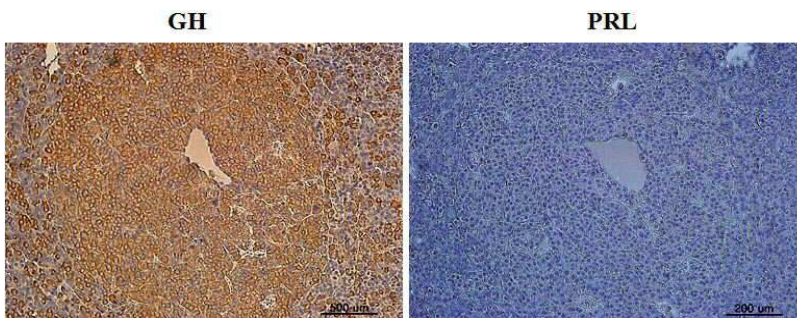
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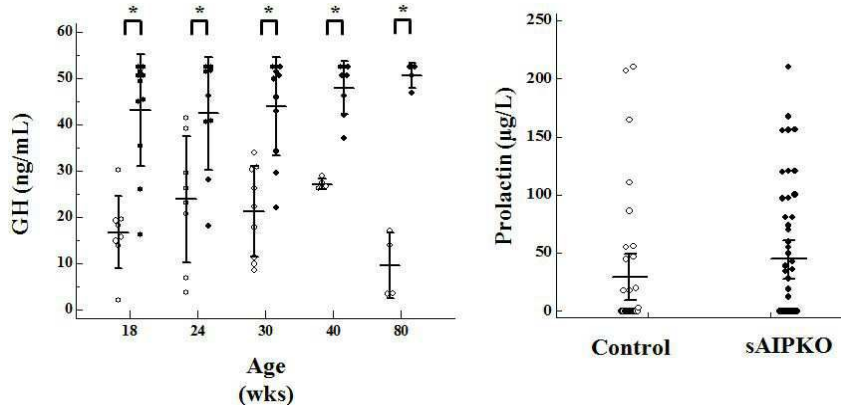
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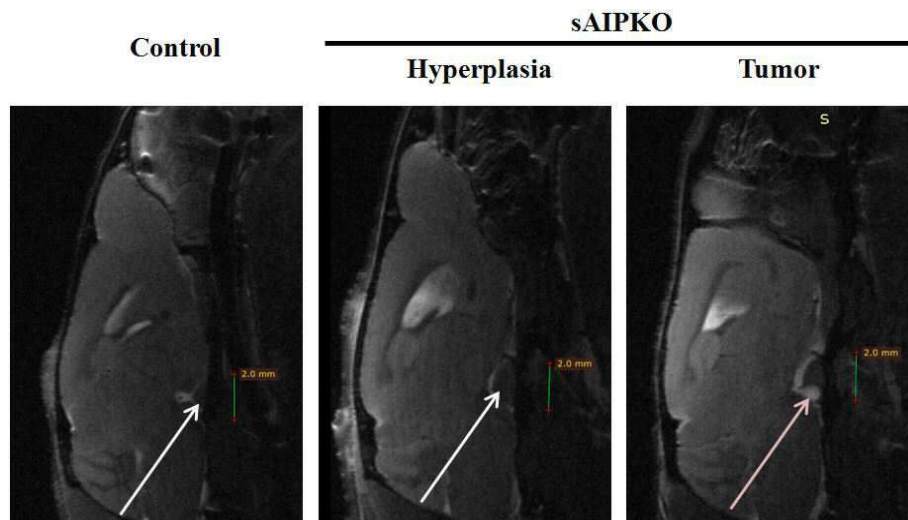
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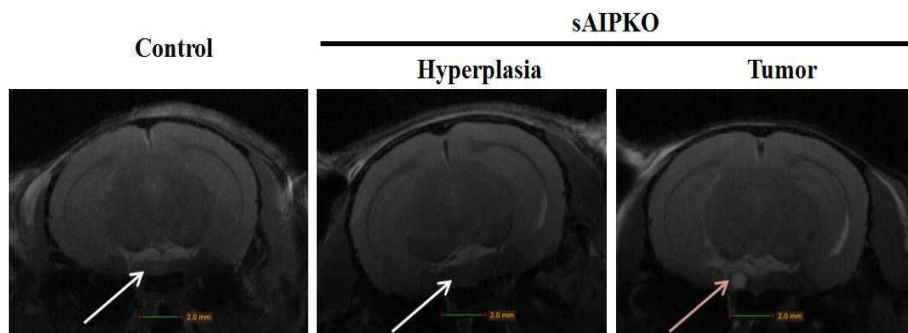
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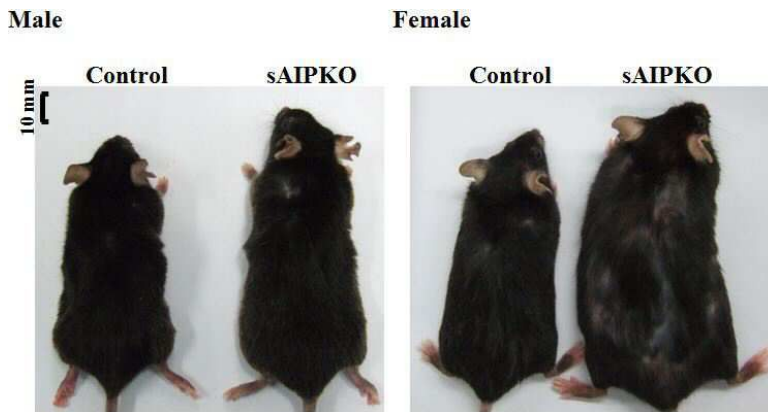
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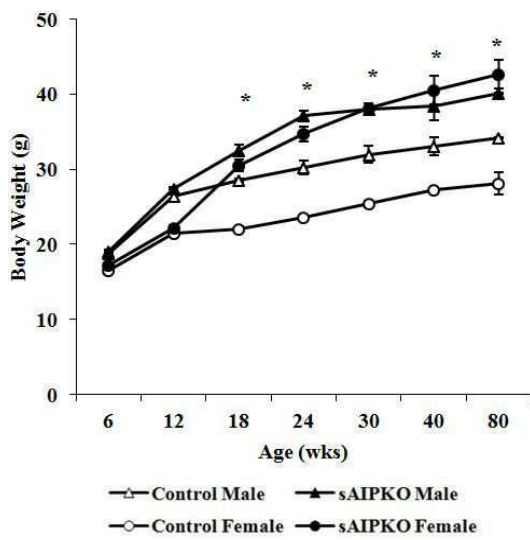
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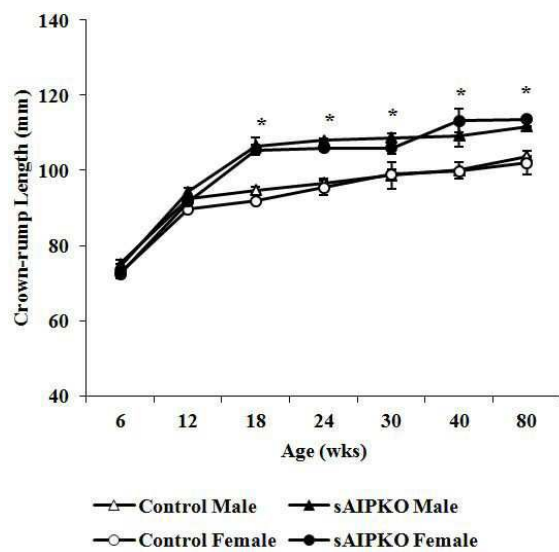
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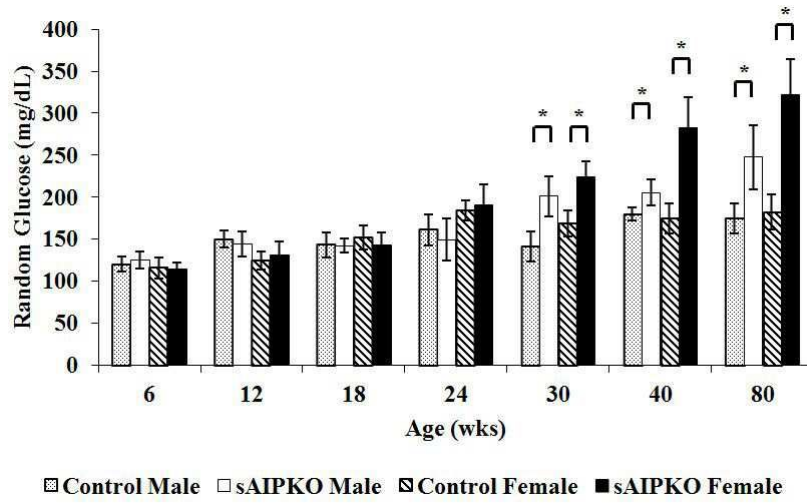
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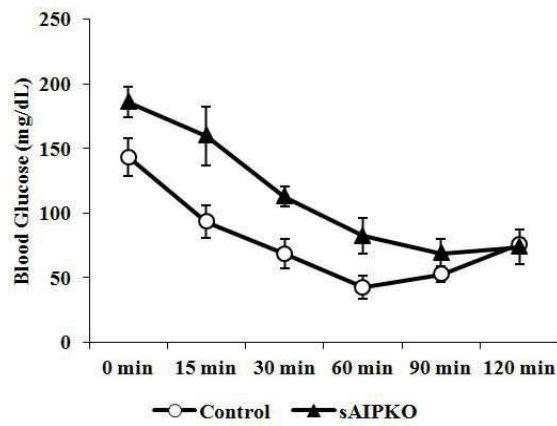
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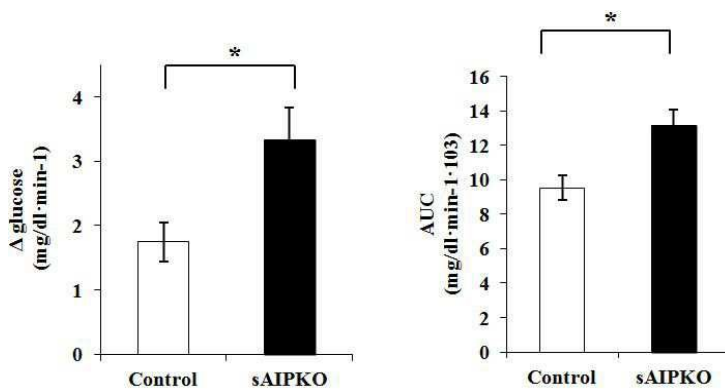
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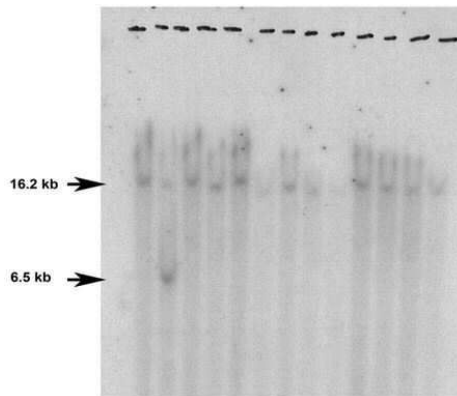
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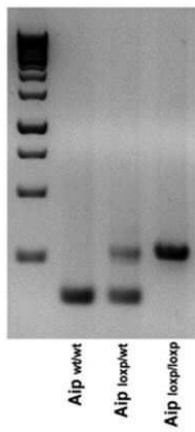
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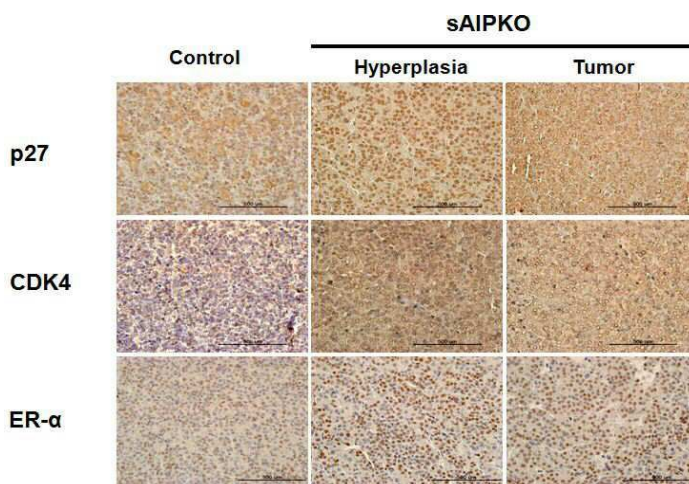
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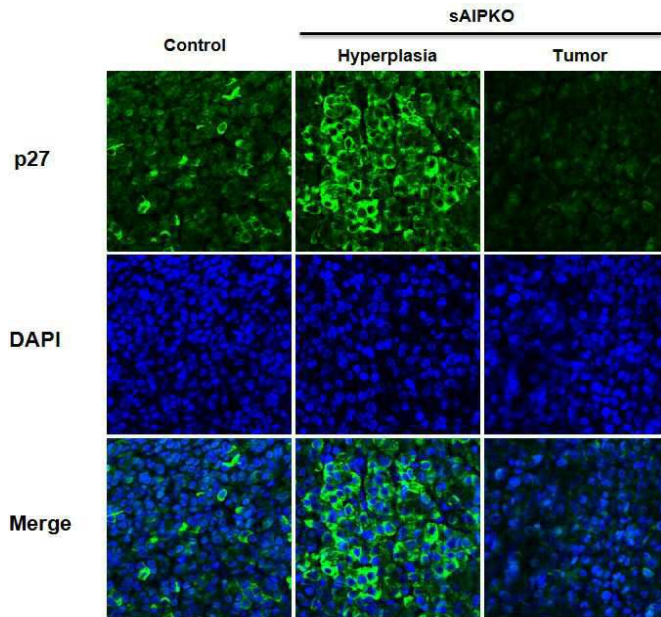
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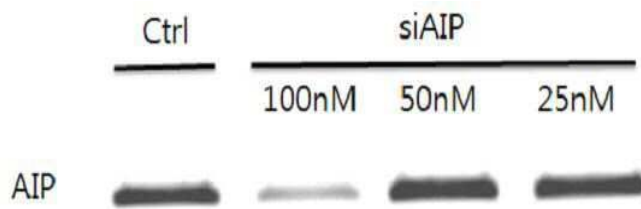
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tatagatttt aaaagtttta tttttttacat ctatggtagt ttttgaggtg cctattataa   6360

agtattacgg aagtttgctg tttttaaagt aaatgtcttt tagtgtgatt tattaagttg   6420

tagtcaccat agtgatagcc cataaataat tgctggaaaa ttgtatttta taacagtaga   6480

aaacatatag tcagtgaagt aaatatttta aaggaaacat tatatagatt tgataaatgt   6540

tgtttataat taagagtttc ttatggaaaa gagattcaga atgataacct ctttttagaga   6600

acaaataagt gacttatttt tttaaagcta gatgactttg aaatgctata ctgtcctgct   6660

tgtacaacat ggtttgggggt gaaggggagg aaagtattaa aaaatctata tcgctagtaa   6720

attgtaataa gttctattaa aacttgtatt tcatatgaaa aatttgctaa tttaatatta   6780

actcatttga taataatact tgtcttttct acctctc   6817

<210>   71

<211>   2284

<212>   DNA

<213>   Homo sapiens

<400>   71

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ggccggagag gactcgaggc ttgagtcctg gtccacgggt cgctggggtg ggtcgctggg   180

gtggctgaag ccagtaccag ctctgcggct ctcccagctc tgctgctctc ccggacttaa   240

catatgaaag attggtataa aatggctggc attttgtctg ataactcac agcaaccctc   300

caagaaagcc atcaccagat caagtgcatt ttgaacagtg tctgagacca actcaaccca   360

gaaaagcaaa atggccctta actcttctac tgaagatggc atcaaaagaa ttcaagatga   420

ctgccccagg gctggcaggc acagttacat atttgtcatg atccctactc tctacagcat   480

catctttgtg gtgggaatat ttggaaacag cttggtggtg atcgtcatct acttttacat   540

gaagctgaag actgtggcca gtgtctttct tctaaatctc gccctggctg acttatgctt   600

tttgctgact ttgcccctgt gggctgtcta taccgctatg gaataccgct ggcccttcgg   660

caatcaccta tgtaagatcg cttcggccag cgtcagtttc aacctctacg ccagcgtgtt   720

cctgctcacg tgtctcagca tcgatcgcta cctggccatt gtccacccga tgaagtctcg   780

cctccgccgc acgatgctgg tggccaaagt cacctgcatc atcatctggc tgatggctgg   840

cttggccagt ttgccagccg tcatccaccg aaatgtgtat ttcattgaga acaccaatat   900

cactgtttgc gctttttcatt acgagtcccg gaattcaacg ctccccatag gactgggcct   960

aaccaagaac atcctgggct tcctgttccc tttcctaatc attcttacca gctatactct   1020

tatatggaaa gctctaaaga aggcttatga aattcagaag aacaagccaa gaaatgatga   1080

catctttagg ataattatgg cgattgtgct tttcttcttc ttctcctggg tcccccacca   1140

aatattcaca ttcctggatg tgctgattca gctgggcgtc atccatgact gtaaaattgc   1200

cgacatcgtg gacactgcca tgcccataac catctgcata gcgtatttta acaactgcct   1260

gaaccctctg ttttacggct ttctggggaa aaaatttaaa aagtatttcc tccagctcct   1320

gaaatatatt cccccaaagg ccaagtcgca ctcaagcctg tctacgaaaa tgagcacgct   1380

ctcctaccgc ccctcagata acatgagctc agccgccaaa aagcctgcgt cttgttctga   1440

ggtggagtga caggttcaaa gcttgctggc aatgtaatgc cctgacagaa accagggcag   1500

catcggacta aatggctcac gaccaaagga ccagtccccc ccccccctc aggatctaag   1560

cagaaaatgc gttcaacaga ctgtagatat tgtctgaagc tctgagagaa agctttgaag   1620

aagtaattat gcaaagctgt cttacattaa tagatgatgg ctgccccaag gacaagtcag   1680

gagctggatg gatttgtggg tttaaaacgg tttgctggca gacacgcaat cgcagcggtc   1740

tcctttttgat ttccacacat aggtatgtag catgtgctaa atatttagac aagaaacaag   1800

aaatggaagt cgaggttact tgttctgctc agttccccaa gggcaaggaa ccttgtttgt   1860

cccttttagtc attagcaatg gagacccacg tgtccctgtt actacacata ctttgaaaag   1920

atctgctaac ctggagtcat caagtttcag gagcccttttg taaaattcag ccagtgtctt   1980

agaaacctgt actgtcccca aacaatgcca gttagtggtg tatttatgta gcagtgtaag   2040

caaagttaca catcaaagtt gcactgcttg taccaaccgt gacatagtag gtatatcagc   2100

tttagttcac atctgagaaa cataaacagt cggtggtgaa tagactacat atcatacaat   2160

ctgccttgtt ctctaaaagt atatatcctc cacatatatg tacatatgta tctctaagct   2220

gtcatttgat gaagtttttgg caatgtatgt ttacctctaa ataaagtaat tttattgtaa   2280

cgta   2284

<210>   72

<211>   681

<212>   PRT

<213>   Homo sapiens

<400>   72

Met Ile Glu Lys Met Gln Gly Ser Arg Met Asp Glu Gln Arg Cys Ser

1   5   10   15

Phe Pro Pro Pro Leu Lys Thr Glu Glu Asp Tyr Ile Pro Tyr Pro Ser

                20   25   30

Val His Glu Val Leu Gly Arg Glu Gly Pro Phe Pro Leu Ile Leu Leu

        35   40   45

Pro Gln Phe Gly Gly Tyr Trp Ile Glu Gly Thr Asn His Glu Ile Thr

        50   55   60

Ser Ile Pro Glu Thr Glu Pro Leu Gln Ser Pro Thr Thr Lys Val Lys

65   70   75   80

Leu Glu Cys Asn Pro Thr Ala Arg Ile Tyr Arg Lys His Phe Leu Gly

                85   90   95

Lys Glu His Phe Asn Tyr Tyr Ser Leu Asp Ala Ala Leu Gly His Leu

                100   105   110

Val Phe Ser Leu Lys Tyr Asp Val Ile Gly Asp Gln Glu His Leu Arg

        115   120   125

Leu Leu Leu Arg Thr Lys Cys Arg Thr Tyr His Asp Val Ile Pro Ile

        130   135   140

Ser Cys Leu Thr Glu Phe Pro Asn Val Val Gln Met Ala Lys Leu Val

145   150   155   160

Cys Glu Asp Val Asn Val Asp Arg Phe Tyr Pro Val Leu Tyr Pro Lys

                165   170   175

Ala Ser Arg Leu Ile Val Thr Phe Asp Glu His Val Ile Ser Asn Asn

                180   185   190

Phe Lys Phe Gly Val Ile Tyr Gln Lys Leu Gly Gln Thr Ser Glu Glu

        195   200   205

Glu Leu Phe Ser Thr Asn Glu Glu Ser Pro Ala Phe Val Glu Phe Leu

        210   215   220

Glu Phe Leu Gly Gln Lys Val Lys Leu Gln Asp Phe Lys Gly Phe Arg

225   230   235   240

Gly Gly Leu Asp Val Thr His Gly Gln Thr Gly Thr Glu Ser Val Tyr
           245   250   255

Cys Asn Phe Arg Asn Lys Glu Ile Met Phe His Val Ser Thr Lys Leu
        260   265   270

Pro Tyr Thr Glu Gly Asp Ala Gln Gln Leu Gln Arg Lys Arg His Ile
     275   280   285

Gly Asn Asp Ile Val Ala Val Val Phe Gln Asp Glu Asn Thr Pro Phe
   290   295   300

Val Pro Asp Met Ile Ala Ser Asn Phe Leu His Ala Tyr Val Val Val
305   310   315   320

Gln Ala Glu Gly Gly Gly Pro Asp Gly Pro Leu Tyr Lys Val Ser Val
           325   330   335

Thr Ala Arg Asp Asp Val Pro Phe Phe Gly Pro Pro Leu Pro Asp Pro
        340   345   350

Ala Val Phe Arg Lys Gly Pro Glu Phe Gln Glu Phe Leu Leu Thr Lys
        355   360   365

Leu Ile Asn Ala Glu Tyr Ala Cys Tyr Lys Ala Glu Lys Phe Ala Lys
        370   375   380

Leu Glu Glu Arg Thr Arg Ala Ala Leu Leu Glu Thr Leu Tyr Glu Glu
385   390   395   400

Leu His Ile His Ser Gln Ser Met Met Gly Leu Gly Gly Asp Glu Asp
        405   410   415

Lys Met Glu Asn Gly Ser Gly Gly Gly Gly Phe Phe Glu Ser Phe Lys
        420   425   430

Arg Val Ile Arg Ser Arg Ser Gln Ser Met Asp Ala Met Gly Leu Ser
        435   440   445

Asn Lys Lys Pro Asn Thr Val Ser Thr Ser His Ser Gly Ser Phe Ala
     450   455   460

Pro Asn Asn Pro Asp Leu Ala Lys Ala Ala Gly Ile Ser Leu Leu Ile
465   470   475   480

Pro Gly Lys Ser Ala Ser Arg Phe Gly Arg Arg Gly Ser Ala Ile Gly
        485   490   495

Ile Gly Thr Val Glu Glu Ser Leu Ile Val Pro Gly Lys Ser Pro Thr
            500   505   510

Arg Lys Lys Ser Gly Pro Phe Gly Ser Arg Arg Ser Ser Ala Ile Gly

            515   520   525

Ile Glu Asn Ile Gln Glu Val Gln Glu Lys Arg Glu Ser Pro Pro Ala
     530   535   540

Gly Gln Lys Thr Pro Asp Ser Gly His Val Ser Gln Glu Pro Lys Ser
545   550   555   560

Glu Asn Ser Ser Thr Gln Ser Ser Pro Glu Met Pro Thr Thr Lys Asn
            565   570   575

Arg Ala Glu Thr Ala Ala Gln Arg Ala Glu Ala Leu Lys Asp Phe Ser
            580   585   590

Arg Ser Ser Ser Ser Ala Ser Ser Phe Ala Ser Val Val Glu Glu Thr
            595   600   605

Glu Gly Val Asp Gly Glu Asp Thr Gly Leu Glu Ser Val Ser Ser Ser
     610   615   620

Gly Thr Pro His Lys Arg Asp Ser Phe Ile Tyr Ser Thr Trp Leu Glu
625   630   635   640

Asp Ser Val Ser Thr Thr Ser Gly Gly Ser Ser Pro Asp Ala Gly Lys
            645   650   655

Leu Gly Asp Pro Ala Cys Pro Glu Ile Lys Ile Gln Leu Glu Ala Ser

            660   665   670

Glu Gln His Met Pro Gln Leu Gly Cys
        675   680

<210>   73

<211>   148

<212>   PRT

<213>   Homo sapiens

<400>   73

Met Ala Ala Ser Pro Ala Arg Pro Ala Val Leu Ala Leu Thr Gly Leu
 1   5   10   15

Ala Leu Leu Leu Leu Leu Cys Trp Gly Pro Gly Gly Ile Ser Gly Asn

```
                    20              25              30
Lys Leu Lys Leu Met Leu Gln Lys Arg Glu Ala Pro Val Pro Thr Lys

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


Glu Tyr Tyr Gly Asp Tyr Tyr Gln Arg His Tyr Asp Glu Asp Ser Ala
            115             120             125
Ile Gly Pro Arg Ser Pro Tyr Gly Phe Arg His Gly Ala Ser Val Asn
        130             135             140
Tyr Asp Asp Tyr
145
```

<210> 74

<211> 1663

<212> PRT

<213> Homo sapiens

<400> 74

```
Met Gly Pro Thr Ser Gly Pro Ser Leu Leu Leu Leu Leu Thr His
    1               5               10              15
Leu Pro Leu Ala Leu Gly Ser Pro Met Tyr Ser Ile Ile Thr Pro Asn

                    20              25              30
Ile Leu Arg Leu Glu Ser Glu Glu Thr Met Val Leu Glu Ala His Asp
            35              40              45
Ala Gln Gly Asp Val Pro Val Thr Val Thr Val His Asp Phe Pro Gly
        50              55              60
Lys Lys Leu Val Leu Ser Ser Glu Lys Thr Val Leu Thr Pro Ala Thr
    65              70              75              80
```

Asn His Met Gly Asn Val Thr Phe Thr Ile Pro Ala Asn Arg Glu Phe

                85   90   95

Lys Ser Glu Lys Gly Arg Asn Lys Phe Val Thr Val Gln Ala Thr Phe

           100   105   110

Gly Thr Gln Val Val Glu Lys Val Val Leu Val Ser Leu Gln Ser Gly

        115   120   125

Tyr Leu Phe Ile Gln Thr Asp Lys Thr Ile Tyr Thr Pro Gly Ser Thr

     130   135   140

Val Leu Tyr Arg Ile Phe Thr Val Asn His Lys Leu Leu Pro Val Gly

145   150   155   160

Arg Thr Val Met Val Asn Ile Glu Asn Pro Glu Gly Ile Pro Val Lys

           165   170   175

Gln Asp Ser Leu Ser Ser Gln Asn Gln Leu Gly Val Leu Pro Leu Ser

        180   185   190

Trp Asp Ile Pro Glu Leu Val Asn Met Gly Gln Trp Lys Ile Arg Ala

        195   200   205

Tyr Tyr Glu Asn Ser Pro Gln Gln Val Phe Ser Thr Glu Phe Glu Val

     210   215   220

Lys Glu Tyr Val Leu Pro Ser Phe Glu Val Ile Val Glu Pro Thr Glu

225   230   235   240

Lys Phe Tyr Tyr Ile Tyr Asn Glu Lys Gly Leu Glu Val Thr Ile Thr

        245   250   255

Ala Arg Phe Leu Tyr Gly Lys Lys Val Glu Gly Thr Ala Phe Val Ile

        260   265   270

Phe Gly Ile Gln Asp Gly Glu Gln Arg Ile Ser Leu Pro Glu Ser Leu

        275   280   285

Lys Arg Ile Pro Ile Glu Asp Gly Ser Gly Glu Val Val Leu Ser Arg

     290   295   300

Lys Val Leu Leu Asp Gly Val Gln Asn Pro Arg Ala Glu Asp Leu Val

305   310   315   320

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

```
                   325                   330                   335
Asp Met Val Gln Ala Glu Arg Ser Gly Ile Pro Ile Val Thr Ser Pro
              340                   345                   350
Tyr Gln Ile His Phe Thr Lys Thr Pro Lys Tyr Phe Lys Pro Gly Met
         355                   360                   365
Pro Phe Asp Leu Met Val Phe Val Thr Asn Pro Asp Gly Ser Pro Ala
     370                   375                   380


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


         450                   455                   460
Leu Arg Pro Gly Glu Thr Leu Asn Val Asn Phe Leu Leu Arg Met Asp
465                   470                   475                   480
Arg Ala His Glu Ala Lys Ile Arg Tyr Tyr Thr Tyr Leu Ile Met Asn
                   485                   490                   495
Lys Gly Arg Leu Leu Lys Ala Gly Arg Gln Val Arg Glu Pro Gly Gln
              500                   505                   510
Asp Leu Val Val Leu Pro Leu Ser Ile Thr Thr Asp Phe Ile Pro Ser
         515                   520                   525


Phe Arg Leu Val Ala Tyr Tyr Thr Leu Ile Gly Ala Ser Gly Gln Arg
         530                   535                   540
Glu Val Val Ala Asp Ser Val Trp Val Asp Val Lys Asp Ser Cys Val
545                   550                   555                   560
Gly Ser Leu Val Val Lys Ser Gly Gln Ser Glu Asp Arg Gln Pro Val
                   565                   570                   575
Pro Gly Gln Gln Met Thr Leu Lys Ile Glu Gly Asp His Gly Ala Arg
```

```
                    580                585                590
Val Val Leu Val Ala Val Asp Lys Gly Val Phe Val Leu Asn Lys Lys


              595                600                605
Asn Lys Leu Thr Gln Ser Lys Ile Trp Asp Val Val Glu Lys Ala Asp
    610                615                620
Ile Gly Cys Thr Pro Gly Ser Gly Lys Asp Tyr Ala Gly Val Phe Ser
625                630                635                640
Asp Ala Gly Leu Thr Phe Thr Ser Ser Gly Gln Gln Thr Ala Gln
              645                650                655
Arg Ala Glu Leu Gln Cys Pro Gln Pro Ala Ala Arg Arg Arg Arg Ser
              660                665                670


Val Gln Leu Thr Glu Lys Arg Met Asp Lys Val Gly Lys Tyr Pro Lys
        675                680                685
Glu Leu Arg Lys Cys Cys Glu Asp Gly Met Arg Glu Asn Pro Met Arg
    690                695                700
Phe Ser Cys Gln Arg Arg Thr Arg Phe Ile Ser Leu Gly Glu Ala Cys
705                710                715                720
Lys Lys Val Phe Leu Asp Cys Cys Asn Tyr Ile Thr Glu Leu Arg Arg
                    725                730                735
Gln His Ala Arg Ala Ser His Leu Gly Leu Ala Arg Ser Asn Leu Asp


              740                745                750
Glu Asp Ile Ile Ala Glu Glu Asn Ile Val Ser Arg Ser Glu Phe Pro
              755                760                765
Glu Ser Trp Leu Trp Asn Val Glu Asp Leu Lys Glu Pro Pro Lys Asn
    770                775                780
Gly Ile Ser Thr Lys Leu Met Asn Ile Phe Leu Lys Asp Ser Ile Thr
785                790                795                800
Thr Trp Glu Ile Leu Ala Val Ser Met Ser Asp Lys Lys Gly Ile Cys
              805                810                815


Val Ala Asp Pro Phe Glu Val Thr Val Met Gln Asp Phe Phe Ile Asp
              820                825                830
```

Leu Arg Leu Pro Tyr Ser Val Val Arg Asn Glu Gln Val Glu Ile Arg
835   840   845

Ala Val Leu Tyr Asn Tyr Arg Gln Asn Gln Glu Leu Lys Val Arg Val
850   855   860

Glu Leu Leu His Asn Pro Ala Phe Cys Ser Leu Ala Thr Thr Lys Arg
865   870   875   880

Arg His Gln Gln Thr Val Thr Ile Pro Pro Lys Ser Ser Leu Ser Val

                    885   890   895

Pro Tyr Val Ile Val Pro Leu Lys Thr Gly Leu Gln Glu Val Glu Val
                    900   905   910

Lys Ala Ala Val Tyr His His Phe Ile Ser Asp Gly Val Arg Lys Ser
                    915   920   925

Leu Lys Val Val Pro Glu Gly Ile Arg Met Asn Lys Thr Val Ala Val
          930   935   940

Arg Thr Leu Asp Pro Glu Arg Leu Gly Arg Glu Gly Val Gln Lys Glu
945   950   955   960

Asp Ile Pro Pro Ala Asp Leu Ser Asp Gln Val Pro Asp Thr Glu Ser
                         965   970   975

Glu Thr Arg Ile Leu Leu Gln Gly Thr Pro Val Ala Gln Met Thr Glu
                    980   985   990

Asp Ala Val Asp Ala Glu Arg Leu Lys His Leu Ile Val Thr Pro Ser
                    995   1000   1005

Gly Cys Gly Glu Gln Asn Met Ile Gly Met Thr Pro Thr Val Ile Ala
          1010   1015   1020

Val His Tyr Leu Asp Glu Thr Glu Gln Trp Glu Lys Phe Gly Leu Glu

1025   1030   1035   1040

Lys Arg Gln Gly Ala Leu Glu Leu Ile Lys Lys Gly Tyr Thr Gln Gln
                         1045   1050   1055

Leu Ala Phe Arg Gln Pro Ser Ser Ala Phe Ala Ala Phe Val Lys Arg
                    1060   1065   1070

Ala Pro Ser Thr Trp Leu Thr Ala Tyr Val Val Lys Val Phe Ser Leu
          1075   1080   1085

Ala Val Asn Leu Ile Ala Ile Asp Ser Gln Val Leu Cys Gly Ala Val

    1090   1095   1100

Lys Trp Leu Ile Leu Glu Lys Gln Lys Pro Asp Gly Val Phe Gln Glu

1105   1110   1115   1120

Asp Ala Pro Val Ile His Gln Glu Met Ile Gly Gly Leu Arg Asn Asn

             1125   1130   1135

Asn Glu Lys Asp Met Ala Leu Thr Ala Phe Val Leu Ile Ser Leu Gln

             1140   1145   1150

Glu Ala Lys Asp Ile Cys Glu Glu Gln Val Asn Ser Leu Pro Gly Ser

          1155   1160   1165

Ile Thr Lys Ala Gly Asp Phe Leu Glu Ala Asn Tyr Met Asn Leu Gln

    1170   1175   1180

Arg Ser Tyr Thr Val Ala Ile Ala Gly Tyr Ala Leu Ala Gln Met Gly

1185   1190   1195   1200

Arg Leu Lys Gly Pro Leu Leu Asn Lys Phe Leu Thr Thr Ala Lys Asp

             1205   1210   1215

Lys Asn Arg Trp Glu Asp Pro Gly Lys Gln Leu Tyr Asn Val Glu Ala

          1220   1225   1230

Thr Ser Tyr Ala Leu Leu Ala Leu Leu Gln Leu Lys Asp Phe Asp Phe

       1235   1240   1245

Val Pro Pro Val Val Arg Trp Leu Asn Glu Gln Arg Tyr Tyr Gly Gly

    1250   1255   1260

Gly Tyr Gly Ser Thr Gln Ala Thr Phe Met Val Phe Gln Ala Leu Ala

1265   1270   1275   1280

Gln Tyr Gln Lys Asp Ala Pro Asp His Gln Glu Leu Asn Leu Asp Val

             1285   1290   1295

Ser Leu Gln Leu Pro Ser Arg Ser Ser Lys Ile Thr His Arg Ile His

       1300   1305   1310

Trp Glu Ser Ala Ser Leu Leu Arg Ser Glu Glu Thr Lys Glu Asn Glu

    1315   1320   1325

Gly Phe Thr Val Thr Ala Glu Gly Lys Gly Gln Gly Thr Leu Ser Val

```
                1330                 1335                 1340
Val Thr Met Tyr His Ala Lys Ala Lys Asp Gln Leu Thr Cys Asn Lys
1345                 1350                 1355                 1360
Phe Asp Leu Lys Val Thr Ile Lys Pro Ala Pro Glu Thr Glu Lys Arg
                1365                 1370                 1375
Pro Gln Asp Ala Lys Asn Thr Met Ile Leu Glu Ile Cys Thr Arg Tyr
                1380                 1385                 1390


Arg Gly Asp Gln Asp Ala Thr Met Ser Ile Leu Asp Ile Ser Met Met
                1395                 1400                 1405
Thr Gly Phe Ala Pro Asp Thr Asp Asp Leu Lys Gln Leu Ala Asn Gly
           1410                 1415                 1420
Val Asp Arg Tyr Ile Ser Lys Tyr Glu Leu Asp Lys Ala Phe Ser Asp
1425                 1430                 1435                 1440
Arg Asn Thr Leu Ile Ile Tyr Leu Asp Lys Val Ser His Ser Glu Asp
                1445                 1450                 1455
Asp Cys Leu Ala Phe Lys Val His Gln Tyr Phe Asn Val Glu Leu Ile


           1460                 1465                 1470
Gln Pro Gly Ala Val Lys Val Tyr Ala Tyr Tyr Asn Leu Glu Glu Ser
                1475                 1480                 1485
Cys Thr Arg Phe Tyr His Pro Glu Lys Glu Asp Gly Lys Leu Asn Lys
           1490                 1495                 1500
Leu Cys Arg Asp Glu Leu Cys Arg Cys Ala Glu Glu Asn Cys Phe Ile
1505                 1510                 1515                 1520
Gln Lys Ser Asp Asp Lys Val Thr Leu Glu Glu Arg Leu Asp Lys Ala
                1525                 1530                 1535


Cys Glu Pro Gly Val Asp Tyr Val Tyr Lys Thr Arg Leu Val Lys Val
                1540                 1545                 1550
Gln Leu Ser Asn Asp Phe Asp Glu Tyr Ile Met Ala Ile Glu Gln Thr
           1555                 1560                 1565
Ile Lys Ser Gly Ser Asp Glu Val Gln Val Gly Gln Gln Arg Thr Phe
      1570                 1575                 1580
Ile Ser Pro Ile Lys Cys Arg Glu Ala Leu Lys Leu Glu Glu Lys Lys
```

```
   1585              1590              1595              1600
```

His Tyr Leu Met Trp Gly Leu Ser Ser Asp Phe Trp Gly Glu Lys Pro

```
                  1605              1610              1615
```

Asn Leu Ser Tyr Ile Ile Gly Lys Asp Thr Trp Val Glu His Trp Pro

```
              1620              1625              1630
```

Glu Glu Asp Glu Cys Gln Asp Glu Glu Asn Gln Lys Gln Cys Gln Asp

```
          1635              1640              1645
```

Leu Gly Ala Phe Thr Glu Ser Met Val Val Phe Gly Cys Pro Asn

```
       1650              1655              1660
```

<210>   75

<211>   306

<212>   PRT

<213>   Homo sapiens

<400>   75

Met Cys Gln Cys Val Arg Ala Cys Val Cys Val Cys Val Cys Ala Cys


```
   1                5                10                15
```

Ala Thr Gln Arg Ala Ser His Ser Ala Leu Pro Gly Thr Thr Ile Ser

```
              20                25                30
```

Val Lys Asp Trp Arg Leu Cys Leu Leu Asp Gln Phe Asp Ala Cys Ala

```
          35                40                45
```

Arg Ser Gly Leu Ser Glu Pro Arg Ser Leu Thr Leu Arg Val Pro Ser

```
       50                55                60
```

Cys Gly Lys Pro Leu Pro Gly Pro Gly Ala Arg Leu Gly Arg Glu Val

```
   65                70                75                80
```

Thr Pro Cys Leu Ser Phe Ala Phe Ala Trp Cys Trp Leu Lys Met Cys

```
                  85                90                95
```

Gln Glu Glu Gln Thr Ser Tyr Met Val Val Gln Thr Ser Glu Glu Gly

```
              100               105               110
```

Leu Ala Ala Asp Ala Glu Leu Pro Gly Pro Leu Leu Met Leu Ala Gln

```
              115               120               125
```

Asn Cys Ala Val Met His Asn Leu Leu Gly Pro Ala Cys Ile Phe Leu

```
       130               135               140
```

Arg Lys Gly Phe Ala Glu Asn Arg Gln Pro Asp Arg Ser Leu Arg Pro

145   150   155   160

Glu Glu Ile Glu Glu Leu Arg Glu Ala Phe Arg Glu Phe Asp Lys Asp

     165   170   175

Lys Asp Gly Tyr Ile Asn Cys Arg Asp Leu Gly Asn Cys Met Arg Thr

    180   185   190

Met Gly Tyr Met Pro Thr Glu Met Glu Leu Ile Glu Leu Ser Gln Gln

    195   200   205

Ile Asn Met Asn Leu Gly Gly His Val Asp Phe Asp Asp Phe Val Glu

  210   215   220

Leu Met Gly Pro Lys Leu Leu Ala Glu Thr Ala Asp Met Ile Gly Val

225   230   235   240

Lys Glu Leu Arg Asp Ala Phe Arg Glu Phe Asp Thr Asn Gly Asp Gly

     245   250   255

Glu Ile Ser Thr Ser Glu Leu Arg Glu Ala Met Arg Lys Leu Leu Gly

    260   265   270

His Gln Val Gly His Arg Asp Ile Glu Glu Ile Ile Arg Asp Val Asp

    275   280   285

Leu Asn Gly Asp Gly Arg Val Asp Phe Glu Glu Phe Val Arg Met Met

   290   295   300

Ser Arg

305

<210> 76

<211> 116

<212> PRT

<213> Homo sapiens

<400> 76

Met Glu Ser Ser Arg Val Arg Leu Leu Pro Leu Leu Gly Ala Ala Leu

 1   5   10   15

Leu Leu Met Leu Pro Leu Leu Gly Thr Arg Ala Gln Glu Asp Ala Glu

    20   25   30

Leu Gln Pro Arg Ala Leu Asp Ile Tyr Ser Ala Val Asp Asp Ala Ser

                35   40   45

His Glu Lys Glu Leu Ile Glu Ala Leu Gln Glu Val Leu Lys Lys Leu
        50   55   60

Lys Ser Lys Arg Val Pro Ile Tyr Glu Lys Lys Tyr Gly Gln Val Pro
 65   70   75   80

Met Cys Asp Ala Gly Glu Gln Cys Ala Val Arg Lys Gly Ala Arg Ile
                85   90   95

Gly Lys Leu Cys Asp Cys Pro Arg Gly Thr Ser Cys Asn Ser Phe Leu
        100   105   110

Leu Lys Cys Leu

        115

<210>   77

<211>   703

<212>   PRT

<213>   Homo sapiens

<400>   77

Met Ala Ala Gln Ala Ala Gly Val Ser Arg Gln Arg Ala Ala Thr Gln
 1   5   10   15

Gly Leu Gly Ser Asn Gln Asn Ala Leu Lys Tyr Leu Gly Gln Asp Phe
                20   25   30

Lys Thr Leu Arg Gln Gln Cys Leu Asp Ser Gly Val Leu Phe Lys Asp
        35   40   45

Pro Glu Phe Pro Ala Cys Pro Ser Ala Leu Gly Tyr Lys Asp Leu Gly

        50   55   60

Pro Gly Ser Pro Gln Thr Gln Gly Ile Ile Trp Lys Arg Pro Thr Glu
 65   70   75   80

Leu Cys Pro Ser Pro Gln Phe Ile Val Gly Gly Ala Thr Arg Thr Asp
                85   90   95

Ile Cys Gln Gly Gly Leu Gly Asp Cys Trp Leu Leu Ala Ala Ile Ala
                100   105   110

Ser Leu Thr Leu Asn Glu Glu Leu Leu Tyr Arg Val Val Pro Arg Asp

```
              115                 120                 125


Gln Asp 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 Ile Asp Asp Arg Leu Pro Thr
145                 150                 155                 160
Lys Asn Gly Gln Leu Leu Phe Leu His Ser Glu Gln Gly Asn Glu Phe
                    165                 170                 175
Trp Ser Ala Leu Leu Glu Lys Ala Tyr Ala Lys Leu Asn Gly Cys Tyr
                180                 185                 190
Glu Ala Leu Ala Gly Gly Ser Thr Val Glu Gly Phe Glu Asp Phe Thr


              195                 200                 205
Gly Gly Ile Ser Glu Phe Tyr Asp Leu Lys Lys Pro Pro Ala Asn Leu
        210                 215                 220
Tyr Gln Ile Ile Arg Lys Ala Leu Cys Ala Gly Ser Leu Leu Gly Cys
225                 230                 235                 240
Ser Ile Asp Val Ser Ser Ala Ala Glu Ala Glu Ala Ile Thr Ser Gln
                    245                 250                 255
Lys Leu Val Lys Ser His Ala Tyr Ser Val Thr Gly Val Glu Glu Val
                260                 265                 270


Asn Phe Gln Gly His Pro Glu Lys Leu Ile Arg Leu Arg Asn Pro Trp
              275                 280                 285
Gly Glu Val Glu Trp Ser Gly Ala Trp Ser Asp Asp Ala Pro Glu Trp
        290                 295                 300
Asn His Ile Asp Pro Arg Arg Lys Glu Glu Leu Asp Lys Lys Val Glu
305                 310                 315                 320
Asp Gly Glu Phe Trp Met Ser Leu Ser Asp Phe Val Arg Gln Phe Ser
                    325                 330                 335
Arg Leu Glu Ile Cys Asn Leu Ser Pro Asp Ser Leu Ser Ser Glu Glu


              340                 345                 350
Val His Lys Trp Asn Leu Val Leu Phe Asn Gly His Trp Thr Arg Gly
        355                 360                 365
```

Ser Thr Ala Gly Gly Cys Gln Asn Tyr Pro Ala Thr Tyr Trp Thr Asn
    370   375   380

Pro Gln Phe Lys Ile Arg Leu Asp Glu Val Asp Glu Asp Gln Glu Glu
385   390   395   400

Ser Ile Gly Glu Pro Cys Cys Thr Val Leu Leu Gly Leu Met Gln Lys
            405   410   415

Asn Arg Arg Trp Arg Lys Arg Ile Gly Gln Gly Met Leu Ser Ile Gly
          420   425   430

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

His Leu Gly Arg Asp Phe Phe Leu Ala Tyr Gln Pro Ser Ala Arg Thr
    450   455   460

Ser Thr Tyr Val Asn Leu Arg Glu Val Ser Gly Arg Ala Arg Leu Pro
465   470   475   480

Pro Gly Glu Tyr Leu Val Val Pro Ser Thr Phe Glu Pro Phe Lys Asp

            485   490   495

Gly Glu Phe Cys Leu Arg Val Phe Ser Glu Lys Lys Ala Gln Ala Leu
          500   505   510

Glu Ile Gly Asp Val Val Ala Gly Asn Pro Tyr Glu Pro His Pro Ser
          515   520   525

Glu Val Asp Gln Glu Asp Asp Gln Phe Arg Arg Leu Phe Glu Lys Leu
          530   535   540

Ala Gly Lys Asp Ser Glu Ile Thr Ala Asn Ala Leu Lys Ile Leu Leu
545   550   555   560

Asn Glu Ala Phe Ser Lys Arg Thr Asp Ile Lys Phe Asp Gly Phe Asn
          565   570   575

Ile Asn Thr Cys Arg Glu Met Ile Ser Leu Leu Asp Ser Asn Gly Thr
          580   585   590

Gly Thr Leu Gly Ala Val Glu Phe Lys Thr Leu Trp Leu Lys Ile Gln
          595   600   605

Lys Tyr Leu Glu Ile Tyr Trp Glu Thr Asp Tyr Asn His Ser Gly Thr
    610   615   620

Ile Asp Ala His Glu Met Arg Thr Ala Leu Arg Lys Ala Gly Phe Thr

625   630   635   640

Leu Asn Ser Gln Val Gln Gln Thr Ile Ala Leu Arg Tyr Ala Cys Ser
             645   650   655

Lys Leu Gly Ile Asn Phe Asp Ser Phe Val Ala Cys Met Ile Arg Leu
          660   665   670

Glu Thr Leu Phe Lys Leu Phe Ser Leu Leu Asp Glu Asp Lys Asp Gly
          675   680   685

Met Val Gln Leu Ser Leu Ala Glu Trp Leu Cys Cys Val Leu Val
      690   695   700

<210>   78
<211>   229
<212>   PRT
<213>   Homo sapiens
<400>   78

Met Ala Arg Leu Ala Leu Ser Pro Val Pro Ser His Trp Met Val Ala
 1   5   10   15

Leu Leu Leu Leu Leu Ser Ala Glu Pro Val Pro Ala Ala Arg Ser Glu
             20   25   30

Asp Arg Tyr Arg Asn Pro Lys Gly Ser Ala Cys Ser Arg Ile Trp Gln
          35   40   45

Ser Pro Arg Phe Ile Ala Arg Lys Arg Gly Phe Thr Val Lys Met His

     50   55   60

Cys Tyr Met Asn Ser Ala Ser Gly Asn Val Ser Trp Leu Trp Lys Gln
 65   70   75   80

Glu Met Asp Glu Asn Pro Gln Gln Leu Lys Leu Glu Lys Gly Arg Met
             85   90   95

Glu Glu Ser Gln Asn Glu Ser Leu Ala Thr Leu Thr Ile Gln Gly Ile
             100   105   110

Arg Phe Glu Asp Asn Gly Ile Tyr Phe Cys Gln Gln Lys Cys Asn Asn
          115   120   125

- 166 -

Thr Ser Glu Val Tyr Gln Gly Cys Gly Thr Glu Leu Arg Val Met Gly

    130   135   140

Phe Ser Thr Leu Ala Gln Leu Lys Gln Arg Asn Thr Leu Lys Asp Gly

145   150   155   160

Ile Ile Met Ile Gln Thr Leu Leu Ile Ile Leu Phe Ile Ile Val Pro

              165   170   175

Ile Phe Leu Leu Leu Asp Lys Asp Asp Ser Lys Ala Gly Met Glu Glu

          180   185   190

Asp His Thr Tyr Glu Gly Leu Asp Ile Asp Gln Thr Ala Thr Tyr Glu

            195   200   205

Asp Ile Val Thr Leu Arg Thr Gly Glu Val Lys Trp Ser Val Gly Glu

      210   215   220

His Pro Gly Gln Glu

225

<210>   79

<211>   2944

<212>   PRT

<213>   Homo sapiens

<400>   79

Met Thr Leu Arg Leu Leu Val Ala Ala Leu Cys Ala Gly Ile Leu Ala

  1   5   10   15

Glu Ala Pro Arg Val Arg Ala Gln His Arg Glu Arg Val Thr Cys Thr

          20   25   30

Arg Leu Tyr Ala Ala Asp Ile Val Phe Leu Leu Asp Gly Ser Ser Ser

          35   40   45

Ile Gly Arg Ser Asn Phe Arg Glu Val Arg Ser Phe Leu Glu Gly Leu

      50   55   60

Val Leu Pro Phe Ser Gly Ala Ala Ser Ala Gln Gly Val Arg Phe Ala

65   70   75   80

Thr Val Gln Tyr Ser Asp Asp Pro Arg Thr Glu Phe Gly Leu Asp Ala

              85   90   95

Leu Gly Ser Gly Gly Asp Val Ile Arg Ala Ile Arg Glu Leu Ser Tyr

```
                100                 105                 110
Lys Gly Gly Asn Thr Arg Thr Gly Ala Ala Ile Leu His Val Ala Asp
            115                 120                 125
His Val Phe Leu Pro Gln Leu Ala Arg Pro Gly Val Pro Lys Val Cys
        130                 135                 140
Ile Leu Ile Thr Asp Gly Lys Ser Gln Asp Leu Val Asp Thr Ala Ala
145                 150                 155                 160
Gln Arg Leu Lys Gly Gln Gly Val Lys Leu Phe Ala Val Gly Ile Lys
                165                 170                 175
```

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

```
                245                 250                 255
Gly Pro Val Thr Gly Tyr Lys Val Gln Tyr Thr Pro Leu Thr Gly Leu
                260                 265                 270
Gly Gln Pro Leu Pro Ser Glu Arg Gln Glu Val Asn Val Pro Ala Gly
            275                 280                 285
Glu Thr Ser Val Arg Leu Arg Gly Leu Arg Pro Leu Thr Glu Tyr Gln
        290                 295                 300
Val Thr Val Ile Ala Leu Tyr Ala Asn Ser Ile Gly Glu Ala Val Ser
305                 310                 315                 320
```

```
Gly Thr Ala Arg Thr Thr Ala Leu Glu Gly Pro Glu Leu Thr Ile Gln
                325                 330                 335
Asn Thr Thr Ala His Ser Leu Leu Val Ala Trp Arg Ser Val Pro Gly
                340                 345                 350
Ala Thr Gly Tyr Arg Val Thr Trp Arg Val Leu Ser Gly Gly Pro Thr
```

```
        355                 360                 365
Gln Gln Gln Glu Leu Gly Pro Gly Gln Gly Ser Val Leu Leu Arg Asp
    370                 375                 380
Leu Glu Pro Gly Thr Asp Tyr Glu Val Thr Val Ser Thr Leu Phe Gly


385                 390                 395                 400
Arg Ser Val Gly Pro Ala Thr Ser Leu Met Ala Arg Thr Asp Ala Ser
                405                 410                 415
Val Glu Gln Thr Leu Arg Pro Val Ile Leu Gly Pro Thr Ser Ile Leu
                420                 425                 430
Leu Ser Trp Asn Leu Val Pro Glu Ala Arg Gly Tyr Arg Leu Glu Trp
        435                 440                 445
Arg Arg Glu Thr Gly Leu Glu Pro Pro Gln Lys Val Val Leu Pro Ser
    450                 455                 460


Asp Val Thr Arg Tyr Gln Leu Asp Gly Leu Gln Pro Gly Thr Glu Tyr
465                 470                 475                 480
Arg Leu Thr Leu Tyr Thr Leu Leu Glu Gly His Glu Val Ala Thr Pro
                485                 490                 495
Ala Thr Val Val Pro Thr Gly Pro Glu Leu Pro Val Ser Pro Val Thr
                500                 505                 510
Asp Leu Gln Ala Thr Glu Leu Pro Gly Gln Arg Val Arg Val Ser Trp
        515                 520                 525
Ser Pro Val Pro Gly Ala Thr Gln Tyr Arg Ile Ile Val Arg Ser Thr


        530                 535                 540
Gln Gly Val Glu Arg Thr Leu Val Leu Pro Gly Ser Gln Thr Ala Phe
545                 550                 555                 560
Asp Leu Asp Asp Val Gln Ala Gly Leu Ser Tyr Thr Val Arg Val Ser
                565                 570                 575
Ala Arg Val Gly Pro Arg Glu Gly Ser Ala Ser Val Leu Thr Val Arg
                580                 585                 590
Arg Glu Pro Glu Thr Pro Leu Ala Val Pro Gly Leu Arg Val Val Val
        595                 600                 605
```

Ser Asp Ala Thr Arg Val Arg Val Ala Trp Gly Pro Val Pro Gly Ala

   610   615   620

Ser Gly Phe Arg Ile Ser Trp Ser Thr Gly Ser Gly Pro Glu Ser Ser

625   630   635   640

Gln Thr Leu Pro Pro Asp Ser Thr Ala Thr Asp Ile Thr Gly Leu Gln

            645   650   655

Pro Gly Thr Thr Tyr Gln Val Ala Val Ser Val Leu Arg Gly Arg Glu

            660   665   670

Glu Gly Pro Ala Ala Val Ile Val Ala Arg Thr Asp Pro Leu Gly Pro

            675   680   685

Val Arg Thr Val His Val Thr Gln Ala Ser Ser Ser Ser Val Thr Ile

   690   695   700

Thr Trp Thr Arg Val Pro Gly Ala Thr Gly Tyr Arg Val Ser Trp His

705   710   715   720

Ser Ala His Gly Pro Glu Lys Ser Gln Leu Val Ser Gly Glu Ala Thr

            725   730   735

Val Ala Glu Leu Asp Gly Leu Glu Pro Asp Thr Glu Tyr Thr Val His

            740   745   750

Val Arg Ala His Val Ala Gly Val Asp Gly Pro Pro Ala Ser Val Val

            755   760   765

Val Arg Thr Ala Pro Glu Pro Val Gly Arg Val Ser Arg Leu Gln Ile

            770   775   780

Leu Asn Ala Ser Ser Asp Val Leu Arg Ile Thr Trp Val Gly Val Thr

785   790   795   800

Gly Ala Thr Ala Tyr Arg Leu Ala Trp Gly Arg Ser Glu Gly Gly Pro

            805   810   815

Met Arg His Gln Ile Leu Pro Gly Asn Thr Asp Ser Ala Glu Ile Arg

            820   825   830

Gly Leu Glu Gly Gly Val Ser Tyr Ser Val Arg Val Thr Ala Leu Val

            835   840   845

Gly Asp Arg Glu Gly Thr Pro Val Ser Ile Val Val Thr Thr Pro Pro

   850   855   860

Glu Ala Pro Pro Ala Leu Gly Thr Leu His Val Val Gln Arg Gly Glu

865   870   875   880

His Ser Leu Arg Leu Arg Trp Glu Pro Val Pro Arg Ala Gln Gly Phe

            885   890   895

Leu Leu His Trp Gln Pro Glu Gly Gly Gln Glu Gln Ser Arg Val Leu

        900   905   910

Gly Pro Glu Leu Ser Ser Tyr His Leu Asp Gly Leu Glu Pro Ala Thr

          915   920   925

Gln Tyr Arg Val Arg Leu Ser Val Leu Gly Pro Ala Gly Glu Gly Pro

       930   935   940

Ser Ala Glu Val Thr Ala Arg Thr Glu Ser Pro Arg Val Pro Ser Ile

945   950   955   960

Glu Leu Arg Val Val Asp Thr Ser Ile Asp Ser Val Thr Leu Ala Trp

         965   970   975

Thr Pro Val Ser Arg Ala Ser Ser Tyr Ile Leu Ser Trp Arg Pro Leu

        980   985   990

Arg Gly Pro Gly Gln Glu Val Pro Gly Ser Pro Gln Thr Leu Pro Gly

        995   1000   1005

Ile Ser Ser Ser Gln Arg Val Thr Gly Leu Glu Pro Gly Val Ser Tyr

    1010   1015   1020

Ile Phe Ser Leu Thr Pro Val Leu Asp Gly Val Arg Gly Pro Glu Ala

1025   1030   1035   1040

Ser Val Thr Gln Thr Pro Val Cys Pro Arg Gly Leu Ala Asp Val Val

          1045   1050   1055

Phe Leu Pro His Ala Thr Gln Asp Asn Ala His Arg Ala Glu Ala Thr

        1060   1065   1070

Arg Arg Val Leu Glu Arg Leu Val Leu Ala Leu Gly Pro Leu Gly Pro

       1075   1080   1085

Gln Ala Val Gln Val Gly Leu Leu Ser Tyr Ser His Arg Pro Ser Pro

    1090   1095   1100

Leu Phe Pro Leu Asn Gly Ser His Asp Leu Gly Ile Ile Leu Gln Arg

```
         1105                1110                1115                1120
Ile Arg Asp Met Pro Tyr Met Asp Pro Ser Gly Asn Asn Leu Gly Thr
                    1125                1130                1135
Ala Val Val Thr Ala His Arg Tyr Met Leu Ala Pro Asp Ala Pro Gly
                1140                1145                1150
Arg Arg Gln His Val Pro Gly Val Met Val Leu Leu Val Asp Glu Pro
            1155                1160                1165
Leu Arg Gly Asp Ile Phe Ser Pro Ile Arg Glu Ala Gln Ala Ser Gly
            1170                1175                1180


Leu Asn Val Val Met Leu Gly Met Ala Gly Ala Asp Pro Glu Gln Leu
1185                1190                1195                1200
Arg Arg Leu Ala Pro Gly Met Asp Ser Val Gln Thr Phe Phe Ala Val
                1205                1210                1215
Asp Asp Gly Pro Ser Leu Asp Gln Ala Val Ser Gly Leu Ala Thr Ala
                1220                1225                1230
Leu Cys Gln Ala Ser Phe Thr Thr Gln Pro Arg Pro Glu Pro Cys Pro
            1235                1240                1245
Val Tyr Cys Pro Lys Gly Gln Lys Gly Glu Pro Gly Glu Met Gly Leu


         1250                1255                1260
Arg Gly Gln Val Gly Pro Pro Gly Asp Pro Gly Leu Pro Gly Arg Thr
1265                1270                1275                1280
Gly Ala Pro Gly Pro Gln Gly Pro Pro Gly Ser Ala Thr Ala Lys Gly
                    1285                1290                1295
Glu Arg Gly Phe Pro Gly Ala Asp Gly Arg Pro Gly Ser Pro Gly Arg
                1300                1305                1310
Ala Gly Asn Pro Gly Thr Pro Gly Ala Pro Gly Leu Lys Gly Ser Pro
                1315                1320                1325


Gly Leu Pro Gly Pro Arg Gly Asp Pro Gly Glu Arg Gly Pro Arg Gly
            1330                1335                1340
Pro Lys Gly Glu Pro Gly Ala Pro Gly Gln Val Ile Gly Gly Glu Gly
1345                1350                1355                1360
Pro Gly Leu Pro Gly Arg Lys Gly Asp Pro Gly Pro Ser Gly Pro Pro
```

                    1365   1370   1375

Gly Pro Arg Gly Pro Leu Gly Asp Pro Gly Pro Arg Gly Pro Pro Gly
              1380   1385   1390

Leu Pro Gly Thr Ala Met Lys Gly Asp Lys Gly Asp Arg Gly Glu Arg

                    1395   1400   1405

Gly Pro Pro Gly Pro Gly Glu Gly Gly Ile Ala Pro Gly Glu Pro Gly
              1410   1415   1420

Leu Pro Gly Leu Pro Gly Ser Pro Gly Pro Gln Gly Pro Val Gly Pro
1425   1430   1435   1440

Pro Gly Lys Lys Gly Glu Lys Gly Asp Ser Glu Asp Gly Ala Pro Gly
                    1445   1450   1455

Leu Pro Gly Gln Pro Gly Ser Pro Gly Glu Gln Gly Pro Arg Gly Pro
              1460   1465   1470

Pro Gly Ala Ile Gly Pro Lys Gly Asp Arg Gly Phe Pro Gly Pro Leu
              1475   1480   1485

Gly Glu Ala Gly Glu Lys Gly Glu Arg Gly Pro Pro Gly Pro Ala Gly
              1490   1495   1500

Ser Arg Gly Leu Pro Gly Val Ala Gly Arg Pro Gly Ala Lys Gly Pro
1505   1510   1515   1520

Glu Gly Pro Pro Gly Pro Thr Gly Arg Gln Gly Glu Lys Gly Glu Pro
                    1525   1530   1535

Gly Arg Pro Gly Asp Pro Ala Val Val Gly Pro Ala Val Ala Gly Pro

                    1540   1545   1550

Lys Gly Glu Lys Gly Asp Val Gly Pro Ala Gly Pro Arg Gly Ala Thr
              1555   1560   1565

Gly Val Gln Gly Glu Arg Gly Pro Pro Gly Leu Val Leu Pro Gly Asp
              1570   1575   1580

Pro Gly Pro Lys Gly Asp Pro Gly Asp Arg Gly Pro Ile Gly Leu Thr
1585   1590   1595   1600

Gly Arg Ala Gly Pro Pro Gly Asp Ser Gly Pro Pro Gly Glu Lys Gly
                    1605   1610   1615

公개특허 10-2015-0142881

Asp Pro Gly Arg Pro Gly Pro Pro Gly Pro Val Gly Pro Arg Gly Arg
         1620   1625   1630

Asp Gly Glu Val Gly Glu Lys Gly Asp Glu Gly Pro Pro Gly Asp Pro
          1635   1640   1645

Gly Leu Pro Gly Lys Ala Gly Glu Arg Gly Leu Arg Gly Ala Pro Gly
        1650   1655   1660

Val Arg Gly Pro Val Gly Glu Lys Gly Asp Gln Gly Asp Pro Gly Glu
1665   1670   1675   1680

Asp Gly Arg Asn Gly Ser Pro Gly Ser Ser Gly Pro Lys Gly Asp Arg

               1685   1690   1695

Gly Glu Pro Gly Pro Pro Gly Pro Pro Gly Arg Leu Val Asp Thr Gly
          1700   1705   1710

Pro Gly Ala Arg Glu Lys Gly Glu Pro Gly Asp Arg Gly Gln Glu Gly
         1715   1720   1725

Pro Arg Gly Pro Lys Gly Asp Pro Gly Leu Pro Gly Ala Pro Gly Glu
        1730   1735   1740

Arg Gly Ile Glu Gly Phe Arg Gly Pro Pro Gly Pro Gln Gly Asp Pro
1745   1750   1755   1760

Gly Val Arg Gly Pro Ala Gly Glu Lys Gly Asp Arg Gly Pro Pro Gly
            1765   1770   1775

Leu Asp Gly Arg Ser Gly Leu Asp Gly Lys Pro Gly Ala Ala Gly Pro
         1780   1785   1790

Ser Gly Pro Asn Gly Ala Ala Gly Lys Ala Gly Asp Pro Gly Arg Asp
        1795   1800   1805

Gly Leu Pro Gly Leu Arg Gly Glu Gln Gly Leu Pro Gly Pro Ser Gly
     1810   1815   1820

Pro Pro Gly Leu Pro Gly Lys Pro Gly Glu Asp Gly Lys Pro Gly Leu

1825   1830   1835   1840

Asn Gly Lys Asn Gly Glu Pro Gly Asp Pro Gly Glu Asp Gly Arg Lys
            1845   1850   1855

Gly Glu Lys Gly Asp Ser Gly Ala Ser Gly Arg Glu Gly Arg Asp Gly
        1860   1865   1870

- 174 -

Pro Lys Gly Glu Arg Gly Ala Pro Gly Ile Leu Gly Pro Gln Gly Pro
       1875   1880   1885

Pro Gly Leu Pro Gly Pro Val Gly Pro Pro Gly Gln Gly Phe Pro Gly
    1890   1895   1900

Val Pro Gly Gly Thr Gly Pro Lys Gly Asp Arg Gly Glu Thr Gly Ser
1905   1910   1915   1920

Lys Gly Glu Gln Gly Leu Pro Gly Glu Arg Gly Leu Arg Gly Glu Pro
       1925   1930   1935

Gly Ser Val Pro Asn Val Asp Arg Leu Leu Glu Thr Ala Gly Ile Lys
      1940   1945   1950

Ala Ser Ala Leu Arg Glu Ile Val Glu Thr Trp Asp Glu Ser Ser Gly
     1955   1960   1965

Ser Phe Leu Pro Val Pro Glu Arg Arg Arg Gly Pro Lys Gly Asp Ser

    1970   1975   1980

Gly Glu Gln Gly Pro Pro Gly Lys Glu Gly Pro Ile Gly Phe Pro Gly
1985   1990   1995   2000

Glu Arg Gly Leu Lys Gly Asp Arg Gly Asp Pro Gly Pro Gln Gly Pro
       2005   2010   2015

Pro Gly Leu Ala Leu Gly Glu Arg Gly Pro Pro Gly Pro Ser Gly Leu
      2020   2025   2030

Ala Gly Glu Pro Gly Lys Pro Gly Ile Pro Gly Leu Pro Gly Arg Ala
      2035   2040   2045

Gly Gly Val Gly Glu Ala Gly Arg Pro Gly Glu Arg Gly Glu Arg Gly
      2050   2055   2060

Glu Lys Gly Glu Arg Gly Glu Gln Gly Arg Asp Gly Pro Pro Gly Leu
2065   2070   2075   2080

Pro Gly Thr Pro Gly Pro Pro Gly Pro Pro Gly Pro Lys Val Ser Val
      2085   2090   2095

Asp Glu Pro Gly Pro Gly Leu Ser Gly Glu Gln Gly Pro Pro Gly Leu
      2100   2105   2110

Lys Gly Ala Lys Gly Glu Pro Gly Ser Asn Gly Asp Gln Gly Pro Lys

                2115   2120   2125

Gly Asp Arg Gly Val Pro Gly Ile Lys Gly Asp Arg Gly Glu Pro Gly
        2130   2135   2140

Pro Arg Gly Gln Asp Gly Asn Pro Gly Leu Pro Gly Glu Arg Gly Met
2145   2150   2155   2160

Ala Gly Pro Glu Gly Lys Pro Gly Leu Gln Gly Pro Arg Gly Pro Pro
                    2165   2170   2175

Gly Pro Val Gly Gly His Gly Asp Pro Gly Pro Pro Gly Ala Pro Gly
            2180   2185   2190

Leu Ala Gly Pro Ala Gly Pro Gln Gly Pro Ser Gly Leu Lys Gly Glu
            2195   2200   2205

Pro Gly Glu Thr Gly Pro Pro Gly Arg Gly Leu Thr Gly Pro Thr Gly
        2210   2215   2220

Ala Val Gly Leu Pro Gly Pro Pro Gly Pro Ser Gly Leu Val Gly Pro
2225   2230   2235   2240

Gln Gly Ser Pro Gly Leu Pro Gly Gln Val Gly Glu Thr Gly Lys Pro
                    2245   2250   2255

Gly Ala Pro Gly Arg Asp Gly Ala Ser Gly Lys Asp Gly Asp Arg Gly

                2260   2265   2270

Ser Pro Gly Val Pro Gly Ser Pro Gly Leu Pro Gly Pro Val Gly Pro
            2275   2280   2285

Lys Gly Glu Pro Gly Pro Thr Gly Ala Pro Gly Gln Ala Val Val Gly
        2290   2295   2300

Leu Pro Gly Ala Lys Gly Glu Lys Gly Ala Pro Gly Gly Leu Ala Gly
2305   2310   2315   2320

Asp Leu Val Gly Glu Pro Gly Ala Lys Gly Asp Arg Gly Leu Pro Gly
                    2325   2330   2335

Pro Arg Gly Glu Lys Gly Glu Ala Gly Arg Ala Gly Glu Pro Gly Asp
                2340   2345   2350

Pro Gly Glu Asp Gly Gln Lys Gly Ala Pro Gly Pro Lys Gly Phe Lys
            2355   2360   2365

Gly Asp Pro Gly Val Gly Val Pro Gly Ser Pro Gly Pro Pro Gly Pro

	2370		2375		2380	

Pro Gly Val Lys Gly Asp Leu Gly Leu Pro Gly Leu Pro Gly Ala Pro

	2385		2390		2395		2400

Gly Val Val Gly Phe Pro Gly Gln Thr Gly Pro Arg Gly Glu Met Gly

	2405		2410		2415

Gln Pro Gly Pro Ser Gly Glu Arg Gly Leu Ala Gly Pro Pro Gly Arg

	2420		2425		2430

Glu Gly Ile Pro Gly Pro Leu Gly Pro Pro Gly Pro Pro Gly Ser Val

	2435		2440		2445

Gly Pro Pro Gly Ala Ser Gly Leu Lys Gly Asp Lys Gly Asp Pro Gly

	2450		2455		2460

Val Gly Leu Pro Gly Pro Arg Gly Glu Arg Gly Glu Pro Gly Ile Arg

	2465		2470		2475		2480

Gly Glu Asp Gly Arg Pro Gly Gln Glu Gly Pro Arg Gly Leu Thr Gly

	2485		2490		2495

Pro Pro Gly Ser Arg Gly Glu Arg Gly Glu Lys Gly Asp Val Gly Ser

	2500		2505		2510

Ala Gly Leu Lys Gly Asp Lys Gly Asp Ser Ala Val Ile Leu Gly Pro

	2515		2520		2525

Pro Gly Pro Arg Gly Ala Lys Gly Asp Met Gly Glu Arg Gly Pro Arg

	2530		2535		2540

Gly Leu Asp Gly Asp Lys Gly Pro Arg Gly Asp Asn Gly Asp Pro Gly

	2545		2550		2555		2560

Asp Lys Gly Ser Lys Gly Glu Pro Gly Asp Lys Gly Ser Ala Gly Leu

	2565		2570		2575

Pro Gly Leu Arg Gly Leu Leu Gly Pro Gln Gly Gln Pro Gly Ala Ala

	2580		2585		2590

Gly Ile Pro Gly Asp Pro Gly Ser Pro Gly Lys Asp Gly Val Pro Gly

	2595		2600		2605

Ile Arg Gly Glu Lys Gly Asp Val Gly Phe Met Gly Pro Arg Gly Leu

	2610		2615		2620

Lys Gly Glu Arg Gly Val Lys Gly Ala Cys Gly Leu Asp Gly Glu Lys
2625   2630   2635   2640

Gly Asp Lys Gly Glu Ala Gly Pro Pro Gly Arg Pro Gly Leu Ala Gly
              2645   2650   2655

His Lys Gly Glu Met Gly Glu Pro Gly Val Pro Gly Gln Ser Gly Ala
              2660   2665   2670

Pro Gly Lys Glu Gly Leu Ile Gly Pro Lys Gly Asp Arg Gly Phe Asp
         2675   2680   2685

Gly Gln Pro Gly Pro Lys Gly Asp Gln Gly Glu Lys Gly Glu Arg Gly

   2690   2695   2700

Thr Pro Gly Ile Gly Gly Phe Pro Gly Pro Ser Gly Asn Asp Gly Ser
2705   2710   2715   2720

Ala Gly Pro Pro Gly Pro Pro Gly Ser Val Gly Pro Arg Gly Pro Glu
              2725   2730   2735

Gly Leu Gln Gly Gln Lys Gly Glu Arg Gly Pro Pro Gly Glu Arg Val
              2740   2745   2750

Val Gly Ala Pro Gly Val Pro Gly Ala Pro Gly Glu Arg Gly Glu Gln
         2755   2760   2765

Gly Arg Pro Gly Pro Ala Gly Pro Arg Gly Glu Lys Gly Glu Ala Ala
      2770   2775   2780

Leu Thr Glu Asp Asp Ile Arg Gly Phe Val Arg Gln Glu Met Ser Gln
2785   2790   2795   2800

His Cys Ala Cys Gln Gly Gln Phe Ile Ala Ser Gly Ser Arg Pro Leu
              2805   2810   2815

Pro Ser Tyr Ala Ala Asp Thr Ala Gly Ser Gln Leu His Ala Val Pro
         2820   2825   2830

Val Leu Arg Val Ser His Ala Glu Glu Glu Glu Arg Val Pro Pro Glu

   2835   2840   2845

Asp Asp Glu Tyr Ser Glu Tyr Ser Glu Tyr Ser Val Glu Glu Tyr Gln
      2850   2855   2860

Asp Pro Glu Ala Pro Trp Asp Ser Asp Asp Pro Cys Ser Leu Pro Leu
2865   2870   2875   2880

- 178 -

Asp Glu Gly Ser Cys Thr Ala Tyr Thr Leu Arg Trp Tyr His Arg Ala
               2885   2890   2895

Val Thr Gly Ser Thr Glu Ala Cys His Pro Phe Val Tyr Gly Gly Cys
          2900   2905   2910

Gly Gly Asn Ala Asn Arg Phe Gly Thr Arg Glu Ala Cys Glu Arg Arg
        2915   2920   2925

Cys Pro Pro Arg Val Val Gln Ser Gln Gly Thr Gly Thr Ala Gln Asp
      2930   2935   2940

<210>   80

<211>   97

<212>   PRT

<213>   Homo sapiens

<400>   80

Met Ala Leu Pro Leu Arg Pro Leu Thr Arg Gly Leu Ala Ser Ala Ala
  1   5   10   15

Lys Gly Gly His Gly Gly Ala Gly Ala Arg Thr Trp Arg Leu Leu Thr
          20   25   30

Phe Val Leu Ala Leu Pro Ser Val Ala Leu Cys Thr Phe Asn Ser Tyr
        35   40   45

Leu His Ser Gly His Arg Pro Arg Pro Glu Phe Arg Pro Tyr Gln His
    50   55   60

Leu Arg Ile Arg Thr Lys Pro Tyr Pro Trp Gly Asp Gly Asn His Thr
 65   70   75   80

Leu Phe His Asn Ser His Val Asn Pro Leu Pro Thr Gly Tyr Glu His
        85   90   95

Pro

<210>

   81

<211>   458

<212>   PRT

<213>   Homo sapiens

<400>   81

Met Ser Asp Leu Leu Ser Val Phe Leu His Leu Leu Leu Phe Lys

1   5   10   15

Leu Val Ala Pro Val Thr Phe Arg His His Arg Tyr Asp Asp Leu Val

         20   25   30

Arg Thr Leu Tyr Lys Val Gln Asn Glu Cys Pro Gly Ile Thr Arg Val

         35   40   45

Tyr Ser Ile Gly Arg Ser Val Glu Gly Arg His Leu Tyr Val Leu Glu

         50   55   60

Phe Ser Asp His Pro Gly Ile His Glu Pro Leu Glu Pro Glu Val Lys

65   70   75   80

Tyr Val Gly Asn Met His Gly Asn Glu Ala Leu Gly Arg Glu Leu Met

              85   90   95

Leu Gln Leu Ser Glu Phe Leu Cys Glu Glu Phe Arg Asn Arg Asn Gln

         100   105   110

Arg Ile Val Gln Leu Ile Gln Asp Thr Arg Ile His Ile Leu Pro Ser

         115   120   125

Met Asn Pro Asp Gly Tyr Glu Val Ala Ala Ala Gln Gly Pro Asn Lys

         130   135   140

Pro Gly Tyr Leu Val Gly Arg Asn Asn Ala Asn Gly Val Asp Leu Asn

145   150   155   160

Arg Asn Phe Pro Asp Leu Asn Thr Tyr Ile Tyr Tyr Asn Glu Lys Tyr

         165   170   175

Gly Gly Pro Asn His His Leu Pro Leu Pro Asp Asn Trp Lys Ser Gln

         180   185   190

Val Glu Pro Glu Thr Arg Ala Val Ile Arg Trp Met His Ser Phe Asn

         195   200   205

Phe Val Leu Ser Ala Asn Leu His Gly Gly Ala Val Val Ala Asn Tyr

         210   215   220

Pro Tyr Asp Lys Ser Phe Glu His Arg Val Arg Gly Val Arg Arg Thr

225   230   235   240

Ala Ser Thr Pro Thr Pro Asp Asp Lys Leu Phe Gln Lys Leu Ala Lys

         245   250   255

Val Tyr Ser Tyr Ala His Gly Trp Met Phe Gln Gly Trp Asn Cys Gly
          260   265   270

Asp Tyr Phe Pro Asp Gly Ile Thr Asn Gly Ala Ser Trp Tyr Ser Leu
     275   280   285

Ser Lys Gly Met Gln Asp Phe Asn Tyr Leu His Thr Asn Cys Phe Glu
   290   295   300

Ile Thr Leu Glu Leu Ser Cys Asp Lys Phe Pro Pro Glu Glu Glu Leu
305   310   315   320

Gln Arg Glu Trp Leu Gly Asn Arg Glu Ala Leu Ile Gln Phe Leu Glu
         325   330   335

Gln Val His Gln Gly Ile Lys Gly Met Val Leu Asp Glu Asn Tyr Asn
         340   345   350

Asn Leu Ala Asn Ala Val Ile Ser Val Ser Gly Ile Asn His Asp Val
         355   360   365

Thr Ser Gly Asp His Gly Asp Tyr Phe Arg Leu Leu Leu Pro Gly Ile
   370   375   380

Tyr Thr Val Ser Ala Thr Ala Pro Gly Tyr Asp Pro Glu Thr Val Thr
385   390   395   400

Val Thr Val Gly Pro Ala Glu Pro Thr Leu Val Asn Phe His Leu Lys
         405   410   415

Arg Ser Ile Pro Gln Val Ser Pro Val Arg Arg Ala Pro Ser Arg Arg
         420   425   430

His Gly Val Arg Ala Lys Val Gln Pro Gln Ala Arg Lys Lys Glu Met
     435   440   445

Glu Met Arg Gln Leu Gln Arg Gly Pro Ala
   450   455

<210> 82

<211> 249

<212> PRT

<213> Homo sapiens

<400> 82

Met Glu Ile Lys His Leu Leu Phe Leu Val Ala Ala Ala Cys Leu Leu

```
1                5               10              15
```

Pro Met Leu Ser Met Lys Lys Ser Ala Arg Asp Gln Phe Asn Lys

```
        20              25              30
```

Leu Val Thr Asp Leu Pro Asn Val Gln Glu Glu Ile Val Asn Ile His

```
        35              40              45
```

Asn Ala Leu Arg Arg Arg Val Val Pro Pro Ala Ser Asn Met Leu Lys

```
    50              55              60
```

Met Ser Trp Ser Glu Glu Ala Ala Gln Asn Ala Arg Ile Phe Ser Lys

```
65              70              75              80
```

Tyr Cys Asp Met Thr Glu Ser Asn Pro Leu Glu Arg Arg Leu Pro Asn

```
                85              90              95
```

Thr Phe Cys Gly Glu Asn Met His Met Thr Ser Tyr Pro Val Ser Trp

```
            100             105             110
```

Ser Ser Val Ile Gly Val Trp Tyr Ser Glu Ser Thr Ser Phe Lys His

```
        115             120             125
```

Gly Glu Trp Thr Thr Thr Asp Asp Asp Ile Thr Thr Asp His Tyr Thr

```
    130             135             140
```

Gln Ile Val Trp Ala Thr Ser Tyr Leu Ile Gly Cys Ala Ile Ala Ser

```
145             150             155             160
```

Cys Arg Gln Gln Gly Ser Pro Arg Tyr Leu Tyr Val Cys His Tyr Cys

```
            165             170             175
```

His Glu Gly Asn Asp Pro Glu Thr Lys Asn Glu Pro Tyr Lys Thr Gly

```
        180             185             190
```

Val Pro Cys Glu Ala Cys Pro Ser Asn Cys Glu Asp Lys Leu Cys Thr

```
        195             200             205
```

Asn Pro Cys Ile Tyr Tyr Asp Glu Tyr Phe Asp Cys Asp Ile Gln Val

```
    210             215             220
```

His Tyr Leu Gly Cys Asn His Ser Thr Thr Ile Leu Phe Cys Lys Ala

```
225             230             235             240
```

Thr Cys Leu Cys Asp Thr Glu Ile Lys

```
            245
```

<210> 83

<211> 268

<212> PRT

<213> Homo sapiens

<400> 83

Met Lys Gln Ile Leu His Pro Ala Leu Glu Thr Thr Asp Pro Cys Ser

1   5   10   15

Thr Gly Phe Val Phe Pro Ala Met Thr Leu Phe Pro Val Leu Leu Phe

                20   25   30

Leu Val Ala Gly Leu Leu Pro Ser Phe Pro Ala Asn Glu Asp Lys Asp

        35   40   45

Pro Ala Phe Thr Ala Leu Leu Thr Thr Gln Thr Gln Val Gln Arg Glu

        50   55   60

Ile Val Asn Lys His Asn Glu Leu Arg Arg Ala Val Ser Pro Pro Ala

65   70   75   80

Arg Asn Met Leu Lys Met Glu Trp Asn Lys Glu Ala Ala Ala Asn Ala

                85   90   95

Gln Lys Trp Ala Asn Gln Cys Asn Tyr Arg His Ser Asn Pro Lys Asp

        100   105   110

Arg Met Thr Ser Leu Lys Cys Gly Glu Asn Leu Tyr Met Ser Ser Ala

        115   120   125

Ser Ser Ser Trp Ser Gln Ala Ile Gln Ser Trp Phe Asp Glu Tyr Asn

    130   135   140

Asp Phe Asp Phe Gly Val Gly Pro Lys Thr Pro Asn Ala Val Val Gly

145   150   155   160

His Tyr Thr Gln Val Val Trp Tyr Ser Ser Tyr Leu Val Gly Cys Gly

                165   170   175

Asn Ala Tyr Cys Pro Asn Gln Lys Val Leu Lys Tyr Tyr Tyr Val Cys

        180   185   190

Gln Tyr Cys Pro Ala Gly Asn Trp Ala Asn Arg Leu Tyr Val Pro Tyr

        195   200   205

Glu Gln Gly Ala Pro Cys Ala Ser Cys Pro Asp Asn Cys Asp Asp Gly

```
              210                  215                  220
Leu Cys Thr Asn Gly Cys Lys Tyr Glu Asp Leu Tyr Ser Asn Cys Lys
225                  230                  235                  240
Ser Leu Lys Leu Thr Leu Thr Cys Lys His Gln Leu Val Arg Asp Ser
                    245                  250                  255
```

```
Cys Lys Ala Ser Cys Asn Cys Ser Asn Ser Ile Tyr
                260                  265
```

<210> 84

<211> 422

<212> PRT

<213> Homo sapiens

<400> 84

```
Met Pro Ala Gly Arg Arg Gly Pro Ala Ala Gln Ser Ala Arg Arg Pro
 1                   5                  10                  15
Pro Pro Leu Leu Pro Leu Leu Leu Leu Leu Cys Val Leu Gly Ala Pro
                    20                  25                  30
Arg Ala Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro Gln Asp Pro
                35                  40                  45
```

```
Thr Leu Leu Ile Gly Ser Ser Leu Leu Ala Thr Cys Ser Val His Gly
        50                  55                  60
Asp Pro Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Leu Asn Gly
65                  70                  75                  80
Arg Arg Leu Pro Pro Glu Leu Ser Arg Val Leu Asn Ala Ser Thr Leu
                    85                  90                  95
Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Arg Ser Gly Asp
                    100                 105                 110
Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly Ser Cys
```

```
              115                 120                 125
Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Val Asn Ile Ser Cys Trp
        130                 135                 140
Ser Lys Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly Ala His
145                 150                 155                 160
```

Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys Leu Arg
               165   170   175

Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr Val Gly Pro
               180   185   190

His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr Pro Tyr Glu
               195   200   205

Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg Ser Asp Val
            210   215   220

Leu Thr Leu Asp Ile Leu Asp Val Val Thr Thr Asp Pro Pro Pro Asp
225   230   235   240

Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu Ser Val Arg
               245   250   255

Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln Ala Lys Tyr
               260   265   270

Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys Val Val Asp
               275   280   285

Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu Lys Pro Gly
            290   295   300

Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr Gly
305   310   315   320

Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro Thr Ala Ala
               325   330   335

Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly Ala Cys Glu
               340   345   350

Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg Glu Leu Lys
               355   360   365

Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser Asn Leu Ser
            370   375   380

Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys Ser His Lys
385   390   395   400

Thr Arg Asn Gln Asp Glu Gly Ile Leu Pro Ser Gly Arg Arg Gly Thr

                    405   410   415
Ala Arg Gly Pro Ala Arg
            420

<210>   85

<211>   196

<212>   PRT

<213>   Homo sapiens

<400>   85

Met Thr Leu Gln Cys Thr Lys Ser Ala Gly Pro Trp Lys Met Val Val
 1   5   10   15

Trp Asp Glu Asp Gly Phe Gln Gly Arg Arg His Glu Phe Thr Ala Glu
                20   25   30

Cys Pro Ser Val Leu Glu Leu Gly Phe Glu Thr Val Arg Ser Leu Lys

            35   40   45
Val Leu Ser Gly Ala Trp Val Gly Phe Glu His Ala Gly Phe Gln Gly
        50   55   60

Gln Gln Tyr Ile Leu Glu Arg Gly Glu Tyr Pro Ser Trp Asp Ala Trp
 65   70   75   80

Gly Gly Asn Thr Ala Tyr Pro Ala Glu Arg Leu Thr Ser Phe Arg Pro
                85   90   95

Ala Ala Cys Ala Asn His Arg Asp Ser Arg Leu Thr Ile Phe Glu Gln
            100   105   110

Glu Asn Phe Leu Gly Lys Lys Gly Glu Leu Ser Asp Asp Tyr Pro Ser
            115   120   125

Leu Gln Ala Met Gly Trp Glu Gly Asn Glu Val Gly Ser Phe His Val
        130   135   140

His Ser Gly Ala Trp Val Cys Ser Gln Phe Pro Gly Tyr Arg Gly Phe
145   150   155   160

Gln Tyr Val Leu Glu Cys Asp His His Ser Gly Asp Tyr Lys His Phe
                165   170   175

Arg Glu Trp Gly Ser His Ala Pro Thr Phe Gln Val Gln Ser Ile Arg

            180   185   190

Arg Ile Gln Gln

    195

<210>   86

<211>   383

<212>   PRT

<213>   Homo sapiens

<400>   86

Met Thr Ala Thr Glu Ala Leu Leu Arg Val Leu Leu Leu Leu Ala

1   5   10   15

Phe Gly His Ser Thr Tyr Gly Ala Glu Cys Phe Pro Ala Cys Asn Pro

               20   25   30

Gln Asn Gly Phe Cys Glu Asp Asp Asn Val Cys Arg Cys Gln Pro Gly

         35   40   45

Trp Gln Gly Pro Leu Cys Asp Gln Cys Val Thr Ser Pro Gly Cys Leu

        50   55   60

His Gly Leu Cys Gly Glu Pro Gly Gln Cys Ile Cys Thr Asp Gly Trp

 65   70   75   80

Asp Gly Glu Leu Cys Asp Arg Asp Val Arg Ala Cys Ser Ser Ala Pro

             85   90   95

Cys Ala Asn Asn Gly Thr Cys Val Ser Leu Asp Asp Gly Leu Tyr Glu

           100   105   110

Cys Ser Cys Ala Pro Gly Tyr Ser Gly Lys Asp Cys Gln Lys Lys Asp

           115   120   125

Gly Pro Cys Val Ile Asn Gly Ser Pro Cys Gln His Gly Gly Thr Cys

           130   135   140

Val Asp Asp Glu Gly Arg Ala Ser His Ala Ser Cys Leu Cys Pro Pro

145   150   155   160

Gly Phe Ser Gly Asn Phe Cys Glu Ile Val Ala Asn Ser Cys Thr Pro

           165   170   175

Asn Pro Cys Glu Asn Asp Gly Val Cys Thr Asp Ile Gly Gly Asp Phe

           180   185   190

Arg Cys Arg Cys Pro Ala Gly Phe Ile Asp Lys Thr Cys Ser Arg Pro

```
            195                 200                 205

Val Thr Asn Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Thr Cys Leu
        210                 215                 220

Gln His Thr Gln Val Ser Tyr Glu Cys Leu Cys Lys Pro Glu Phe Thr
225                 230                 235                 240

Gly Leu Thr Cys Val Lys Lys Arg Ala Leu Ser Pro Gln Gln Val Thr
                245                 250                 255

Arg Leu Pro Ser Gly Tyr Gly Leu Ala Tyr Arg Leu Thr Pro Gly Val


                260                 265                 270

His Glu Leu Pro Val Gln Gln Pro Glu His Arg Ile Leu Lys Val Ser
                275                 280                 285

Met Lys Glu Leu Asn Lys Lys Thr Pro Leu Leu Thr Glu Gly Gln Ala
        290                 295                 300

Ile Cys Phe Thr Ile Leu Gly Val Leu Thr Ser Leu Val Val Leu Gly
305                 310                 315                 320

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


Leu Arg Tyr Asn His Met Leu Arg Lys Lys Lys Asn Leu Leu Leu Gln
                340                 345                 350

Tyr Asn Ser Gly Glu Asp Leu Ala Val Asn Ile Ile Phe Pro Glu Lys
        355                 360                 365

Ile Asp Met Thr Thr Phe Ser Lys Glu Ala Gly Asp Glu Glu Ile
    370                 375                 380
```

<210> 87

<211> 569

<212> PRT

<213> Homo sapiens

<400> 87

```
Met Lys Lys Lys Leu Val Val Leu Gly Leu Leu Ala Val Val Leu Val
  1                 5                  10                 15



Leu Val Ile Val Gly Leu Cys Leu Trp Leu Pro Ser Ala Ser Lys Glu
                20                  25                 30
```

Pro Asp Asn His Val Tyr Thr Arg Ala Ala Val Ala Ala Asp Ala Lys

      35   40   45

Gln Cys Ser Lys Ile Gly Arg Asp Ala Leu Arg Asp Gly Gly Ser Ala

     50   55   60

Val Asp Ala Ala Ile Ala Ala Leu Leu Cys Val Gly Leu Met Asn Ala

65   70   75   80

His Ser Met Gly Ile Gly Gly Gly Leu Phe Leu Thr Ile Tyr Asn Ser

                   85   90   95

Thr Thr Arg Lys Ala Glu Val Ile Asn Ala Arg Glu Val Ala Pro Arg

         100   105   110

Leu Ala Phe Ala Thr Met Phe Asn Ser Ser Glu Gln Ser Gln Lys Gly

        115   120   125

Gly Leu Ser Val Ala Val Pro Gly Glu Ile Arg Gly Tyr Glu Leu Ala

     130   135   140

His Gln Arg His Gly Arg Leu Pro Trp Ala Arg Leu Phe Gln Pro Ser

145   150   155   160

Ile Gln Leu Ala Arg Gln Gly Phe Pro Val Gly Lys Gly Leu Ala Ala

               165   170   175

Ala Leu Glu Asn Lys Arg Thr Val Ile Glu Gln Gln Pro Val Leu Cys

        180   185   190

Glu Val Phe Cys Arg Asp Arg Lys Val Leu Arg Glu Gly Glu Arg Leu

        195   200   205

Thr Leu Pro Gln Leu Ala Asp Thr Tyr Glu Thr Leu Ala Ile Glu Gly

     210   215   220

Ala Gln Ala Phe Tyr Asn Gly Ser Leu Thr Ala Gln Ile Val Lys Asp

225   230   235   240

Ile Gln Ala Ala Gly Gly Ile Val Thr Ala Glu Asp Leu Asn Asn Tyr

         245   250   255

Arg Ala Glu Leu Ile Glu His Pro Leu Asn Ile Ser Leu Gly Asp Val

        260   265   270

Val Leu Tyr Met Pro Ser Ala Pro Leu Ser Gly Pro Val Leu Ala Leu

        275   280   285

Ile Leu Asn Ile Leu Lys Gly Tyr Asn Phe Ser Arg Glu Ser Val Glu
290   295   300

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

Arg Phe Ala Tyr Ala Lys Arg Thr Leu Leu Gly Asp Pro Lys Phe Val
                325   330   335

Asp Val Thr Glu Val Val Arg Asn Met Thr Ser Glu Phe Phe Ala Ala
                340   345   350

Gln Leu Arg Ala Gln Ile Ser Asp Asp Thr Thr His Pro Ile Ser Tyr
                355   360   365

Tyr Lys Pro Glu Phe Tyr Thr Pro Asp Asp Gly Gly Thr Ala His Leu

        370   375   380

Ser Val Val Ala Glu Asp Gly Ser Ala Val Ser Ala Thr Ser Thr Ile
385   390   395   400

Asn Leu Tyr Phe Gly Ser Lys Val Arg Ser Pro Val Ser Gly Ile Leu
                405   410   415

Phe Asn Asn Glu Met Asp Asp Phe Ser Ser Pro Ser Ile Thr Asn Glu
                420   425   430

Phe Gly Val Pro Pro Ser Pro Ala Asn Phe Ile Gln Pro Gly Lys Gln
                435   440   445

Pro Leu Ser Ser Met Cys Pro Thr Ile Met Val Gly Gln Asp Gly Gln
        450   455   460

Val Arg Met Val Val Gly Ala Ala Gly Gly Thr Gln Ile Thr Thr Ala
465   470   475   480

Thr Ala Leu Ala Ile Ile Tyr Asn Leu Trp Phe Gly Tyr Asp Val Lys
                485   490   495

Arg Ala Val Glu Glu Pro Arg Leu His Asn Gln Leu Leu Pro Asn Val
                500   505   510

Thr Thr Val Glu Arg Asn Ile Asp Gln Ala Val Thr Ala Ala Leu Glu

        515   520   525

Thr Arg His His His Thr Gln Ile Ala Ser Thr Phe Ile Ala Val Val

```
                 530                   535                   540
Gln Ala Ile Val Arg Thr Ala Gly Gly Trp Ala Ala Ala Ser Asp Ser

545                   550                   555                   560
Arg Lys Gly Gly Glu Pro Ala Gly Tyr

                 565
```

<210> 88

<211> 1233

<212> PRT

<213> Homo sapiens

<400> 88

```
Met Pro Pro Ser Trp Ser Pro Leu Met Cys Gly Arg Ala Ala Glu Ala


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

                 20                   25                   30
Arg Arg Leu Gly Ala Gly Ala Arg Ala Ala Pro Arg Arg Ala Met Asp

            35                   40                   45
Gly Arg Thr Pro Arg Pro Gln Asp Ala Pro Ala Arg Arg Glu Ile Ala

       50                   55                   60
Gly Ser Trp Arg Lys Pro Lys Ala Lys Ala Pro Leu Pro Pro Ala Glu

 65                   70                   75                   80


Thr Lys Tyr Thr Asp Val Ser Ser Ala Ala Asp Ser Val Glu Ser Thr
                      85                   90                   95
Ala Phe Ile Met Glu Gln Lys Glu Asn Met Ile Asp Lys Asp Val Glu
                 100                  105                  110
Leu Ser Val Val Leu Pro Gly Asp Ile Ile Lys Ser Thr Thr Val His
            115                  120                  125
Gly Ser Lys Pro Met Met Asp Leu Leu Ile Phe Leu Cys Ala Gln Tyr
       130                  135                  140
His Leu Asn Pro Ser Ser Tyr Thr Ile Asp Leu Leu Ser Ala Glu Gln


145                  150                  155                  160
Asn His Ile Lys Phe Lys Pro Asn Thr Pro Ile Gly Met Leu Glu Val
                 165                  170                  175
```

Glu Lys Val Ile Leu Lys Pro Lys Met Leu Asp Lys Lys Pro Thr
                180   185   190

Pro Ile Ile Pro Glu Lys Thr Val Arg Val Val Ile Asn Phe Lys Lys
          195   200   205

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

Leu Ala Pro Ile Ile Cys Ser Lys Cys Glu Phe Asp Pro Leu His Thr
225   230   235   240

Leu Leu Leu Lys Asp Tyr Gln Ser Gln Glu Pro Leu Asp Leu Thr Lys
               245   250   255

Ser Leu Asn Asp Leu Gly Leu Arg Glu Leu Tyr Ala Met Asp Val Asn
          260   265   270

Arg Ala Thr Ser Val Thr Val Phe Ser Lys Ser Ser Leu Gln Glu Ser
          275   280   285

Cys Gln Ile Ser Gln Asn Leu Asp Ile Met Lys Glu Lys Glu Asn Lys

     290   295   300

Gly Phe Phe Ser Phe Phe Gln Arg Ser Lys Lys Lys Arg Asp Gln Thr
305   310   315   320

Ala Ser Ala Pro Ala Thr Pro Leu Val Asn Lys His Arg Pro Thr Phe
               325   330   335

Thr Arg Ser Asn Thr Ile Ser Lys Pro Tyr Ile Ser Asn Thr Leu Pro
          340   345   350

Ser Asp Ala Pro Lys Lys Arg Arg Ala Pro Leu Pro Pro Met Pro Ala
          355   360   365

Ser Gln Ser Val Pro Gln Asp Leu Ala His Ile Gln Glu Arg Pro Ala
          370   375   380

Ser Cys Ile Val Lys Ser Met Ser Val Asp Glu Thr Asp Lys Ser Pro
385   390   395   400

Cys Glu Ala Gly Arg Val Arg Ala Gly Ser Leu Gln Leu Ser Ser Met
               405   410   415

Ser Ala Gly Asn Ser Ser Leu Arg Arg Thr Lys Arg Lys Ala Pro Ser
               420   425   430

Pro Pro Ser Lys Ile Pro Pro His Gln Ser Asp Glu Asn Ser Arg Val

            435   440   445

Thr Ala Leu Gln Pro Val Asp Gly Val Pro Pro Asp Ser Ala Ser Glu

    450   455   460

Ala Asn Ser Pro Glu Glu Leu Ser Ser Pro Glu Thr Phe His Pro Gly

465   470   475   480

Leu Ser Ser Gln Glu Gln Cys Thr Ala Pro Lys Leu Met Glu Glu Thr

            485   490   495

Ser Val Phe Glu Cys Pro Gly Thr Pro Glu Ala Ala Ile Thr Ser Leu

            500   505   510

Thr Ser Gly Ile Ser Ser Asp Tyr Ser Leu Glu Glu Ile Asp Glu Lys

            515   520   525

Glu Glu Leu Ser Glu Val Pro Lys Val Glu Ala Glu Asn Ile Ser Pro

    530   535   540

Lys Ser Gln Asp Ile Pro Phe Val Ser Thr Asp Ile Ile Asn Thr Leu

545   550   555   560

Lys Asn Asp Pro Asp Ser Ala Leu Gly Asn Gly Ser Gly Glu Phe Ser

            565   570   575

Gln Asn Ser Met Glu Glu Lys Gln Glu Thr Lys Ser Thr Asp Gly Gln

            580   585   590

Glu Pro His Ser Val Val Tyr Asp Thr Ser Asn Gly Lys Lys Val Val

            595   600   605

Asp Ser Ile Arg Asn Leu Lys Ser Leu Gly Pro Asn Gln Glu Asn Val

    610   615   620

Val Gln Asn Glu Ile Ile Val Tyr Pro Glu Asn Thr Glu Asp Asn Met

625   630   635   640

Lys Asn Gly Val Lys Lys Thr Glu Ile Asn Val Glu Gly Val Ala Lys

            645   650   655

Asn Asn Asn Ile Asp Met Glu Val Glu Arg Pro Ser Asn Ser Glu Ala

            660   665   670

His Glu Thr Asp Thr Ala Ile Ser Tyr Lys Glu Asn His Leu Ala Ala

```
              675                 680                 685
Ser Ser Val Pro Asp Gln Lys Leu Asn Gln Pro Ser Ala Glu Lys Thr
     690                 695                 700
Lys Asp Ala Ala Ile Gln Thr Thr Pro Ser Cys Asn Ser Phe Asp Gly
705                 710                 715                 720
Lys His Gln Asp His Asn Leu Ser Asp Ser Lys Val Glu Glu Cys Val


              725                 730                 735
Gln Thr Ser Asn Asn Asn Ile Ser Thr Gln His Ser Cys Leu Ser Ser
              740                 745                 750
Gln Asp Ser Val Asn Thr Ser Arg Glu Phe Arg Ser Gln Gly Thr Leu
          755                 760                 765
Ile Ile His Ser Glu Asp Pro Leu Thr Val Lys Asp Pro Ile Cys Ala
      770                 775                 780
His Gly Asn Asp Asp Leu Leu Pro Pro Val Asp Arg Ile Asp Lys Asn
785                 790                 795                 800


Ser Thr Ala Ser Tyr Leu Lys Asn Tyr Pro Leu Tyr Arg Gln Asp Tyr
                  805                 810                 815
Asn Pro Lys Pro Lys Pro Ser Asn Glu Ile Thr Arg Glu Tyr Ile Pro
              820                 825                 830
Lys Ile Gly Met Thr Thr Tyr Lys Ile Val Pro Pro Lys Ser Leu Glu
          835                 840                 845
Ile Ser Lys Asp Trp Gln Ser Glu Thr Ile Glu Tyr Lys Asp Asp Gln
      850                 855                 860
Asp Met His Ala Leu Gly Lys Lys His Thr His Glu Asn Val Lys Glu


865                 870                 875                 880
Thr Ala Ile Gln Thr Glu Asp Ser Ala Ile Ser Glu Ser Pro Glu Glu
                  885                 890                 895
Pro Leu Pro Asn Leu Lys Pro Lys Pro Asn Leu Arg Thr Glu His Gln
              900                 905                 910
Val Pro Ser Ser Val Ser Ser Pro Asp Asp Ala Met Val Ser Pro Leu
          915                 920                 925
Lys Pro Ala Pro Lys Met Thr Arg Asp Thr Gly Thr Ala Pro Phe Ala
```

930		935		940	

Pro Asn Leu Glu Glu Ile Asn Asn Ile Leu Glu Ser Lys Phe Lys Ser
945   950   955   960

Arg Ala Ser Asn Ala Gln Ala Lys Pro Ser Ser Phe Phe Leu Gln Met
    965   970   975

Gln Lys Arg Val Ser Gly His Tyr Val Thr Ser Ala Ala Ala Lys Ser
    980   985   990

Val His Ala Ala Pro Asn Pro Ala Pro Lys Glu Leu Thr Asn Lys Glu
    995   1000   1005

Ala Glu Arg Asp Met Leu Pro Ser Pro Glu Gln Thr Leu Ser Pro Leu

    1010   1015   1020

Ser Lys Met Pro His Ser Val Pro Gln Pro Leu Val Glu Lys Thr Asp
1025   1030   1035   1040

Asp Asp Val Ile Gly Gln Ala Pro Ala Glu Ala Ser Pro Pro Pro Ile
    1045   1050   1055

Ala Pro Lys Pro Val Thr Ile Pro Ala Ser Gln Val Ser Thr Gln Asn
    1060   1065   1070

Leu Lys Thr Leu Lys Thr Phe Gly Ala Pro Arg Pro Tyr Ser Ser Ser
    1075   1080   1085

Gly Pro Ser Pro Phe Ala Leu Ala Val Val Lys Arg Ser Gln Ser Phe
    1090   1095   1100

Ser Lys Glu Arg Thr Glu Ser Pro Ser Ala Ser Ala Leu Val Gln Pro
1105   1110   1115   1120

Pro Ala Asn Thr Glu Glu Gly Lys Thr His Ser Val Asn Lys Phe Val
    1125   1130   1135

Asp Ile Pro Gln Leu Gly Val Ser Asp Lys Glu Asn Asn Ser Ala His
    1140   1145   1150

Asn Glu Gln Asn Ser Gln Ile Pro Thr Pro Thr Asp Gly Pro Ser Phe

    1155   1160   1165

Thr Val Met Arg Gln Ser Ser Leu Thr Phe Gln Ser Ser Asp Pro Glu
    1170   1175   1180

Gln Met Arg Gln Ser Leu Leu Thr Ala Ile Arg Ser Gly Glu Ala Ala

1185   1190   1195   1200

Ala Lys Leu Lys Arg Val Thr Ile Pro Ser Asn Thr Ile Ser Val Asn

               1205   1210   1215

Gly Arg Ser Arg Leu Ser His Ser Met Ser Pro Asp Ala Gln Asp Gly

          1220   1225   1230

His

<210>   89

<211>   129

<212>   PRT

<213>   Homo sapiens

<400>   89

Met Ser Gly Arg Gly Lys Gln Gly Gly Lys Val Arg Ala Lys Ala Lys

 1   5   10   15

Ser Arg Ser Ser Arg Ala Gly Leu Gln Phe Pro Val Gly Arg Val His

               20   25   30

Arg Leu Leu Arg Lys Gly Asn Tyr Ala Glu Arg Val Gly Ala Gly Ala

          35   40   45

Pro Val Tyr Leu Ala Ala Val Leu Glu Tyr Leu Thr Ala Glu Ile Leu

    50   55   60

Glu Leu Ala Gly Asn Ala Ala Arg Asp Asn Lys Lys Thr Arg Ile Ile

 65   70   75   80

Pro Arg His Leu Gln Leu Ala Ile Arg Asn Asp Glu Glu Leu Asn Lys

               85   90   95

Leu Leu Gly Lys Val Thr Ile Ala Gln Gly Gly Val Leu Pro Asn Ile

               100   105   110

Gln Ala Val Leu Leu Pro Lys Lys Thr Glu Ser Gln Lys Thr Lys Ser

          115   120   125

Lys

<210>   90

<211>   662

<212>   PRT

<213>   Homo sapiens

<400>   90

Met Met Glu Pro Glu Glu Tyr Arg Glu Arg Gly Arg Glu Met Val Asp
 1   5   10   15

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

Asp Val Gln Pro Gly Tyr Leu Arg Ala Gln Leu Pro Glu Ser Ala Pro
            35   40   45

Glu Asp Pro Asp Ser Trp Asp Ser Ile Phe Gly Asp Ile Glu Arg Ile

            50   55   60

Ile Met Pro Gly Val Val His Trp Gln Ser Pro His Met His Ala Tyr
 65   70   75   80

Tyr Pro Ala Leu Thr Ser Trp Pro Ser Leu Leu Gly Asp Met Leu Ala
                85   90   95

Asp Ala Ile Asn Cys Leu Gly Phe Thr Trp Ala Ser Ser Pro Ala Cys
                100   105   110

Thr Glu Leu Glu Met Asn Val Met Asp Trp Leu Ala Lys Met Leu Gly
            115   120   125

Leu Pro Glu His Phe Leu His His His Pro Ser Ser Gln Gly Gly Gly
            130   135   140

Val Leu Gln Ser Thr Val Ser Glu Ser Thr Leu Ile Ala Leu Leu Ala
145   150   155   160

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

Asp Glu Ser Cys Leu Asn Ala Arg Leu Val Ala Tyr Ala Ser Asp Gln
                180   185   190

Ala His Ser Ser Val Glu Lys Ala Gly Leu Ile Ser Leu Val Lys Met

                195   200   205

Lys Phe Leu Pro Val Asp Asp Asn Phe Ser Leu Arg Gly Glu Ala Leu
            210   215   220

Gln Lys Ala Ile Glu Glu Asp Lys Gln Arg Gly Leu Val Pro Val Phe
225   230   235   240

Val Cys Ala Thr Leu Gly Thr Thr Gly Val Cys Ala Phe Asp Cys Leu
                 245   250   255

Ser Glu Leu Gly Pro Ile Cys Ala Arg Glu Gly Leu Trp Leu His Ile
                 260   265   270

Asp Ala Ala Tyr Ala Gly Thr Ala Phe Leu Cys Pro Glu Phe Arg Gly
                 275   280   285

Phe Leu Lys Gly Ile Glu Tyr Ala Asp Ser Phe Thr Phe Asn Pro Ser
     290   295   300

Lys Trp Met Met Val His Phe Asp Cys Thr Gly Phe Trp Val Lys Asp
305   310   315   320

Lys Tyr Lys Leu Gln Gln Thr Phe Ser Val Asn Pro Ile Tyr Leu Arg
                 325   330   335

His Ala Asn Ser Gly Val Ala Thr Asp Phe Met His Trp Gln Ile Pro

                 340   345   350

Leu Ser Arg Arg Phe Arg Ser Val Lys Leu Trp Phe Val Ile Arg Ser
                 355   360   365

Phe Gly Val Lys Asn Leu Gln Ala His Val Arg His Gly Thr Glu Met
     370   375   380

Ala Lys Tyr Phe Glu Ser Leu Val Arg Asn Asp Pro Ser Phe Glu Ile
385   390   395   400

Pro Ala Lys Arg His Leu Gly Leu Val Val Phe Arg Leu Lys Gly Pro
                 405   410   415

Asn Cys Leu Thr Glu Asn Val Leu Lys Glu Ile Ala Lys Ala Gly Arg
                 420   425   430

Leu Phe Leu Ile Pro Ala Thr Ile Gln Asp Lys Leu Ile Ile Arg Phe
     435   440   445

Thr Val Thr Ser Gln Phe Thr Thr Arg Asp Asp Ile Leu Arg Asp Trp
     450   455   460

Asn Leu Ile Arg Asp Ala Ala Thr Leu Ile Leu Ser Gln His Cys Thr
465   470   475   480

Ser Gln Pro Ser Pro Arg Val Gly Asn Leu Ile Ser Gln Ile Arg Gly

                    485   490   495

Ala Arg Ala Trp Ala Cys Gly Thr Ser Leu Gln Ser Val Ser Gly Ala
            500   505   510

Gly Asp Asp Pro Val Gln Ala Arg Lys Ile Ile Lys Gln Pro Gln Arg
            515   520   525

Val Gly Ala Gly Pro Met Lys Arg Glu Asn Gly Leu His Leu Glu Thr
        530   535   540

Leu Leu Asp Pro Val Asp Asp Cys Phe Ser Glu Glu Ala Pro Asp Ala
545   550   555   560

Thr Lys His Lys Leu Ser Ser Phe Leu Phe Ser Tyr Leu Ser Val Gln
                    565   570   575

Thr Lys Lys Lys Thr Val Arg Ser Leu Ser Cys Asn Ser Val Pro Val
            580   585   590

Ser Ala Gln Lys Pro Leu Pro Thr Glu Ala Ser Val Lys Asn Gly Gly
            595   600   605

Ser Ser Arg Val Arg Ile Phe Ser Arg Phe Pro Glu Asp Met Met Met
        610   615   620

Leu Lys Lys Ser Ala Phe Lys Lys Leu Ile Lys Phe Tyr Ser Val Pro

625   630   635   640

Ser Phe Pro Glu Cys Ser Ser Gln Cys Gly Leu Gln Leu Pro Cys Cys
                    645   650   655

Pro Leu Gln Ala Met Val
            660

<210>   91

<211>   136

<212>   PRT

<213>   Homo sapiens

<400>   91

Met Ala Arg Thr Lys Gln Thr Ala Arg Lys Ser Thr Gly Gly Lys Ala
    1   5   10   15

Pro Arg Lys Gln Leu Ala Thr Lys Ala Ala Arg Lys Ser Ala Pro Ala

                       20   25   30

Thr Gly Gly Val Lys Lys Pro His Arg Tyr Arg Pro Gly Thr Val Ala

            35   40   45

Leu Arg Glu Ile Arg Arg Tyr Gln Lys Ser Thr Glu Leu Leu Ile Arg

          50   55   60

Lys Leu Pro Phe Gln Arg Leu Val Arg Glu Ile Ala Gln Asp Phe Lys

65   70   75   80

Thr Asp Leu Arg Phe Gln Ser Ser Ala Val Met Ala Leu Gln Glu Ala

                   85   90   95

Cys Glu Ala Tyr Leu Val Gly Leu Phe Glu Asp Thr Asn Leu Cys Ala

                   100   105   110

Ile His Ala Lys Arg Val Thr Ile Met Pro Lys Asp Ile Gln Leu Ala

             115   120   125

Arg Arg Ile Arg Gly Glu Arg Ala

    130   135

<210> 92

<211> 367

<212> PRT

<213> Homo sapiens

<400> 92

Met Ala Tyr Arg Val Leu Gly Arg Ala Gly Pro Pro Gln Pro Arg Arg

  1   5   10   15

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

                   20   25   30

Leu Cys Tyr Ser Phe Leu Cys Cys Cys Asp Asp Leu Gly Arg Ser Arg

            35   40   45

Leu Leu Gly Ala Pro Arg Cys Leu Arg Gly Pro Ser Ala Gly Gly Gln

          50   55   60

Lys Leu Leu Gln Lys Ser Arg Pro Cys Asp Pro Ser Gly Pro Thr Pro

65   70   75   80

Ser Glu Pro Ser Ala Pro Ser Ala Pro Ala Ala Ala Val Pro Ala Pro

                                 85   90   95

Arg Leu Ser Gly Ser Asn His Ser Gly Ser Pro Lys Leu Gly Thr Lys

             100   105   110

Arg Leu Pro Gln Ala Leu Ile Val Gly Val Lys Lys Gly Gly Thr Arg

        115   120   125

Ala Val Leu Glu Phe Ile Arg Val His Pro Asp Val Arg Ala Leu Gly

    130   135   140

Thr Glu Pro His Phe Phe Asp Arg Asn Tyr Gly Arg Gly Leu Asp Trp

145   150   155   160

Tyr Arg Ser Leu Met Pro Arg Thr Leu Glu Ser Gln Ile Thr Leu Glu

             165   170   175

Lys Thr Pro Ser Tyr Phe Val Thr Gln Glu Ala Pro Arg Arg Ile Phe

        180   185   190

Asn Met Ser Arg Asp Thr Lys Leu Ile Val Val Val Arg Asn Pro Val

        195   200   205

Thr Arg Ala Ile Ser Asp Tyr Thr Gln Thr Leu Ser Lys Lys Pro Asp

    210   215   220

Ile Pro Thr Phe Glu Gly Leu Ser Phe Arg Asn Arg Thr Leu Gly Leu

225   230   235   240

Val Asp Val Ser Trp Asn Ala Ile Arg Ile Gly Met Tyr Val Leu His

             245   250   255

Leu Glu Ser Trp Leu Gln Tyr Phe Pro Leu Ala Gln Ile His Phe Val

             260   265   270

Ser Gly Glu Arg Leu Ile Thr Asp Pro Ala Gly Glu Met Gly Arg Val

             275   280   285

Gln Asp Phe Leu Gly Ile Lys Arg Phe Ile Thr Asp Lys His Phe Tyr

    290   295   300

Phe Asn Lys Thr Lys Gly Phe Pro Cys Leu Lys Lys Thr Glu Ser Ser

305   310   315   320

Leu Leu Pro Arg Cys Leu Gly Lys Ser Lys Gly Arg Thr His Val Gln

<div style="text-align:center">325   330   335</div>

Ile Asp Pro Glu Val Ile Asp Gln Leu Arg Glu Phe Tyr Arg Pro Tyr

<div style="text-align:center">340   345   350</div>

Asn Ile Lys Phe Tyr Glu Thr Val Gly Gln Asp Phe Arg Trp Glu

<div style="text-align:center">355   360   365</div>

<210> 93

<211> 103

<212> PRT

<213> Homo sapiens

<400> 93

Met Ser Gly Arg Gly Lys Gly Gly Lys Gly Leu Gly Lys Gly Gly Ala

1   5   10   15

Lys Arg His Arg Lys Val Leu Arg Asp Asn Ile Gln Gly Ile Thr Lys

20   25   30

Pro Ala Ile Arg Arg Leu Ala Arg Arg Gly Gly Val Lys Arg Ile Ser

35   40   45

Gly Leu Ile Tyr Glu Glu Thr Arg Gly Val Leu Lys Val Phe Leu Glu

50   55   60

Asn Val Ile Arg Asp Ala Val Thr Tyr Thr Glu His Ala Lys Arg Lys

65   70   75   80

Thr Val Thr Ala Met Asp Val Val Tyr Ala Leu Lys Arg Gln Gly Arg

85   90   95

Thr Leu Tyr Gly Phe Gly Gly

100

<210> 94

<211> 283

<212> PRT

<213> Homo sapiens

<400> 94

Met Ala His Arg Gly Ala His Phe Ala Phe Arg Ser Arg Trp Gln Lys

1   5   10   15

Thr Asp Asp Glu Leu Cys Arg His Ser Met Ser Phe Ile Leu His Lys

<div style="text-align:center">- 202 -</div>

```
                20                  25                  30
Ala Ile Arg Asn Asp Phe Phe Gln Ser Tyr Leu Tyr Leu Leu Glu Lys
        35                  40                  45
Ile Pro Leu Val Lys Leu Tyr Ala Leu Thr Ser Gln Val Ile Asn Gly
    50                  55                  60
Glu Met Gln Phe Tyr Ala Arg Ala Lys Leu Phe Tyr Gln Glu Val Pro
65                  70                  75                  80
Ala Thr Glu Glu Gly Met Met Gly Asn Phe Ile Glu Leu Ser Ser Pro


                    85                  90                  95
Asp Ile Gln Ala Ser Gln Lys Phe Leu Arg Lys Phe Val Gly Gly Pro
            100                 105                 110
Gly Arg Ala Gly Thr Asp Cys Ala Leu Asp Cys Gly Ser Gly Ile Gly
        115                 120                 125
Arg Val Ser Lys His Val Leu Leu Pro Val Phe Asn Ser Val Glu Leu
    130                 135                 140
Val Asp Met Met Glu Ser Phe Leu Leu Glu Ala Gln Asn Tyr Leu Gln
145                 150                 155                 160


Val Lys Gly Asp Lys Val Glu Ser Tyr His Cys Tyr Ser Leu Gln Glu
                165                 170                 175
Phe Thr Pro Pro Phe Arg Arg Tyr Asp Val Ile Trp Ile Gln Trp Val
            180                 185                 190
Ser Gly His Leu Thr Asp Lys Asp Leu Leu Ala Phe Leu Ser Arg Cys
        195                 200                 205
Arg Asp Gly Leu Lys Glu Asn Gly Ile Ile Ile Leu Lys Asp Asn Val
    210                 215                 220
Ala Arg Glu Gly Cys Ile Leu Asp Leu Ser Asp Ser Ser Val Thr Arg


225                 230                 235                 240
Asp Met Asp Ile Leu Arg Ser Leu Ile Arg Lys Ser Gly Leu Val Val
            245                 250                 255
Leu Gly Gln Glu Lys Gln Asp Gly Phe Pro Glu Gln Cys Ile Pro Val
        260                 265                 270
Trp Met Phe Ala Leu His Ser Asp Arg His Ser
```

<210>   95

<211>   240

<212>   PRT

<213>   Homo sapiens

<400>   95

Met Tyr Leu Arg Arg Ala Val Ser Lys Thr Leu Ala Leu Pro Leu Arg

1   5   10   15

Ala Pro Pro Asn Pro Ala Pro Leu Gly Lys Asp Ala Ser Leu Arg Arg
                20   25   30

Met Ser Ser Asn Arg Phe Pro Gly Ser Ser Gly Ser Asn Met Ile Tyr
        35   40   45

Tyr Leu Val Val Gly Val Thr Val Ser Ala Gly Gly Tyr Tyr Ala Tyr
     50   55   60

Lys Thr Val Thr Ser Asp Gln Ala Lys His Thr Glu His Lys Thr Asn
65   70   75   80

Leu Lys Glu Lys Thr Lys Ala Glu Ile His Pro Phe Gln Gly Glu Lys
                85   90   95

Glu Asn Val Ala Glu Thr Glu Lys Ala Ser Ser Glu Ala Pro Glu Glu
        100   105   110

Leu Ile Val Glu Ala Glu Val Val Asp Ala Glu Glu Ser Pro Ser Ala
        115   120   125

Thr Val Val Val Ile Lys Glu Ala Ser Ala Cys Pro Gly His Val Glu
     130   135   140

Ala Ala Pro Glu Thr Thr Ala Val Ser Ala Glu Thr Gly Pro Glu Val

145   150   155   160

Thr Asp Ala Ala Ala Arg Glu Thr Thr Glu Val Asn Pro Glu Thr Thr
                165   170   175

Pro Glu Val Thr Asn Ala Ala Leu Asp Glu Ala Val Thr Ile Asp Asn
        180   185   190

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

Glu Glu Glu Asn Ser Pro Ala Glu Ser Glu Ser Ser Ala Gly Asp Asp
210   215   220

Leu Gln Glu Glu Ala Ser Val Gly Ser Glu Ala Ala Ser Ala Gln Gly
225   230   235   240

<210>   96
<211>   267
<212>   PRT
<213>   Homo sapiens
<400>   96

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>   97

<211>   78

<212>   PRT

<213>   Homo sapiens

<400>   97

Met Asp Cys Cys Thr Glu Asn Ala Cys Ser Lys Pro Asp Asp Asp Ile

  1   5   10   15

Leu Asp Ile Pro Leu Asp Asp Pro Gly Ala Asn Ala Ala Ala Ala Lys

                    20   25   30

Ile Gln Ala Ser Phe Arg Gly His Met Ala Arg Lys Lys Ile Lys Ser

          35   40   45

Gly Glu Arg Gly Arg Lys Gly Pro Gly Pro Gly Gly Pro Gly Gly Ala

          50   55   60

Gly Val Ala Arg Gly Gly Ala Gly Gly Gly Pro Ser Gly Asp

 65   70   75

<210>   98

<211>   267

<212>   PRT

<213>   Homo sapiens

<400>   98

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

Gly Leu Leu Ala Thr Val Arg Ala Glu Cys Ser Gln Asp Cys Ala Thr
              20   25   30

Cys Ser Tyr Arg Leu Val Arg Pro Ala Asp Ile Asn Phe Leu Ala Cys
              35   40   45

Val Met Glu Cys Glu Gly Lys Leu Pro Ser Leu Lys Ile Trp Glu Thr
          50   55   60

Cys Lys Glu Leu Leu Gln Leu Ser Lys Pro Glu Leu Pro Gln Asp Gly
65   70   75   80

Thr Ser Thr Leu Arg Glu Asn Ser Lys Pro Glu Glu Ser His Leu Leu
                  85   90   95

Ala Lys Arg Tyr Gly Gly Phe Met Lys Arg Tyr Gly Gly Phe Met Lys
                  100   105   110

Lys Met Asp Glu Leu Tyr Pro Met Glu Pro Glu Glu Glu Ala Asn Gly
                  115   120   125

Ser Glu Ile Leu Ala Lys Arg Tyr Gly Gly Phe Met Lys Lys Asp Ala
          130   135   140

Glu Glu Asp Asp Ser Leu Ala Asn Ser Ser Asp Leu Leu Lys Glu Leu
145   150   155   160

Leu Glu Thr Gly Asp Asn Arg Glu Arg Ser His His Gln Asp Gly Ser
                  165   170   175

Asp Asn Glu Glu Glu Val Ser Lys Arg Tyr Gly Gly Phe Met Arg Gly
                  180   185   190

Leu Lys Arg Ser Pro Gln Leu Glu Asp Glu Ala Lys Glu Leu Gln Lys
                  195   200   205

Arg Tyr Gly Gly Phe Met Arg Arg Val Gly Arg Pro Glu Trp Trp Met
          210   215   220

Asp Tyr Gln Lys Arg Tyr Gly Gly Phe Leu Lys Arg Phe Ala Glu Ala
225   230   235   240

Leu Pro Ser Asp Glu Glu Gly Glu Ser Tyr Ser Lys Glu Val Pro Glu

```
                    245                    250                    255
Met Glu Lys Arg Tyr Gly Gly Phe Met Arg Phe
                    260                    265
```

```
<210>    99
<211>    115
<212>    PRT
<213>    Homo sapiens
<400>    99
```

```
Met Gln Ala Gln Ala Pro Val Val Val Val Thr Gln Pro Gly Val Gly
 1                5                   10                   15

Pro Gly Pro Ala Pro Gln Asn Ser Asn Trp Gln Thr Gly Met Cys Asp
                    20                   25                   30

Cys Phe Ser Asp Cys Gly Val Cys Leu Cys Gly Thr Phe Cys Phe Pro
                    35                   40                   45

Cys Leu Gly Cys Gln Val Ala Ala Asp Met Asn Glu Cys Cys Leu Cys
                 50                   55                   60

Gly Thr Ser Val Ala Met Arg Thr Leu Tyr Arg Thr Arg Tyr Gly Ile
65                   70                   75                   80

Pro Gly Ser Ile Cys Asp Asp Tyr Met Ala Thr Leu Cys Cys Pro His
                       85                   90                   95

Cys Thr Leu Cys Gln Ile Lys Arg Asp Ile Asn Arg Arg Arg Ala Met
                 100                  105                  110

Arg Thr Phe
          115
```

```
<210>    100
<211>    206
<212>    PRT
<213>    Homo sapiens
<400>    100
```

```
Met Ala Leu Pro Cys Thr Leu Gly Leu Gly Met Leu Leu Ala Leu Pro
 1                5                   10                   15

Gly Ala Leu Gly Ser Gly Gly Ser Ala Glu Asp Ser Val Gly Ser Ser
                    20                   25                   30
```

Ser Val Thr Val Val Leu Leu Leu Leu Leu Leu Leu Leu Ala Thr
     35   40   45

Gly Leu Ala Leu Ala Trp Arg Arg Leu Ser Arg Asp Ser Gly Gly Tyr

     50   55   60

Tyr His Pro Ala Arg Leu Gly Ala Ala Leu Trp Gly Arg Thr Arg Arg
65   70   75   80

Leu Leu Trp Ala Ser Pro Pro Gly Arg Trp Leu Gln Ala Arg Ala Glu
          85   90   95

Leu Gly Ser Thr Asp Asn Asp Leu Glu Arg Gln Glu Asp Glu Gln Asp
          100   105   110

Thr Asp Tyr Asp His Val Ala Asp Gly Gly Leu Gln Ala Asp Pro Gly
         115   120   125

Glu Gly Glu Gln Gln Cys Gly Glu Ala Ser Ser Pro Glu Gln Val Pro
         130   135   140

Val Arg Ala Glu Glu Ala Arg Asp Ser Asp Thr Glu Gly Asp Leu Val
145   150   155   160

Leu Gly Ser Pro Gly Pro Ala Ser Ala Gly Gly Ser Ala Glu Ala Leu
         165   170   175

Leu Ser Asp Leu His Ala Phe Ala Gly Ser Ala Ala Trp Asp Asp Ser
         180   185   190

Ala Arg Ala Ala Gly Gly Gln Gly Leu His Val Thr Ala Leu

        195   200   205

<210>   101

<211>   148

<212>   PRT

<213>   Homo sapiens

<400>   101

Met Glu Thr Gly Ala Leu Arg Arg Pro Gln Leu Leu Pro Leu Leu Leu
  1   5   10   15

Leu Leu Cys Gly Gly Cys Pro Arg Ala Gly Gly Cys Asn Glu Thr Gly
          20   25   30

Met Leu Glu Arg Leu Pro Leu Cys Gly Lys Ala Phe Ala Asp Met Met

```
                35                40                45
Gly Lys Val Asp Val Trp Lys Trp Cys Asn Leu Ser Glu Phe Ile Val


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


Leu Thr Val Ala Met Ala Gly Leu Val Val Trp Arg Ser Lys Arg Thr
        130               135               140
Asp Thr Leu Leu
145
```

<210>   102

<211>   184

<212>   PRT

<213>   Homo sapiens

<400>   102

```
Met Asp Gly Leu Arg Gln Arg Val Glu His Phe Leu Glu Gln Arg Asn
 1                 5                10                15
Leu Val Thr Glu Val Leu Gly Ala Leu Glu Ala Lys Thr Gly Val Glu
                    20                25                30
Lys Arg Tyr Leu Ala Ala Gly Ala Val Thr Leu Leu Ser Leu Tyr Leu


                35                40                45
Leu Phe Gly Tyr Gly Ala Ser Leu Leu Cys Asn Leu Ile Gly Phe Val
        50                55                60
Tyr Pro Ala Tyr Ala Ser Ile Lys Ala Ile Glu Ser Pro Ser Lys Asp
 65                70                75                80
Asp Asp Thr Val Trp Leu Thr Tyr Trp Val Val Tyr Ala Leu Phe Gly
                    85                90                95
```

Leu Ala Glu Phe Phe Ser Asp Leu Leu Leu Ser Trp Phe Pro Phe Tyr
            100   105   110

Tyr Val Gly Lys Cys Ala Phe Leu Leu Phe Cys Met Ala Pro Arg Pro
            115   120   125

Trp Asn Gly Ala Leu Met Leu Tyr Gln Arg Val Val Arg Pro Leu Phe
        130   135   140

Leu Arg His His Gly Ala Val Asp Arg Ile Met Asn Asp Leu Ser Gly
145   150   155   160

Arg Ala Leu Asp Ala Ala Ala Gly Ile Thr Arg Asn Val Lys Pro Ser
                165   170   175

Gln Thr Pro Gln Pro Lys Asp Lys

                180

<210>   103
<211>   211
<212>   PRT
<213>   Homo sapiens
<400>   103

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

Arg Lys Glu Leu Lys Ile Val Ile Val Gly Asp Gly Gly Cys Gly Lys
            20   25   30

Thr Ser Leu Leu Met Val Tyr Ser Gln Gly Ser Phe Pro Glu His Tyr
        35   40   45

Ala Pro Ser Val Phe Glu Lys Tyr Thr Ala Ser Val Thr Val Gly Ser

        50   55   60

Lys Glu Val Thr Leu Asn Leu Tyr Asp Thr Ala Gly Gln Glu Asp Tyr
 65   70   75   80

Asp Arg Leu Arg Pro Leu Ser Tyr Gln Asn Thr His Leu Val Leu Ile
                85   90   95

Cys Tyr Asp Val Met Asn Pro Thr Ser Tyr Asp Asn Val Leu Ile Lys
            100   105   110

Trp Phe Pro Glu Val Thr His Phe Cys Arg Gly Ile Pro Met Val Leu

```
                    115                 120                 125

Ile Gly Cys Lys Thr Asp Leu Arg Lys Asp Lys Glu Gln Leu Arg Lys
         130                 135                 140

Leu Arg Ala Ala Gln Leu Glu Pro Ile Thr Tyr Met Gln Gly Leu Ser
145                 150                 155                 160

Ala Cys Glu Gln Ile Arg Ala Ala Leu Tyr Leu Glu Cys Ser Ala Lys
                    165                 170                 175

Phe Arg Glu Asn Val Glu Asp Val Phe Arg Glu Ala Ala Lys Val Ala
                    180                 185                 190

Leu Ser Ala Leu Lys Lys Ala Gln Arg Gln Lys Lys Arg Arg Leu Cys


                    195                 200                 205

Leu Leu Leu
       210
```

<210> 104

<211> 292

<212> PRT

<213> Homo sapiens

<400> 104

```
Met Ser Ser Leu Tyr Pro Ser Leu Glu Asp Leu Lys Val Asp Gln Ala
 1               5                  10                  15

Ile Gln Ala Gln Val Arg Ala Ser Pro Lys Met Pro Ala Leu Pro Val
                 20                  25                  30

Gln Ala Thr Ala Ile Ser Pro Pro Pro Val Leu Tyr Pro Asn Leu Ala
         35                  40                  45


Glu Leu Glu Asn Tyr Met Gly Leu Ser Leu Ser Ser Gln Glu Val Gln
         50                  55                  60

Glu Ser Leu Leu Gln Ile Pro Glu Gly Asp Ser Thr Ala Val Ser Gly
 65                  70                  75                  80

Pro Gly Pro Gly Gln Met Val Ala Pro Val Thr Gly Tyr Ser Leu Gly
                     85                  90                  95

Val Arg Arg Ala Glu Ile Lys Pro Gly Val Arg Glu Ile His Leu Cys
                 100                 105                 110
```

Lys Asp Glu Arg Gly Lys Thr Gly Leu Arg Leu Arg Lys Val Asp Gln

        115   120   125

Gly Leu Phe Val Gln Leu Val Gln Ala Asn Thr Pro Ala Ser Leu Val

     130   135   140

Gly Leu Arg Phe Gly Asp Gln Leu Leu Gln Ile Asp Gly Arg Asp Cys

145   150   155   160

Ala Gly Trp Ser Ser His Lys Ala His Gln Val Val Lys Lys Ala Ser

        165   170   175

Gly Asp Lys Ile Val Val Val Val Arg Asp Arg Pro Phe Gln Arg Thr

        180   185   190

Val Thr Met His Lys Asp Ser Met Gly His Val Gly Phe Val Ile Lys

        195   200   205

Lys Gly Lys Ile Val Ser Leu Val Lys Gly Ser Ser Ala Ala Arg Asn

     210   215   220

Gly Leu Leu Thr Asn His Tyr Val Cys Glu Val Asp Gly Gln Asn Val

225   230   235   240

Ile Gly Leu Lys Asp Lys Lys Ile Met Glu Ile Leu Ala Thr Ala Gly

        245   250   255

Asn Val Val Thr Leu Thr Ile Ile Pro Ser Val Ile Tyr Glu His Met

        260   265   270

Val Lys Lys Leu Pro Pro Val Leu Leu His His Thr Met Asp His Ser

        275   280   285

Ile Pro Asp Ala

     290

<210> 105

<211> 437

<212> PRT

<213> Homo sapiens

<400> 105

Met Asp Gly Asn Asp Asn Val Thr Leu Leu Phe Ala Pro Leu Leu Arg

  1   5   10   15

Asp Asn Tyr Thr Leu Ala Pro Asn Ala Ser Ser Leu Gly Pro Gly Thr

```
                20                  25                  30

Asp Leu Ala Leu Ala Pro Ala Ser Ser Ala Gly Pro Gly Pro Gly Leu
        35                  40                  45

Ser Leu Gly Pro Gly Pro Ser Phe Gly Phe Ser Pro Gly Pro Thr Pro
    50                  55                  60

Thr Pro Glu Pro Thr Thr Ser Gly Leu Ala Gly Gly Ala Ala Ser His
65                  70                  75                  80

Gly Pro Ser Pro Phe Pro Arg Pro Trp Ala Pro His Ala Leu Pro Phe
                85                  90                  95

Trp Asp Thr Pro Leu Asn His Gly Leu Asn Val Phe Val Gly Ala Ala


                100                 105                 110

Leu Cys Ile Thr Met Leu Gly Leu Gly Cys Thr Val Asp Val Asn His
        115                 120                 125

Phe Gly Ala His Val Arg Arg Pro Val Gly Ala Leu Leu Ala Ala Leu
    130                 135                 140

Cys Gln Phe Gly Leu Leu Pro Leu Leu Ala Phe Leu Leu Ala Leu Ala
145                 150                 155                 160

Phe Lys Leu Asp Glu Val Ala Ala Val Ala Val Leu Leu Cys Gly Cys
                165                 170                 175



Cys Pro Gly Gly Asn Leu Ser Asn Leu Met Ser Leu Leu Val Asp Gly
                180                 185                 190

Asp Met Asn Leu Ser Ile Ile Met Thr Ile Ser Ser Thr Leu Leu Ala
        195                 200                 205

Leu Val Leu Met Pro Leu Cys Leu Trp Ile Tyr Ser Trp Ala Trp Ile
    210                 215                 220

Asn Thr Pro Ile Val Gln Leu Leu Pro Leu Gly Thr Val Thr Leu Thr
225                 230                 235                 240

Leu Cys Ser Thr Leu Ile Pro Ile Gly Leu Gly Val Phe Ile Arg Tyr


                245                 250                 255

Lys Tyr Ser Arg Val Ala Asp Tyr Ile Val Lys Val Ser Leu Trp Ser
        260                 265                 270
```

Leu Leu Val Thr Leu Val Val Leu Phe Ile Met Thr Gly Thr Met Leu
          275   280   285

Gly Pro Glu Leu Leu Ala Ser Ile Pro Ala Ala Val Tyr Val Ile Ala
         290   295   300

Ile Phe Met Pro Leu Ala Gly Tyr Ala Ser Gly Tyr Gly Leu Ala Thr
305   310   315   320

Leu Phe His Leu Pro Pro Asn Cys Lys Arg Thr Val Cys Leu Glu Thr
                   325   330   335

Gly Ser Gln Asn Val Gln Leu Cys Thr Ala Ile Leu Lys Leu Ala Phe
                   340   345   350

Pro Pro Gln Phe Ile Gly Ser Met Tyr Met Phe Pro Leu Leu Tyr Ala
          355   360   365

Leu Phe Gln Ser Ala Glu Ala Gly Ile Phe Val Leu Ile Tyr Lys Met
     370   375   380

Tyr Gly Ser Glu Met Leu His Lys Arg Asp Pro Leu Asp Glu Asp Glu

385   390   395   400

Asp Thr Asp Ile Ser Tyr Lys Lys Leu Lys Glu Glu Glu Met Ala Asp
                   405   410   415

Thr Ser Tyr Gly Thr Val Lys Ala Glu Asn Ile Ile Met Met Glu Thr
          420   425   430

Ala Gln Thr Ser Leu
          435

<210>   106

<211>   147

<212>   PRT

<213>   Homo sapiens

<400>   106

Met Ala Pro Gly Pro Trp Pro Val Ser Cys Leu Arg Gly Gly Pro Leu
 1   5   10   15

Gly Leu Thr Tyr Leu Ser Leu Leu Leu Ile Pro Ala Ala Ala Gly Thr
                  20   25   30

Tyr Cys Glu Cys Ser Leu Gly Leu Ser Arg Glu Ala Leu Ile Ala Leu

```
              35              40              45
Leu Val Val Leu Ala Gly Ile Ser Ala Ser Cys Phe Cys Ala Leu Val
        50              55              60
Ile Val Ala Ile Gly Val Leu Arg Ala Lys Gly Glu Thr Cys Pro Arg
 65              70              75              80
Gln Val Asp Asn Arg Leu Val Glu Asn Phe Gly Val Gln Glu Asp Leu


                85              90              95
Met Asp Leu His Pro Val Tyr Val Glu Ser Gln Leu Met Asp Ala Asp
               100             105             110
Leu Glu Val Ser Leu Val Pro Pro Leu Glu Asp Gln Ser Leu Val Ala
               115             120             125
Ile Pro Met Glu Ala Ser Ser Glu Glu Pro Pro Pro Pro Pro Pro Leu
        130             135             140
Pro Pro Glu
145
<210>      107
<211>      1172
<212>      PRT
<213>      Homo sapiens


<400>      107
Met Val Trp Arg Leu Val Leu Leu Ala Leu Trp Val Trp Pro Ser Thr
  1              5              10              15
Gln Ala Gly His Gln Asp Lys Asp Thr Thr Phe Asp Leu Phe Ser Ile
               20              25              30
Ser Asn Ile Asn Arg Lys Thr Ile Gly Ala Lys Gln Phe Arg Gly Pro
        35              40              45
Asp Pro Gly Val Pro Ala Tyr Arg Phe Val Arg Phe Asp Tyr Ile Pro
        50              55              60
Pro Val Asn Ala Asp Asp Leu Ser Lys Ile Thr Lys Ile Met Arg Gln


 65              70              75              80
Lys Glu Gly Phe Phe Leu Thr Ala Gln Leu Lys Gln Asp Gly Lys Ser
                85              90              95
```

Arg Gly Thr Leu Leu Ala Leu Glu Gly Pro Gly Leu Ser Gln Arg Gln
                100   105   110

Phe Glu Ile Val Ser Asn Gly Pro Ala Asp Thr Leu Asp Leu Thr Tyr
          115   120   125

Trp Ile Asp Gly Thr Arg His Val Val Ser Leu Glu Asp Val Gly Leu
     130   135   140

Ala Asp Ser Gln Trp Lys Asn Val Thr Val Gln Val Ala Gly Glu Thr
145   150   155   160

Tyr Ser Leu His Val Gly Cys Asp Leu Ile Asp Ser Phe Ala Leu Asp
                165   170   175

Glu Pro Phe Tyr Glu His Leu Gln Ala Glu Lys Ser Arg Met Tyr Val
                180   185   190

Ala Lys Gly Ser Ala Arg Glu Ser His Phe Arg Gly Leu Leu Gln Asn
          195   200   205

Val His Leu Val Phe Glu Asn Ser Val Glu Asp Ile Leu Ser Lys Lys

     210   215   220

Gly Cys Gln Gln Gly Gln Gly Ala Glu Ile Asn Ala Ile Ser Glu Asn
225   230   235   240

Thr Glu Thr Leu Arg Leu Gly Pro His Val Thr Thr Glu Tyr Val Gly
                245   250   255

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

Leu Gly Asn Met Val Gln Glu Leu Ser Gly Leu His Val Leu Val Asn
          275   280   285

Gln Leu Ser Glu Asn Leu Lys Arg Val Ser Asn Asp Asn Gln Phe Leu
     290   295   300

Trp Glu Leu Ile Gly Gly Pro Pro Lys Thr Arg Asn Met Ser Ala Cys
305   310   315   320

Trp Gln Asp Gly Arg Phe Phe Ala Glu Asn Glu Thr Trp Val Val Asp
          325   330   335

Ser Cys Thr Thr Cys Thr Cys Lys Lys Phe Lys Thr Ile Cys His Gln
          340   345   350

Ile Thr Cys Pro Pro Ala Thr Cys Ala Ser Pro Ser Phe Val Glu Gly

          355   360   365

Glu Cys Cys Pro Ser Cys Leu His Ser Val Asp Gly Glu Glu Gly Trp

     370   375   380

Ser Pro Trp Ala Glu Trp Thr Gln Cys Ser Val Thr Cys Gly Ser Gly

385   390   395   400

Thr Gln Gln Arg Gly Arg Ser Cys Asp Val Thr Ser Asn Thr Cys Leu

          405   410   415

Gly Pro Ser Ile Gln Thr Arg Ala Cys Ser Leu Ser Lys Cys Asp Thr

          420   425   430

Arg Ile Arg Gln Asp Gly Gly Trp Ser His Trp Ser Pro Trp Ser Ser

          435   440   445

Cys Ser Val Thr Cys Gly Val Gly Asn Ile Thr Arg Ile Arg Leu Cys

     450   455   460

Asn Ser Pro Val Pro Gln Met Gly Gly Lys Asn Cys Lys Gly Ser Gly

465   470   475   480

Arg Glu Thr Lys Ala Cys Gln Gly Ala Pro Cys Pro Ile Asp Gly Arg

          485   490   495

Trp Ser Pro Trp Ser Pro Trp Ser Ala Cys Thr Val Thr Cys Ala Gly

          500   505   510

Gly Ile Arg Glu Arg Thr Arg Val Cys Asn Ser Pro Glu Pro Gln Tyr

          515   520   525

Gly Gly Lys Ala Cys Val Gly Asp Val Gln Glu Arg Gln Met Cys Asn

     530   535   540

Lys Arg Ser Cys Pro Val Asp Gly Cys Leu Ser Asn Pro Cys Phe Pro

545   550   555   560

Gly Ala Gln Cys Ser Ser Phe Pro Asp Gly Ser Trp Ser Cys Gly Ser

          565   570   575

Cys Pro Val Gly Phe Leu Gly Asn Gly Thr His Cys Glu Asp Leu Asp

          580   585   590

Glu Cys Ala Leu Val Pro Asp Ile Cys Phe Ser Thr Ser Lys Val Pro

```
                595                 600                 605
Arg Cys Val Asn Thr Gln Pro Gly Phe His Cys Leu Pro Cys Pro Pro
        610                 615                 620
Arg Tyr Arg Gly Asn Gln Pro Val Gly Val Gly Leu Glu Ala Ala Lys
625                 630                 635                 640
Thr Glu Lys Gln Val Cys Glu Pro Glu Asn Pro Cys Lys Asp Lys Thr


                    645                 650                 655
His Asn Cys His Lys His Ala Glu Cys Ile Tyr Leu Gly His Phe Ser
                660                 665                 670
Asp Pro Met Tyr Lys Cys Glu Cys Gln Thr Gly Tyr Ala Gly Asp Gly
            675                 680                 685
Leu Ile Cys Gly Glu Asp Ser Asp Leu Asp Gly Trp Pro Asn Leu Asn
    690                 695                 700
Leu Val Cys Ala Thr Asn Ala Thr Tyr His Cys Ile Lys Asp Asn Cys
705                 710                 715                 720


Pro His Leu Pro Asn Ser Gly Gln Glu Asp Phe Asp Lys Asp Gly Ile
                    725                 730                 735
Gly Asp Ala Cys Asp Asp Asp Asp Asn Asp Gly Val Thr Asp Glu
                740                 745                 750
Lys Asp Asn Cys Gln Leu Leu Phe Asn Pro Arg Gln Ala Asp Tyr Asp
            755                 760                 765
Lys Asp Glu Val Gly Asp Arg Cys Asp Asn Cys Pro Tyr Val His Asn
    770                 775                 780
Pro Ala Gln Ile Asp Thr Asp Asn Asn Gly Glu Gly Asp Ala Cys Ser


785                 790                 795                 800
Val Asp Ile Asp Gly Asp Asp Val Phe Asn Glu Arg Asp Asn Cys Pro
                    805                 810                 815
Tyr Val Tyr Asn Thr Asp Gln Arg Asp Thr Asp Gly Asp Gly Val Gly
                820                 825                 830
Asp His Cys Asp Asn Cys Pro Leu Val His Asn Pro Asp Gln Thr Asp
            835                 840                 845
Val Asp Asn Asp Leu Val Gly Asp Gln Cys Asp Asn Asn Glu Asp Ile
```

<pre>
        850   855   860
</pre>

Asp Asp Asp Gly His Gln Asn Asn Gln Asp Asn Cys Pro Tyr Ile Ser

<pre>
865   870   875   880
</pre>

Asn Ala Asn Gln Ala Asp His Asp Arg Asp Gly Gln Gly Asp Ala Cys

<pre>
                885   890   895
</pre>

Asp Pro Asp Asp Asp Asn Asp Gly Val Pro Asp Asp Arg Asp Asn Cys

<pre>
             900   905   910
</pre>

Arg Leu Val Phe Asn Pro Asp Gln Glu Asp Leu Asp Gly Asp Gly Arg

<pre>
          915   920   925
</pre>

Gly Asp Ile Cys Lys Asp Asp Phe Asp Asn Asp Asn Ile Pro Asp Ile

<pre>
        930   935   940
</pre>

Asp Asp Val Cys Pro Glu Asn Asn Ala Ile Ser Glu Thr Asp Phe Arg

<pre>
945   950   955   960
</pre>

Asn Phe Gln Met Val Pro Leu Asp Pro Lys Gly Thr Thr Gln Ile Asp

<pre>
                965   970   975
</pre>

Pro Asn Trp Val Ile Arg His Gln Gly Lys Glu Leu Val Gln Thr Ala

<pre>
             980   985   990
</pre>

Asn Ser Asp Pro Gly Ile Ala Val Gly Phe Asp Glu Phe Gly Ser Val

<pre>
          995   1000   1005
</pre>

Asp Phe Ser Gly Thr Phe Tyr Val Asn Thr Asp Arg Asp Asp Asp Tyr

<pre>
          1010   1015   1020
</pre>

Ala Gly Phe Val Phe Gly Tyr Gln Ser Ser Ser Arg Phe Tyr Val Val

<pre>
1025   1030   1035   1040
</pre>

Met Trp Lys Gln Val Thr Gln Thr Tyr Trp Glu Asp Gln Pro Thr Arg

<pre>
                1045   1050   1055
</pre>

Ala Tyr Gly Tyr Ser Gly Val Ser Leu Lys Val Val Asn Ser Thr Thr

<pre>
             1060   1065   1070
</pre>

Gly Thr Gly Glu His Leu Arg Asn Ala Leu Trp His Thr Gly Asn Thr

<pre>
          1075   1080   1085
</pre>

Pro Gly Gln Val Arg Thr Leu Trp His Asp Pro Arg Asn Ile Gly Trp

<pre>
          1090   1095   1100
</pre>

Lys Asp Tyr Thr Ala Tyr Arg Trp His Leu Thr His Arg Pro Lys Thr
1105   1110   1115   1120

Gly Tyr Ile Arg Val Leu Val His Glu Gly Lys Gln Val Met Ala Asp
                1125   1130   1135

Ser Gly Pro Ile Tyr Asp Gln Thr Tyr Ala Gly Gly Arg Leu Gly Leu
            1140   1145   1150

Phe Val Phe Ser Gln Glu Met Val Tyr Phe Ser Asp Leu Lys Tyr Glu
            1155   1160   1165

Cys Arg Asp Ile
    1170

<210>   108

<211>   132

<212>   PRT

<213>   Homo sapiens

<400>   108

Met Ala Ser Gln Asn Arg Asp Pro Ala Ala Thr Ser Val Ala Ala Ala
    1   5   10   15

Arg Lys Gly Ala Glu Pro Ser Gly Gly Ala Ala Arg Gly Pro Val Gly
                20   25   30

Lys Arg Leu Gln Gln Glu Leu Met Thr Leu Met Ala Val Gly Ser Ile

            35   40   45

Arg Thr Ser Ser Thr Val Cys Leu Leu Ser Gly Pro Arg Glu Thr Gln
        50   55   60

Asp Ser Ser Lys Pro Leu Val Trp Gly Leu Gly Trp Asp Met Arg Leu
    65   70   75   80

Leu Leu Glu Leu Thr Leu Gln Leu Phe Leu Gln Met Pro Glu Pro Asn
                85   90   95

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

Thr Ala Phe Lys Lys Tyr Leu Gln Glu Thr Tyr Ser Lys Gln Val Thr
            115   120   125

Ser Gln Glu Pro

130

<210> 109

<211> 615

<212> PRT

<213> Homo sapiens

<400> 109

Met Lys Ala Leu Arg Leu Ser Ala Ser Ala Leu Phe Cys Leu Leu Leu
1   5   10   15

Ile Asn Gly Leu Gly Ala Ala Pro Pro Gly Arg Pro Glu Ala Gln Pro
                20   25   30

Pro Pro Leu Ser Ser Glu His Lys Glu Pro Val Ala Gly Asp Ala Val

            35   40   45

Pro Gly Pro Lys Asp Gly Ser Ala Pro Glu Val Arg Gly Ala Arg Asn
        50   55   60

Ser Glu Pro Gln Asp Glu Gly Glu Leu Phe Gln Gly Val Asp Pro Arg
65   70   75   80

Ala Leu Ala Ala Val Leu Leu Gln Ala Leu Asp Arg Pro Ala Ser Pro
                85   90   95

Pro Ala Pro Ser Gly Ser Gln Gln Gly Pro Glu Glu Glu Ala Ala Glu
                100   105   110

Ala Leu Leu Thr Glu Thr Val Arg Ser Gln Thr His Ser Leu Pro Ala
            115   120   125

Pro Glu Ser Pro Glu Pro Ala Ala Pro Pro Arg Pro Gln Thr Pro Glu
        130   135   140

Asn Gly Pro Glu Ala Ser Asp Pro Ser Glu Glu Leu Glu Ala Leu Ala
145   150   155   160

Ser Leu Leu Gln Glu Leu Arg Asp Phe Ser Pro Ser Ser Ala Lys Arg
                165   170   175

Gln Gln Glu Thr Ala Ala Ala Glu Thr Glu Thr Arg Thr His Thr Leu

            180   185   190

Thr Arg Val Asn Leu Glu Ser Pro Gly Pro Glu Arg Val Trp Arg Ala
        195   200   205

Ser Trp Gly Glu Phe Gln Ala Arg Val Pro Glu Arg Ala Pro Leu Pro
    210   215   220

Pro Pro Ala Pro Ser Gln Phe Gln Ala Arg Met Pro Asp Ser Gly Pro
225   230   235   240

Leu Pro Glu Thr His Lys Phe Gly Glu Gly Val Ser Ser Pro Lys Thr
        245   250   255

His Leu Gly Glu Ala Leu Ala Pro Leu Ser Lys Ala Tyr Gln Gly Val
        260   265   270

Ala Ala Pro Phe Pro Lys Ala Arg Arg Pro Glu Ser Ala Leu Leu Gly
      275   280   285

Gly Ser Glu Ala Gly Glu Arg Leu Leu Gln Gln Gly Leu Ala Gln Val
    290   295   300

Glu Ala Gly Arg Arg Gln Ala Glu Ala Thr Arg Gln Ala Ala Ala Gln
305   310   315   320

Glu Glu Arg Leu Ala Asp Leu Ala Ser Asp Leu Leu Leu Gln Tyr Leu

        325   330   335

Leu Gln Gly Gly Ala Arg Gln Arg Gly Leu Gly Gly Arg Gly Leu Gln
        340   345   350

Glu Ala Ala Glu Glu Arg Glu Ser Ala Arg Glu Glu Glu Glu Ala Glu
      355   360   365

Gln Glu Arg Arg Gly Gly Glu Glu Arg Val Gly Glu Glu Asp Glu Glu
      370   375   380

Ala Ala Glu Ala Glu Ala Glu Ala Glu Glu Ala Glu Arg Ala Arg Gln
385   390   395   400

Asn Ala Leu Leu Phe Ala Glu Glu Glu Asp Gly Glu Ala Gly Ala Glu
        405   410   415

Asp Lys Arg Ser Gln Glu Glu Thr Pro Gly His Arg Arg Lys Glu Ala
        420   425   430

Glu Gly Thr Glu Glu Gly Gly Glu Glu Glu Asp Asp Glu Glu Met Asp
        435   440   445

Pro Gln Thr Ile Asp Ser Leu Ile Glu Leu Ser Thr Lys Leu His Leu
      450   455   460

Pro Ala Asp Asp Val Val Ser Ile Ile Glu Glu Val Glu Glu Lys Arg

465   470   475   480

Lys Arg Lys Lys Asn Ala Pro Pro Glu Pro Val Pro Pro Arg Ala
                485   490   495

Ala Pro Ala Pro Thr His Val Arg Ser Pro Gln Pro Pro Pro Ala
                500   505   510

Pro Ala Pro Ala Arg Asp Glu Leu Pro Asp Trp Asn Glu Val Leu Pro
                515   520   525

Pro Trp Asp Arg Glu Glu Asp Glu Val Tyr Pro Pro Gly Pro Tyr His
                530   535   540

Pro Phe Pro Asn Tyr Ile Arg Pro Arg Thr Leu Gln Pro Pro Ser Ala
545   550   555   560

Leu Arg Arg Arg His Tyr His His Ala Leu Pro Pro Ser Arg His Tyr
                565   570   575

Pro Gly Arg Glu Ala Gln Ala Arg Arg Ala Gln Glu Glu Ala Glu Ala
                580   585   590

Glu Glu Arg Arg Leu Gln Glu Gln Glu Glu Leu Glu Asn Tyr Ile Glu
                595   600   605

His Val Leu Leu Arg Arg Pro

      610   615

<210>   110

<211>   271

<212>   PRT

<213>   Homo sapiens

<400>   110

Met Val Gly Ala Leu Cys Gly Cys Trp Phe Arg Leu Gly Gly Ala Arg
    1   5   10   15

Pro Leu Ile Pro Leu Gly Pro Thr Val Val Gln Thr Ser Met Ser Arg
                20   25   30

Ser Gln Val Ala Leu Leu Gly Leu Ser Leu Leu Leu Met Leu Leu Leu
                35   40   45

Tyr Val Gly Leu Pro Gly Pro Pro Glu Gln Thr Ser Cys Leu Trp Gly

          50   55   60

Asp Pro Asn Val Thr Val Leu Ala Gly Leu Thr Pro Gly Asn Ser Pro

  65   70   75   80

Ile Phe Tyr Arg Glu Val Leu Pro Leu Asn Gln Ala His Arg Val Glu

                  85   90   95

Val Val Leu Leu His Gly Lys Ala Phe Asn Ser His Thr Trp Glu Gln

                 100   105   110

Leu Gly Thr Leu Gln Leu Leu Ser Gln Arg Gly Tyr Arg Ala Val Ala

                 115   120   125

Leu Asp Leu Pro Gly Phe Gly Asn Ser Ala Pro Ser Lys Glu Ala Ser

                 130   135   140

Thr Glu Ala Gly Arg Ala Ala Leu Leu Glu Arg Ala Leu Arg Asp Leu

 145   150   155   160

Glu Val Gln Asn Ala Val Leu Val Ser Pro Ser Leu Ser Gly His Tyr

                 165   170   175

Ala Leu Pro Phe Leu Met Arg Gly His His Gln Leu His Gly Phe Val

                 180   185   190

Pro Ile Ala Pro Thr Ser Thr Gln Asn Tyr Thr Gln Glu Gln Phe Trp

                 195   200   205

Ala Val Lys Thr Pro Thr Leu Ile Leu Tyr Gly Glu Leu Asp His Ile

                 210   215   220

Leu Ala Arg Glu Ser Leu Arg Gln Leu Arg His Leu Pro Asn His Ser

 225   230   235   240

Val Val Lys Leu Arg Asn Ala Gly His Ala Cys Tyr Leu His Lys Pro

                 245   250   255

Gln Asp Phe His Leu Val Leu Leu Ala Phe Leu Asp His Leu Pro

                 260   265   270

<210>   111

<211>   256

<212>   PRT

<213>   Homo sapiens

<400>   111

Met Phe Gln Thr Gly Gly Leu Ile Val Phe Tyr Gly Leu Leu Ala Gln

1   5   10   15

Thr Met Ala Gln Phe Gly Gly Leu Pro Val Pro Leu Asp Gln Thr Leu

                20   25   30

Pro Leu Asn Val Asn Pro Ala Leu Pro Leu Ser Pro Thr Gly Leu Ala

            35   40   45

Gly Ser Leu Thr Asn Ala Leu Ser Asn Gly Leu Leu Ser Gly Gly Leu

        50   55   60

Leu Gly Ile Leu Glu Asn Leu Pro Leu Leu Asp Ile Leu Lys Pro Gly

 65   70   75   80

Gly Gly Thr Ser Gly Gly Leu Leu Gly Gly Leu Leu Gly Lys Val Thr

                85   90   95

Ser Val Ile Pro Gly Leu Asn Asn Ile Ile Asp Ile Lys Val Thr Asp

            100   105   110

Pro Gln Leu Leu Glu Leu Gly Leu Val Gln Ser Pro Asp Gly His Arg

        115   120   125

Leu Tyr Val Thr Ile Pro Leu Gly Ile Lys Leu Gln Val Asn Thr Pro

        130   135   140

Leu Val Gly Ala Ser Leu Leu Arg Leu Ala Val Lys Leu Asp Ile Thr

145   150   155   160

Ala Glu Ile Leu Ala Val Arg Asp Lys Gln Glu Arg Ile His Leu Val

                165   170   175

Leu Gly Asp Cys Thr His Ser Pro Gly Ser Leu Gln Ile Ser Leu Leu

            180   185   190

Asp Gly Leu Gly Pro Leu Pro Ile Gln Gly Leu Leu Asp Ser Leu Thr

        195   200   205

Gly Ile Leu Asn Lys Val Leu Pro Glu Leu Val Gln Gly Asn Val Cys

        210   215   220

Pro Leu Val Asn Glu Val Leu Arg Gly Leu Asp Ile Thr Leu Val His

225   230   235   240

Asp Ile Val Asn Met Leu Ile His Gly Leu Gln Phe Val Ile Lys Val

                245   250   255

<210> 112

<211> 1745

<212> PRT

<213> Homo sapiens

<400> 112

Met Gly Asn Arg Arg Asp Leu Gly Gln Pro Arg Ala Gly Leu Cys Leu

 1   5   10   15

Leu Leu Ala Ala Leu Gln Leu Leu Pro Gly Thr Gln Ala Asp Pro Val

                20   25   30

Asp Val Leu Lys Ala Leu Gly Val Gln Gly Gly Gln Ala Gly Val Pro

             35   40   45

Glu Gly Pro Gly Phe Cys Pro Gln Arg Thr Pro Glu Gly Asp Arg Ala

     50   55   60

Phe Arg Ile Gly Gln Ala Ser Thr Leu Gly Ile Pro Thr Trp Glu Leu

 65   70   75   80

Phe Pro Glu Gly His Phe Pro Glu Asn Phe Ser Leu Leu Ile Thr Leu

                85   90   95

Arg Gly Gln Pro Ala Asn Gln Ser Val Leu Leu Ser Ile Tyr Asp Glu

             100   105   110

Arg Gly Ala Arg Gln Leu Gly Leu Ala Leu Gly Pro Ala Leu Gly Leu

             115   120   125

Leu Gly Asp Pro Phe Arg Pro Leu Pro Gln Gln Val Asn Leu Thr Asp

             130   135   140

Gly Arg Trp His Arg Val Ala Val Ser Ile Asp Gly Glu Met Val Thr

145   150   155   160

Leu Val Ala Asp Cys Glu Ala Gln Pro Pro Val Leu Gly His Gly Pro

                165   170   175

Arg Phe Ile Ser Ile Ala Gly Leu Thr Val Leu Gly Thr Gln Asp Leu

             180   185   190

Gly Glu Lys Thr Phe Glu Gly Asp Ile Gln Glu Leu Leu Ile Ser Pro

                195   200   205
Asp Pro Gln Ala Ala Phe Gln Ala Cys Glu Arg Tyr Leu Pro Asp Cys

            210   215   220
Asp Asn Leu Ala Pro Ala Ala Thr Val Ala Pro Gln Gly Glu Pro Glu
225   230   235   240
Thr Pro Arg Pro Arg Arg Lys Gly Lys Gly Lys Gly Arg Lys Lys Gly
                    245   250   255
Arg Gly Arg Lys Gly Lys Gly Arg Lys Lys Asn Lys Glu Ile Trp Thr
                260   265   270
Ser Ser Pro Pro Pro Asp Ser Ala Glu Asn Gln Thr Ser Thr Asp Ile
            275   280   285

Pro Lys Thr Glu Thr Pro Ala Pro Asn Leu Pro Pro Thr Pro Thr Pro
        290   295   300
Leu Val Val Thr Ser Thr Val Thr Thr Gly Leu Asn Ala Thr Ile Leu
305   310   315   320
Glu Arg Ser Leu Asp Pro Asp Ser Gly Thr Glu Leu Gly Thr Leu Glu
                    325   330   335
Thr Lys Ala Ala Arg Glu Asp Glu Glu Gly Asp Asp Ser Thr Met Gly
                340   345   350
Pro Asp Phe Arg Ala Ala Glu Tyr Pro Ser Arg Thr Gln Phe Gln Ile

            355   360   365
Phe Pro Gly Ala Gly Glu Lys Gly Ala Lys Gly Glu Pro Ala Val Ile
        370   375   380
Glu Lys Gly Gln Gln Phe Glu Gly Pro Pro Gly Ala Pro Gly Pro Gln
385   390   395   400
Gly Val Val Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Phe Pro Gly
                    405   410   415
Asp Pro Gly Pro Pro Gly Pro Ala Gly Leu Pro Gly Ile Pro Gly Ile
                420   425   430

Asp Gly Ile Arg Gly Pro Pro Gly Thr Val Ile Met Met Pro Phe Gln
                435   440   445

Phe Ala Gly Gly Ser Phe Lys Gly Pro Pro Val Ser Phe Gln Gln Ala
    450   455   460

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

Pro Gly Pro Val Gly Leu Thr Gly Arg Pro Gly Pro Val Gly Leu Pro
            485   490   495

Gly His Pro Gly Leu Lys Gly Glu Glu Gly Ala Glu Gly Pro Gln Gly

             500   505   510

Pro Arg Gly Leu Gln Gly Pro His Gly Pro Pro Gly Arg Val Gly Lys
        515   520   525

Met Gly Arg Pro Gly Ala Asp Gly Ala Arg Gly Leu Pro Gly Asp Thr
    530   535   540

Gly Pro Lys Gly Asp Arg Gly Phe Asp Gly Leu Pro Gly Leu Pro Gly
545   550   555   560

Glu Lys Gly Gln Arg Gly Asp Phe Gly His Val Gly Gln Pro Gly Pro
            565   570   575

Pro Gly Glu Asp Gly Glu Arg Gly Ala Glu Gly Pro Pro Gly Pro Thr
            580   585   590

Gly Gln Ala Gly Glu Pro Gly Pro Arg Gly Leu Leu Gly Pro Arg Gly
        595   600   605

Ser Pro Gly Pro Thr Gly Arg Pro Gly Val Thr Gly Ile Asp Gly Ala
    610   615   620

Pro Gly Ala Lys Gly Asn Val Gly Pro Pro Gly Glu Pro Gly Pro Pro
625   630   635   640

Gly Gln Gln Gly Asn His Gly Ser Gln Gly Leu Pro Gly Pro Gln Gly

             645   650   655

Leu Ile Gly Thr Pro Gly Glu Lys Gly Pro Pro Gly Asn Pro Gly Ile
        660   665   670

Pro Gly Leu Pro Gly Ser Asp Gly Pro Leu Gly His Pro Gly His Glu
        675   680   685

Gly Pro Thr Gly Glu Lys Gly Ala Gln Gly Pro Pro Gly Ser Ala Gly
    690   695   700

Pro Pro Gly Tyr Pro Gly Pro Arg Gly Val Lys Gly Thr Ser Gly Asn

705   710   715   720

Arg Gly Leu Gln Gly Glu Lys Gly Glu Lys Gly Glu Asp Gly Phe Pro

                725   730   735

Gly Phe Lys Gly Asp Val Gly Leu Lys Gly Asp Gln Gly Lys Pro Gly

                740   745   750

Ala Pro Gly Pro Arg Gly Glu Asp Gly Pro Glu Gly Pro Lys Gly Gln

                755   760   765

Ala Gly Gln Ala Gly Glu Glu Gly Pro Pro Gly Ser Ala Gly Glu Lys

                770   775   780

Gly Lys Leu Gly Val Pro Gly Leu Pro Gly Tyr Pro Gly Arg Pro Gly

785   790   795   800

Pro Lys Gly Ser Ile Gly Phe Pro Gly Pro Leu Gly Pro Ile Gly Glu

                805   810   815

Lys Gly Lys Ser Gly Lys Thr Gly Gln Pro Gly Leu Glu Gly Glu Arg

                820   825   830

Gly Pro Pro Gly Ser Arg Gly Glu Arg Gly Gln Pro Gly Ala Thr Gly

                835   840   845

Gln Pro Gly Pro Lys Gly Asp Val Gly Gln Asp Gly Ala Pro Gly Ile

                850   855   860

Pro Gly Glu Lys Gly Leu Pro Gly Leu Gln Gly Pro Pro Gly Phe Pro

865   870   875   880

Gly Pro Lys Gly Pro Pro Gly His Gln Gly Lys Asp Gly Arg Pro Gly

                885   890   895

His Pro Gly Gln Arg Gly Glu Leu Gly Phe Gln Gly Gln Thr Gly Pro

                900   905   910

Pro Gly Pro Ala Gly Val Leu Gly Pro Gln Gly Lys Thr Gly Glu Val

                915   920   925

Gly Pro Leu Gly Glu Arg Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly

930   935   940

Glu Gln Gly Leu Pro Gly Leu Glu Gly Arg Glu Gly Ala Lys Gly Glu

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945              950              955              960
Leu Gly Pro Pro Gly Pro Leu Gly Lys Glu Gly Pro Ala Gly Leu Arg
              965              970              975
Gly Phe Pro Gly Pro Lys Gly Gly Pro Gly Asp Pro Gly Pro Thr Gly
              980              985              990
Leu Lys Gly Asp Lys Gly Pro Pro Gly Pro Val Gly Ala Asn Gly Ser
        995              1000             1005


Pro Gly Glu Arg Gly Pro Leu Gly Pro Ala Gly Gly Ile Gly Leu Pro
        1010             1015             1020
Gly Gln Ser Gly Ser Glu Gly Pro Val Gly Pro Ala Gly Lys Lys Gly
1025             1030             1035             1040
Ser Arg Gly Glu Arg Gly Pro Pro Gly Pro Thr Gly Lys Asp Gly Ile
              1045             1050             1055
Pro Gly Pro Leu Gly Pro Leu Gly Pro Pro Gly Ala Ala Gly Pro Ser
              1060             1065             1070
Gly Glu Glu Gly Asp Lys Gly Asp Val Gly Ala Pro Gly His Lys Gly


        1075             1080             1085
Ser Lys Gly Asp Lys Gly Asp Ala Gly Pro Pro Gly Gln Pro Gly Ile
        1090             1095             1100
Arg Gly Pro Ala Gly His Pro Gly Pro Pro Gly Ala Asp Gly Ala Gln
1105             1110             1115             1120
Gly Arg Arg Gly Pro Pro Gly Leu Phe Gly Gln Lys Gly Asp Asp Gly
              1125             1130             1135
Val Arg Gly Phe Val Gly Val Ile Gly Pro Pro Gly Leu Gln Gly Leu
              1140             1145             1150


Pro Gly Pro Pro Gly Glu Lys Gly Glu Val Gly Asp Val Gly Ser Met
        1155             1160             1165
Gly Pro His Gly Ala Pro Gly Pro Arg Gly Pro Gln Gly Pro Thr Gly
        1170             1175             1180
Ser Glu Gly Thr Pro Gly Leu Pro Gly Gly Val Gly Gln Pro Gly Ala
1185             1190             1195             1200
Val Gly Glu Lys Gly Glu Arg Gly Asp Ala Gly Asp Pro Gly Pro Pro
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              1205                1210                1215
Gly Ala Pro Gly Ile Pro Gly Pro Lys Gly Asp Ile Gly Glu Lys Gly


              1220                1225                1230
Asp Ser Gly Pro Ser Gly Ala Ala Gly Pro Pro Gly Lys Lys Gly Pro
         1235                1240                1245
Pro Gly Glu Asp Gly Ala Lys Gly Ser Val Gly Pro Thr Gly Leu Pro
      1250                1255                1260
Gly Asp Leu Gly Pro Pro Gly Asp Pro Gly Val Ser Gly Ile Asp Gly
 1265                1270                1275                1280
Ser Pro Gly Glu Lys Gly Asp Pro Gly Asp Val Gly Gly Pro Gly Pro
                1285                1290                1295


Pro Gly Ala Ser Gly Glu Pro Gly Ala Pro Gly Pro Pro Gly Lys Arg
              1300                1305                1310
Gly Pro Ser Gly His Met Gly Arg Glu Gly Arg Glu Gly Glu Lys Gly
         1315                1320                1325
Ala Lys Gly Glu Pro Gly Pro Asp Gly Pro Pro Gly Arg Thr Gly Pro
      1330                1335                1340
Met Gly Ala Arg Gly Pro Pro Gly Arg Val Gly Pro Glu Gly Leu Arg
 1345                1350                1355                1360
Gly Ile Pro Gly Pro Val Gly Glu Pro Gly Leu Leu Gly Ala Pro Gly


              1365                1370                1375
Gln Met Gly Pro Pro Gly Pro Leu Gly Pro Ser Gly Leu Pro Gly Leu
              1380                1385                1390
Lys Gly Asp Thr Gly Pro Lys Gly Glu Lys Gly His Ile Gly Leu Ile
         1395                1400                1405
Gly Leu Ile Gly Pro Pro Gly Glu Ala Gly Glu Lys Gly Asp Gln Gly
      1410                1415                1420
Leu Pro Gly Val Gln Gly Pro Pro Gly Pro Lys Gly Asp Pro Gly Pro
 1425                1430                1435                1440


Pro Gly Pro Ile Gly Ser Leu Gly His Pro Gly Pro Pro Gly Val Ala
              1445                1450                1455
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Gly Pro Leu Gly Gln Lys Gly Ser Lys Gly Ser Pro Gly Ser Met Gly
          1460   1465   1470

Pro Arg Gly Asp Thr Gly Pro Ala Gly Pro Pro Gly Pro Pro Gly Ala
         1475   1480   1485

Pro Ala Glu Leu His Gly Leu Arg Arg Arg Arg Phe Val Pro Val
     1490   1495   1500

Pro Leu Pro Val Val Glu Gly Gly Leu Glu Glu Val Leu Ala Ser Leu

1505   1510   1515   1520

Thr Ser Leu Ser Leu Glu Leu Glu Gln Leu Arg Arg Pro Pro Gly Thr
         1525   1530   1535

Ala Glu Arg Pro Gly Leu Val Cys His Glu Leu His Arg Asn His Pro
         1540   1545   1550

His Leu Pro Asp Gly Glu Tyr Trp Ile Asp Pro Asn Gln Gly Cys Ala
        1555   1560   1565

Arg Asp Ser Phe Arg Val Phe Cys Asn Phe Thr Ala Gly Gly Glu Thr
    1570   1575   1580

Cys Leu Tyr Pro Asp Lys Lys Phe Glu Ile Val Lys Leu Ala Ser Trp
1585   1590   1595   1600

Ser Lys Glu Lys Pro Gly Gly Trp Tyr Ser Thr Phe Arg Arg Gly Lys
         1605   1610   1615

Lys Phe Ser Tyr Val Asp Ala Asp Gly Ser Pro Val Asn Val Val Gln
         1620   1625   1630

Leu Asn Phe Leu Lys Leu Leu Ser Ala Thr Ala Arg Gln Asn Phe Thr
         1635   1640   1645

Tyr Ser Cys Gln Asn Ala Ala Ala Trp Leu Asp Glu Ala Thr Gly Asp

   1650   1655   1660

Tyr Ser His Ser Ala Arg Phe Leu Gly Thr Asn Gly Glu Glu Leu Ser
1665   1670   1675   1680

Phe Asn Gln Thr Thr Ala Ala Thr Val Ser Val Pro Gln Asp Gly Cys
         1685   1690   1695

Arg Leu Arg Lys Gly Gln Thr Lys Thr Leu Phe Glu Phe Ser Ser Ser
         1700   1705   1710

Arg Ala Gly Phe Leu Pro Leu Trp Asp Val Ala Ala Thr Asp Phe Gly

      1715   1720   1725

Gln Thr Asn Gln Lys Phe Gly Phe Glu Leu Gly Pro Val Cys Phe Ser

     1730   1735   1740

Ser

174

<210>   113

<211>   387

<212>   PRT

<213>   Homo sapiens

<400>   113

Met Ala Ala Ile Pro Ala Leu Asp Pro Glu Ala Glu Pro Ser Met Asp

 1   5   10   15

Val Ile Leu Val Gly Ser Ser Glu Leu Ser Ser Ser Val Ser Pro Gly

        20   25   30

Thr Gly Arg Asp Leu Ile Ala Tyr Glu Val Lys Ala Asn Gln Arg Asn

        35   40   45

Ile Glu Asp Ile Cys Ile Cys Cys Gly Ser Leu Gln Val His Thr Gln

     50   55   60

His Pro Leu Phe Glu Gly Gly Ile Cys Ala Pro Cys Lys Asp Lys Phe

 65   70   75   80

Leu Asp Ala Leu Phe Leu Tyr Asp Asp Asp Gly Tyr Gln Ser Tyr Cys

        85   90   95

Ser Ile Cys Cys Ser Gly Glu Thr Leu Leu Ile Cys Gly Asn Pro Asp

        100   105   110

Cys Thr Arg Cys Tyr Cys Phe Glu Cys Val Asp Ser Leu Val Gly Pro

        115   120   125

Gly Thr Ser Gly Lys Val His Ala Met Ser Asn Trp Val Cys Tyr Leu

     130   135   140

Cys Leu Pro Ser Ser Arg Ser Gly Leu Leu Gln Arg Arg Arg Lys Trp

145   150   155   160

Arg Ser Gln Leu Lys Ala Phe Tyr Asp Arg Glu Ser Glu Asn Pro Leu

                      165   170   175
Glu Met Phe Glu Thr Val Pro Val Trp Arg Arg Gln Pro Val Arg Val

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

Ser Trp Tyr Leu Phe Gln Phe His Arg Leu Leu Gln Tyr Ala Arg Pro
                260   265   270
Lys Pro Gly Ser Pro Arg Pro Phe Phe Trp Met Phe Val Asp Asn Leu
            275   280   285
Val Leu Asn Lys Glu Asp Leu Asp Val Ala Ser Arg Phe Leu Glu Met
      290   295   300
Glu Pro Val Thr Ile Pro Asp Val His Gly Gly Ser Leu Gln Asn Ala
305   310   315   320
Val Arg Val Trp Ser Asn Ile Pro Ala Ile Arg Ser Ser Arg His Trp

                      325   330   335
Ala Leu Val Ser Glu Glu Glu Leu Ser Leu Leu Ala Gln Asn Lys Gln
                340   345   350
Ser Ser Lys Leu Ala Ala Lys Trp Pro Thr Lys Leu Val Lys Asn Cys
            355   360   365
Phe Leu Pro Leu Arg Glu Tyr Phe Lys Tyr Phe Ser Thr Glu Leu Thr
      370   375   380
Ser Ser Leu
385
<210>   114
<211>   380
<212>   PRT

<213>   Homo sapiens

<400>   114

Met Met Phe Ser Gly Phe Asn Ala Asp Tyr Glu Ala Ser Ser Ser Arg
1   5   10   15

Cys Ser Ser Ala Ser Pro Ala Gly Asp Ser Leu Ser Tyr Tyr His Ser
            20   25   30

Pro Ala Asp Ser Phe Ser Ser Met Gly Ser Pro Val Asn Ala Gln Asp
        35   40   45

Phe Cys Thr Asp Leu Ala Val Ser Ser Ala Asn Phe Ile Pro Thr Val
        50   55   60

Thr Ala Ile Ser Thr Ser Pro Asp Leu Gln Trp Leu Val Gln Pro Ala

65   70   75   80

Leu Val Ser Ser Val Ala Pro Ser Gln Thr Arg Ala Pro His Pro Phe
                85   90   95

Gly Val Pro Ala Pro Ser Ala Gly Ala Tyr Ser Arg Ala Gly Val Val
                100   105   110

Lys Thr Met Thr Gly Gly Arg Ala Gln Ser Ile Gly Arg Arg Gly Lys
            115   120   125

Val Glu Gln Leu Ser Pro Glu Glu Glu Lys Arg Arg Ile Arg Arg
        130   135   140

Glu Arg Asn Lys Met Ala Ala Ala Lys Cys Arg Asn Arg Arg Arg Glu
145   150   155   160

Leu Thr Asp Thr Leu Gln Ala Glu Thr Asp Gln Leu Glu Asp Glu Lys
                165   170   175

Ser Ala Leu Gln Thr Glu Ile Ala Asn Leu Leu Lys Glu Lys Glu Lys
                180   185   190

Leu Glu Phe Ile Leu Ala Ala His Arg Pro Ala Cys Lys Ile Pro Asp
            195   200   205

Asp Leu Gly Phe Pro Glu Glu Met Ser Val Ala Ser Leu Asp Leu Thr

210   215   220

Gly Gly Leu Pro Glu Val Ala Thr Pro Glu Ser Glu Glu Ala Phe Thr

```
        225                 230                 235                 240

Leu Pro Leu Leu Asn Asp Pro Glu Pro Lys Pro Ser Val Glu Pro Val
                        245                 250                 255

Lys Ser Ile Ser Ser Met Glu Leu Lys Thr Glu Pro Phe Asp Asp Phe
                260                 265                 270

Leu Phe Pro Ala Ser Ser Arg Pro Ser Gly Ser Glu Thr Ala Arg Ser
            275                 280                 285


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

Pro Leu His Ser Gly Ser Leu Gly Met Gly Pro Met Ala Thr Glu Leu
        305                 310                 315                 320

Glu Pro Leu Cys Thr Pro Val Val Thr Cys Thr Pro Ser Cys Thr Ala
                        325                 330                 335

Tyr Thr Ser Ser Phe Val Phe Thr Tyr Pro Glu Ala Asp Ser Phe Pro
                340                 345                 350

Ser Cys Ala Ala Ala His Arg Lys Gly Ser Ser Ser Asn Glu Pro Ser


                355                 360                 365

Ser Asp Ser Leu Ser Ser Pro Thr Leu Leu Ala Leu
            370                 375                 380
```

<210> 115

<211> 890

<212> PRT

<213> Homo sapiens

<400> 115

```
Met Glu Gly Gly Gly Lys Pro Asn Ser Ser Ser Asn Ser Arg Asp Asp
  1                  5                  10                 15

Gly Asn Ser Val Phe Pro Ala Lys Ala Ser Ala Thr Gly Ala Gly Pro
                20                  25                  30

Ala Ala Ala Glu Lys Arg Leu Gly Thr Pro Pro Gly Gly Gly Gly Ala


                35                  40                  45

Gly Ala Lys Glu His Gly Asn Ser Val Cys Phe Lys Val Asp Gly Gly
            50                  55                  60
```

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Glu Glu Pro Ala Gly Gly
65   70   75   80

Phe Glu Asp Ala Glu Gly Pro Arg Arg Gln Tyr Gly Phe Met Gln Arg
                    85   90   95

Gln Phe Thr Ser Met Leu Gln Pro Gly Val Asn Lys Phe Ser Leu Arg
                100   105   110

Met Phe Gly Ser Gln Lys Ala Val Glu Lys Glu Gln Glu Arg Val Lys
              115   120   125

Thr Ala Gly Phe Trp Ile Ile His Pro Tyr Ser Asp Phe Arg Phe Tyr
         130   135   140

Trp Asp Leu Ile Met Leu Ile Met Met Val Gly Asn Leu Val Ile Ile
145   150   155   160

Pro Val Gly Ile Thr Phe Phe Thr Glu Gln Thr Thr Thr Pro Trp Ile
                    165   170   175

Ile Phe Asn Val Ala Ser Asp Thr Val Phe Leu Leu Asp Leu Ile Met

         180   185   190

Asn Phe Arg Thr Gly Thr Val Asn Glu Asp Ser Ser Glu Ile Ile Leu
         195   200   205

Asp Pro Lys Val Ile Lys Met Asn Tyr Leu Lys Ser Trp Phe Val Val
         210   215   220

Asp Phe Ile Ser Ser Ile Pro Val Asp Tyr Ile Phe Leu Ile Val Glu
225   230   235   240

Lys Gly Met Asp Ser Glu Val Tyr Lys Thr Ala Arg Ala Leu Arg Ile
                    245   250   255

Val Arg Phe Thr Lys Ile Leu Ser Leu Leu Arg Leu Leu Arg Leu Ser
         260   265   270

Arg Leu Ile Arg Tyr Ile His Gln Trp Glu Glu Ile Phe His Met Thr
         275   280   285

Tyr Asp Leu Ala Ser Ala Val Val Arg Ile Phe Asn Leu Ile Gly Met
         290   295   300

Met Leu Leu Leu Cys His Trp Asp Gly Cys Leu Gln Phe Leu Val Pro
305   310   315   320

Leu Leu Gln Asp Phe Pro Pro Asp Cys Trp Val Ser Leu Asn Glu Met

                       325   330   335

Val Asn Asp Ser Trp Gly Lys Gln Tyr Ser Tyr Ala Leu Phe Lys Ala

          340   345   350

Met Ser His Met Leu Cys Ile Gly Tyr Gly Ala Gln Ala Pro Val Ser

        355   360   365

Met Ser Asp Leu Trp Ile Thr Met Leu Ser Met Ile Val Gly Ala Thr

     370   375   380

Cys Tyr Ala Met Phe Val Gly His Ala Thr Ala Leu Ile Gln Ser Leu

385   390   395   400

Asp Ser Ser Arg Arg Gln Tyr Gln Glu Lys Tyr Lys Gln Val Glu Gln

           405   410   415

Tyr Met Ser Phe His Lys Leu Pro Ala Asp Met Arg Gln Lys Ile His

         420   425   430

Asp Tyr Tyr Glu His Arg Tyr Gln Gly Lys Ile Phe Asp Glu Glu Asn

         435   440   445

Ile Leu Asn Glu Leu Asn Asp Pro Leu Arg Glu Glu Ile Val Asn Phe

     450   455   460

Asn Cys Arg Lys Leu Val Ala Thr Met Pro Leu Phe Ala Asn Ala Asp

465   470   475   480

Pro Asn Phe Val Thr Ala Met Leu Ser Lys Leu Arg Phe Glu Val Phe

         485   490   495

Gln Pro Gly Asp Tyr Ile Ile Arg Glu Gly Ala Val Gly Lys Lys Met

         500   505   510

Tyr Phe Ile Gln His Gly Val Ala Gly Val Ile Thr Lys Ser Ser Lys

        515   520   525

Glu Met Lys Leu Thr Asp Gly Ser Tyr Phe Gly Glu Ile Cys Leu Leu

     530   535   540

Thr Lys Gly Arg Arg Thr Ala Ser Val Arg Ala Asp Thr Tyr Cys Arg

545   550   555   560

Leu Tyr Ser Leu Ser Val Asp Asn Phe Asn Glu Val Leu Glu Glu Tyr

```
                565                     570                     575
Pro Met Met Arg Arg Ala Phe Glu Thr Val Ala Ile Asp Arg Leu Asp
                580                     585                     590
Arg Ile Gly Lys Lys Asn Ser Ile Leu Leu Gln Lys Phe Gln Lys Asp
                595                     600                     605
Leu Asn Thr Gly Val Phe Asn Asn Gln Glu Asn Glu Ile Leu Lys Gln


                610                     615                     620
Ile Val Lys His Asp Arg Glu Met Val Gln Ala Ile Ala Pro Ile Asn
625                     630                     635                     640
Tyr Pro Gln Met Thr Thr Leu Asn Ser Thr Ser Ser Thr Thr Thr Pro
                645                     650                     655
Thr Ser Arg Met Arg Thr Gln Ser Pro Pro Val Tyr Thr Ala Thr Ser
                660                     665                     670
Leu Ser His Ser Asn Leu His Ser Pro Ser Pro Ser Thr Gln Thr Pro
                675                     680                     685


Gln Pro Ser Ala Ile Leu Ser Pro Cys Ser Tyr Thr Thr Ala Val Cys
                690                     695                     700
Ser Pro Pro Val Gln Ser Pro Leu Ala Ala Arg Thr Phe His Tyr Ala
705                     710                     715                     720
Ser Pro Thr Ala Ser Gln Leu Ser Leu Met Gln Gln Gln Pro Gln Gln
                725                     730                     735
Gln Val Gln Gln Ser Gln Pro Pro Gln Thr Gln Pro Gln Gln Pro Ser
                740                     745                     750
Pro Gln Pro Gln Thr Pro Gly Ser Ser Thr Pro Lys Asn Glu Val His


                755                     760                     765
Lys Ser Thr Gln Ala Leu His Asn Thr Asn Leu Thr Arg Glu Val Arg
                770                     775                     780
Pro Leu Ser Ala Ser Gln Pro Ser Leu Pro His Glu Val Ser Thr Leu
785                     790                     795                     800
Ile Ser Arg Pro His Pro Thr Val Gly Glu Ser Leu Ala Ser Ile Pro
                805                     810                     815
Gln Pro Val Thr Ala Val Pro Gly Thr Gly Leu Gln Ala Gly Gly Arg
```

- 240 -

                    820   825   830

Ser Thr Val Pro Gln Arg Val Thr Leu Phe Arg Gln Met Ser Ser Gly
            835   840   845

Ala Ile Pro Pro Asn Arg Gly Val Pro Pro Ala Pro Pro Pro Pro Ala
        850   855   860

Ala Ala Leu Pro Arg Glu Ser Ser Ser Val Leu Asn Thr Asp Pro Asp
865   870   875   880

Ala Glu Lys Pro Arg Phe Ala Ser Asn Leu
                    885   890

<210>   116

<211>   538

<212>   PRT

<213>   Homo sapiens

<400>   116

Met Phe Phe Leu Tyr Thr Asp Phe Phe Leu Ser Leu Val Ala Val Pro
    1   5   10   15

Ala Ala Ala Pro Val Cys Gln Pro Lys Ser Ala Thr Asn Gly Gln Pro
                    20   25   30

Pro Ala Pro Ala Pro Thr Pro Thr Pro Arg Leu Ser Ile Ser Ser Arg
            35   40   45

Ala Thr Val Val Ala Arg Met Glu Gly Thr Ser Gln Gly Gly Leu Gln
        50   55   60

Thr Val Met Lys Trp Lys Thr Val Val Ala Ile Phe Val Val Val Val

65   70   75   80

Val Tyr Leu Val Thr Gly Gly Leu Val Phe Arg Ala Leu Glu Gln Pro
                    85   90   95

Phe Glu Ser Ser Gln Lys Asn Thr Ile Ala Leu Glu Lys Ala Glu Phe
                    100   105   110

Leu Arg Asp His Val Cys Val Ser Pro Gln Glu Leu Glu Thr Leu Ile
            115   120   125

Gln His Ala Leu Asp Ala Asp Asn Ala Gly Val Ser Pro Ile Gly Asn

                    130   135   140

Ser Ser Asn Asn Ser Ser His Trp Asp Leu Gly Ser Ala Phe Phe Phe
145   150   155   160
Ala Gly Thr Val Ile Thr Thr Ile Gly Tyr Gly Asn Ile Ala Pro Ser
                    165   170   175
Thr Glu Gly Gly Lys Ile Phe Cys Ile Leu Tyr Ala Ile Phe Gly Ile
                    180   185   190
Pro Leu Phe Gly Phe Leu Leu Ala Gly Ile Gly Asp Gln Leu Gly Thr
                    195   200   205
Ile Phe Gly Lys Ser Ile Ala Arg Val Glu Lys Val Phe Arg Lys Lys

                    210   215   220
Gln Val Ser Gln Thr Lys Ile Arg Val Ile Ser Thr Ile Leu Phe Ile
225   230   235   240
Leu Ala Gly Cys Ile Val Phe Val Thr Ile Pro Ala Val Ile Phe Lys
                    245   250   255
Tyr Ile Glu Gly Trp Thr Ala Leu Glu Ser Ile Tyr Phe Val Val Val
                    260   265   270
Thr Leu Thr Thr Val Gly Phe Gly Asp Phe Val Ala Gly Gly Asn Ala
                    275   280   285

Gly Ile Asn Tyr Arg Glu Trp Tyr Lys Pro Leu Val Trp Phe Trp Ile
                    290   295   300
Leu Val Gly Leu Ala Tyr Phe Ala Ala Val Leu Ser Met Ile Gly Asp
305   310   315   320
Trp Leu Arg Val Leu Ser Lys Lys Thr Lys Glu Glu Val Gly Glu Ile
                    325   330   335
Lys Ala His Ala Ala Glu Trp Lys Ala Asn Val Thr Ala Glu Phe Arg
                    340   345   350
Glu Thr Arg Arg Arg Leu Ser Val Glu Ile His Asp Lys Leu Gln Arg

                    355   360   365
Ala Ala Thr Ile Arg Ser Met Glu Arg Arg Arg Leu Gly Leu Asp Gln
                    370   375   380

Arg Ala His Ser Leu Asp Met Leu Ser Pro Glu Lys Arg Ser Val Phe
385   390   395   400

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

Asn Asn Arg Pro Asn Asn Leu Arg Leu Lys Gly Pro Glu Gln Leu Asn
                420   425   430

Lys His Gly Gln Gly Ala Ser Glu Asp Asn Ile Ile Asn Lys Phe Gly
                435   440   445

Ser Thr Ser Arg Leu Thr Lys Arg Lys Asn Lys Asp Leu Lys Lys Thr
                450   455   460

Leu Pro Glu Asp Val Gln Lys Ile Tyr Lys Thr Phe Arg Asn Tyr Ser
465   470   475   480

Leu Asp Glu Glu Lys Lys Glu Glu Glu Thr Glu Lys Met Cys Asn Ser
                485   490   495

Asp Asn Ser Ser Thr Ala Met Leu Thr Asp Cys Ile Gln Gln His Ala

                500   505   510

Glu Leu Glu Asn Gly Met Ile Pro Thr Asp Thr Lys Asp Arg Glu Pro
                515   520   525

Glu Asn Asn Ser Leu Leu Glu Asp Arg Asn

    530   535

<210>   117
<211>   611
<212>   PRT
<213>   Homo sapiens
<400>   117

Met Trp Leu Ala Lys Ala Cys Trp Ser Ile Gln Ser Glu Met Pro Cys
  1   5   10   15

Ile Gln Ala Gln Tyr Gly Thr Pro Ala Pro Ser Pro Gly Pro Arg Asp

                20   25   30

His Leu Ala Ser Asp Pro Leu Thr Pro Glu Phe Ile Lys Pro Thr Met
                35   40   45

Asp Leu Ala Ser Pro Glu Ala Ala Pro Ala Ala Pro Thr Ala Leu Pro

```
          50                    55                    60
Ser Phe Ser Thr Phe Met Asp Gly Tyr Thr Gly Glu Phe Asp Thr Phe
 65                    70                    75                    80
Leu Tyr Gln Leu Pro Gly Thr Val Gln Pro Cys Ser Ser Ala Ser Ser
                   85                    90                    95


Ser Ala Ser Ser Thr Ser Ser Ser Ser Ala Thr Ser Pro Ala Ser Ala
                  100                   105                   110
Ser Phe Lys Phe Glu Asp Phe Gln Val Tyr Gly Cys Tyr Pro Gly Pro
                  115                   120                   125
Leu Ser Gly Pro Val Asp Glu Ala Leu Ser Ser Ser Gly Ser Asp Tyr
              130                   135                   140
Tyr Gly Ser Pro Cys Ser Ala Pro Ser Pro Ser Thr Pro Ser Phe Gln
145                   150                   155                   160
Pro Pro Gln Leu Ser Pro Trp Asp Gly Ser Phe Gly His Phe Ser Pro


                  165                   170                   175
Ser Gln Thr Tyr Glu Gly Leu Arg Ala Trp Thr Glu Gln Leu Pro Lys
                  180                   185                   190
Ala Ser Gly Pro Pro Gln Pro Pro Ala Phe Phe Ser Phe Ser Pro Pro
                  195                   200                   205
Thr Gly Pro Ser Pro Ser Leu Ala Gln Ser Pro Leu Lys Leu Phe Pro
              210                   215                   220
Ser Gln Ala Thr His Gln Leu Gly Glu Gly Glu Ser Tyr Ser Met Pro
225                   230                   235                   240


Thr Ala Phe Pro Gly Leu Ala Pro Thr Ser Pro His Leu Glu Gly Ser
                  245                   250                   255
Gly Ile Leu Asp Thr Pro Val Thr Ser Thr Lys Ala Arg Ser Gly Ala
                  260                   265                   270
Pro Gly Gly Ser Glu Gly Arg Cys Ala Val Cys Gly Asp Asn Ala Ser
              275                   280                   285
Cys Gln His Tyr Gly Val Arg Thr Cys Glu Gly Cys Lys Gly Phe Phe
              290                   295                   300
```

Lys Arg Thr Val Gln Lys Asn Ala Lys Tyr Ile Cys Leu Ala Asn Lys

305   310   315   320

Asp Cys Pro Val Asp Lys Arg Arg Arg Asn Arg Cys Gln Phe Cys Arg
                325   330   335

Phe Gln Lys Cys Leu Ala Val Gly Met Val Lys Glu Val Val Arg Thr
                340   345   350

Asp Ser Leu Lys Gly Arg Arg Gly Arg Leu Pro Ser Lys Pro Lys Gln
                355   360   365

Pro Pro Asp Ala Ser Pro Ala Asn Leu Leu Thr Ser Leu Val Arg Ala
        370   375   380

His Leu Asp Ser Gly Pro Ser Thr Ala Lys Leu Asp Tyr Ser Lys Phe
385   390   395   400

Gln Glu Leu Val Leu Pro His Phe Gly Lys Glu Asp Ala Gly Asp Val
                405   410   415

Gln Gln Phe Tyr Asp Leu Leu Ser Gly Ser Leu Glu Val Ile Arg Lys
                420   425   430

Trp Ala Glu Lys Ile Pro Gly Phe Ala Glu Leu Ser Pro Ala Asp Gln
                435   440   445

Asp Leu Leu Leu Glu Ser Ala Phe Leu Glu Leu Phe Ile Leu Arg Leu

        450   455   460

Ala Tyr Arg Ser Lys Pro Gly Glu Gly Lys Leu Ile Phe Cys Ser Gly
465   470   475   480

Leu Val Leu His Arg Leu Gln Cys Ala Arg Gly Phe Gly Asp Trp Ile
                485   490   495

Asp Ser Ile Leu Ala Phe Ser Arg Ser Leu His Ser Leu Leu Val Asp
                500   505   510

Val Pro Ala Phe Ala Cys Leu Ser Ala Leu Val Leu Ile Thr Asp Arg
        515   520   525

His Gly Leu Gln Glu Pro Arg Arg Val Glu Glu Leu Gln Asn Arg Ile
        530   535   540

Ala Ser Cys Leu Lys Glu His Val Ala Ala Val Ala Gly Glu Pro Gln

```
         545                550                555                560
Pro Ala Ser Cys Leu Ser Arg Leu Leu Gly Lys Leu Pro Glu Leu Arg
                        565                570                575
Thr Leu Cys Thr Gln Gly Leu Gln Arg Ile Phe Tyr Leu Lys Leu Glu
                    580                585                590
Asp Leu Val Pro Pro Pro Pro Ile Ile Asp Lys Ile Phe Met Asp Thr


              595                600                605
Leu Pro Phe
      610
```

<210> 118

<211> 263

<212> PRT

<213> Homo sapiens

<400> 118

```
Met Arg Ile Phe Arg Pro Trp Arg Leu Arg Cys Pro Ala Leu His Leu
  1                5                10                15
Pro Ser Leu Ser Val Phe Ser Leu Arg Trp Lys Leu Pro Ser Leu Thr
                    20                25                30
Thr Asp Glu Thr Met Cys Lys Ser Val Thr Thr Asp Glu Trp Lys Lys
              35                40                45


Val Phe Tyr Glu Lys Met Glu Glu Ala Lys Pro Ala Asp Ser Trp Asp
          50                55                60
Leu Ile Ile Asp Pro Asn Leu Lys His Asn Val Leu Ser Pro Gly Trp
 65                70                75                80
Lys Gln Tyr Leu Glu Leu His Ala Ser Gly Arg Phe His Cys Ser Trp
                    85                90                95
Cys Trp His Thr Trp Gln Ser Pro Tyr Val Val Ile Leu Phe His Met
                    100                105                110
Phe Leu Asp Arg Ala Gln Arg Ala Gly Ser Val Arg Met Arg Val Phe


              115                120                125
Lys Gln Leu Cys Tyr Glu Cys Gly Thr Ala Arg Leu Asp Glu Ser Ser
          130                135                140
```

Met Leu Glu Glu Asn Ile Glu Gly Leu Val Asp Asn Leu Ile Thr Ser
145   150   155   160

Leu Arg Glu Gln Cys Tyr Gly Glu Arg Gly Gly Gln Tyr Arg Ile His
                165   170   175

Val Ala Ser Arg Gln Asp Asn Arg Arg His Arg Gly Glu Phe Cys Glu
                180   185   190

Ala Cys Gln Glu Gly Ile Val His Trp Lys Pro Ser Glu Lys Leu Leu
                195   200   205

Glu Glu Glu Ala Thr Thr Tyr Thr Phe Ser Arg Ala Pro Ser Pro Thr
                210   215   220

Lys Ser Gln Asp Gln Thr Gly Ser Gly Trp Asn Phe Cys Ser Ile Pro
225   230   235   240

Trp Cys Leu Phe Trp Ala Thr Val Leu Leu Leu Ile Ile Tyr Leu Gln
                245   250   255

Phe Ser Phe Arg Ser Ser Val

                260

<210>   119

<211>   124

<212>   PRT

<213>   Homo sapiens

<400>   119

Met Pro Ala Cys Arg Leu Gly Pro Leu Ala Ala Ala Leu Leu Leu Ser
 1   5   10   15

Leu Leu Leu Phe Gly Phe Thr Leu Val Ser Gly Thr Gly Ala Glu Lys
                20   25   30

Thr Gly Val Cys Pro Glu Leu Gln Ala Asp Gln Asn Cys Thr Gln Glu
                35   40   45

Cys Val Ser Asp Ser Glu Cys Ala Asp Asn Leu Lys Cys Cys Ser Ala

 50   55   60

Gly Cys Ala Thr Phe Cys Ser Leu Pro Asn Asp Lys Glu Gly Ser Cys
 65   70   75   80

Pro Gln Val Asn Ile Asn Phe Pro Gln Leu Gly Leu Cys Arg Asp Gln

```
                    85                  90                  95
Cys Gln Val Asp Ser Gln Cys Pro Gly Gln Met Lys Cys Cys Arg Asn
            100                 105                 110
Gly Cys Gly Lys Val Ser Cys Val Thr Pro Asn Phe
        115                 120
```

<210>   120

<211>   343

<212>   PRT

<213>   Homo sapiens

<400>   120

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

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

Leu Asn Asp Trp Met Glu Glu Glu Tyr Arg His Ile Pro Gly Glu Tyr
        130                 135                 140
Val Arg Phe Thr Gly Tyr Pro Cys Ser Trp Thr Phe Tyr His His Leu
145                 150                 155                 160
Arg Gln Glu Ile Leu Gln Glu Phe Thr Leu His Asp His Val Arg Glu
                165                 170                 175
```

Glu Ala Gln Lys Phe Leu Arg Gly Leu Gln Val Asn Gly Ser Arg Pro
            180   185   190

Gly Thr Phe Val Gly Val His Val Arg Arg Gly Asp Tyr Val His Val

            195   200   205

Met Pro Lys Val Trp Lys Gly Val Val Ala Asp Arg Arg Tyr Leu Gln
        210   215   220

Gln Ala Leu Asp Trp Phe Arg Ala Arg Tyr Ser Ser Leu Ile Phe Val
225   230   235   240

Val Thr Ser Asn Gly Met Ala Trp Cys Arg Glu Asn Ile Asp Thr Ser
                245   250   255

His Gly Asp Val Val Phe Ala Gly Asp Gly Ile Glu Gly Ser Pro Ala
            260   265   270

Lys Asp Phe Ala Leu Leu Thr Gln Cys Asn His Thr Ile Met Thr Ile
            275   280   285

Gly Thr Phe Gly Ile Trp Ala Ala Tyr Leu Thr Gly Gly Asp Thr Ile
        290   295   300

Tyr Leu Ala Asn Tyr Thr Leu Pro Asp Ser Pro Phe Leu Lys Ile Phe
305   310   315   320

Lys Pro Glu Ala Ala Phe Leu Pro Glu Trp Thr Gly Ile Ala Ala Asp
                325   330   335

Leu Ser Pro Leu Leu Lys His

            340

<210>   121

<211>   119

<212>   PRT

<213>   Homo sapiens

<400>   121

Met Lys Ala Leu Ser Pro Val Arg Gly Cys Tyr Glu Ala Val Cys Cys
  1   5   10   15

Leu Ser Glu Arg Ser Leu Ala Ile Ala Arg Gly Arg Gly Lys Gly Pro
            20   25   30

Ala Ala Glu Glu Pro Leu Ser Leu Leu Asp Asp Met Asn His Cys Tyr

<pre>
              35   40   45
Ser Arg Leu Arg Glu Leu Val Pro Gly Val Pro Arg Gly Thr Gln Leu

              50   55   60
Ser Gln Val Glu Ile Leu Gln Arg Val Ile Asp Tyr Ile Leu Asp Leu
 65   70   75   80
Gln Val Val Leu Ala Glu Pro Ala Pro Gly Pro Pro Asp Gly Pro His
                  85   90   95
Leu Pro Ile Gln Thr Ala Glu Leu Thr Pro Glu Leu Val Ile Ser Asn
                 100   105   110
Asp Lys Arg Ser Phe Cys His
         115
</pre>

<210>   122

<211

>   159

<212>   PRT

<213>   Homo sapiens

<400>   122

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

Met Ser Ala Arg Ala Glu Ala Ile Lys Ala Leu Val Lys Pro Lys Glu
 65   70   75   80
Val Lys Pro Lys Ile Pro Lys Gly Val Ser Arg Lys Leu Asp Arg Leu
                  85   90   95
Ala Tyr Ile Ala His Pro Lys Leu Gly Lys Arg Ala Arg Ala Arg Ile
                 100   105   110
Ala Lys Gly Leu Arg Leu Cys Arg Pro Lys Ala Lys Ala Lys Ala Lys
         115   120   125
</pre>

Ala Lys Asp Gln Thr Lys Ala Gln Ala Ala Ala Pro Ala Ser Val Pro

        130   135   140

Ala Gln Ala Pro Lys Arg Thr Gln Ala Pro Thr Lys Ala Ser Glu

145   150   155

<210>   123

<211>   417

<212>   PRT

<213>   Homo sapiens

<400>   123

Met Gly Ser Ala His Pro Arg Pro Trp Leu Arg Leu Arg Pro Gln Pro

 1   5   10   15

Gln Pro Arg Pro Ala Leu Trp Val Leu Leu Phe Phe Leu Leu Leu Leu

        20   25   30

Ala Ala Ala Met Pro Arg Ser Ala Pro Asn Asp Ile Leu Asp Leu Arg

        35   40   45

Leu Pro Pro Glu Pro Val Leu Asn Ala Asn Thr Val Cys Leu Thr Leu

     50   55   60

Pro Gly Leu Ser Arg Arg Gln Met Glu Val Cys Val Arg His Pro Asp

 65   70   75   80

Val Ala Ala Ser Ala Ile Gln Gly Ile Gln Ile Ala Ile His Glu Cys

           85   90   95

Gln His Gln Phe Arg Asp Gln Arg Trp Asn Cys Ser Ser Leu Glu Thr

        100   105   110

Arg Asn Lys Ile Pro Tyr Glu Ser Pro Ile Phe Ser Arg Gly Phe Arg

        115   120   125

Glu Ser Ala Phe Ala Tyr Ala Ile Ala Ala Ala Gly Val Val His Ala

        130   135   140

Val Ser Asn Ala Cys Ala Leu Gly Lys Leu Lys Ala Cys Gly Cys Asp

145   150   155   160

Ala Ser Arg Arg Gly Asp Glu Glu Ala Phe Arg Arg Lys Leu His Arg

          165   170   175

Leu Gln Leu Asp Ala Leu Gln Arg Gly Lys Gly Leu Ser His Gly Val

                      180   185   190

Pro Glu His Pro Ala Leu Pro Thr Ala Ser Pro Gly Leu Gln Asp Ser
        195   200   205

Trp Glu Trp Gly Gly Cys Ser Pro Asp Met Gly Phe Gly Glu Arg Phe
        210   215   220

Ser Lys Asp Phe Leu Asp Ser Arg Glu Pro His Arg Asp Ile His Ala
225   230   235   240

Arg Met Arg Leu His Asn Asn Arg Val Gly Arg Gln Ala Val Met Glu
               245   250   255

Asn Met Arg Arg Lys Cys Lys Cys His Gly Thr Ser Gly Ser Cys Gln
            260   265   270

Leu Lys Thr Cys Trp Gln Val Thr Pro Glu Phe Arg Thr Val Gly Ala
        275   280   285

Leu Leu Arg Ser Arg Phe His Arg Ala Thr Leu Ile Arg Pro His Asn
      290   295   300

Arg Asn Gly Gly Gln Leu Glu Pro Gly Pro Ala Gly Ala Pro Ser Pro
305   310   315   320

Ala Pro Gly Ala Pro Gly Pro Arg Arg Arg Ala Ser Pro Ala Asp Leu

                      325   330   335

Val Tyr Phe Glu Lys Ser Pro Asp Phe Cys Glu Arg Glu Pro Arg Leu
        340   345   350

Asp Ser Ala Gly Thr Val Gly Arg Leu Cys Asn Lys Ser Ser Ala Gly
        355   360   365

Ser Asp Gly Cys Gly Ser Met Cys Cys Gly Arg Gly His Asn Ile Leu
        370   375   380

Arg Gln Thr Arg Ser Glu Arg Cys His Cys Arg Phe His Trp Cys Cys
385   390   395   400

Phe Val Val Cys Glu Glu Cys Arg Ile Thr Glu Trp Val Ser Val Cys
               405   410   415

Lys

<210> 124

<211> 1791

<212> PRT

<213> Homo sapiens

<400> 124

Met Met Cys Leu Lys Ile Leu Arg Ile Ser Leu Ala Ile Leu Ala Gly
1   5   10   15

Trp Ala Leu Cys Ser Ala Asn Ser Glu Leu Gly Trp Thr Arg Lys Lys
                20   25   30

Ser Leu Val Glu Arg Glu His Leu Asn Gln Val Leu Leu Glu Gly Glu

                35   40   45

Arg Cys Trp Leu Gly Ala Lys Val Arg Arg Pro Arg Ala Ser Pro Gln
        50   55   60

His His Leu Phe Gly Val Tyr Pro Ser Arg Ala Gly Asn Tyr Leu Arg
 65   70   75   80

Pro Tyr Pro Val Gly Glu Gln Glu Ile His His Thr Gly Arg Ser Lys
                    85   90   95

Pro Asp Thr Glu Gly Asn Ala Val Ser Leu Val Pro Pro Asp Leu Thr
                100   105   110

Glu Asn Pro Ala Gly Leu Arg Gly Ala Val Glu Glu Pro Ala Ala Pro
                115   120   125

Trp Val Gly Asp Ser Pro Ile Gly Gln Ser Glu Leu Leu Gly Asp Asp
        130   135   140

Asp Ala Tyr Leu Gly Asn Gln Arg Ser Lys Glu Ser Leu Gly Glu Ala
145   150   155   160

Gly Ile Gln Lys Gly Ser Ala Met Ala Ala Thr Thr Thr Thr Ala Ile
                165   170   175

Phe Thr Thr Leu Asn Glu Pro Lys Pro Glu Thr Gln Arg Arg Gly Trp

                180   185   190

Ala Lys Ser Arg Gln Arg Arg Gln Val Trp Lys Arg Arg Ala Glu Asp
        195   200   205

Gly Gln Gly Asp Ser Gly Ile Ser Ser His Phe Gln Pro Trp Pro Lys
    210   215   220

His Ser Leu Lys His Arg Val Lys Lys Ser Pro Pro Glu Glu Ser Asn
225   230   235   240

Gln Asn Gly Gly Glu Gly Ser Tyr Arg Glu Ala Glu Thr Phe Asn Ser
            245   250   255

Gln Val Gly Leu Pro Ile Leu Tyr Phe Ser Gly Arg Arg Glu Arg Leu
         260   265   270

Leu Leu Arg Pro Glu Val Leu Ala Glu Ile Pro Arg Glu Ala Phe Thr
        275   280   285

Val Glu Ala Trp Val Lys Pro Glu Gly Gly Gln Asn Asn Pro Ala Ile
    290   295   300

Ile Ala Gly Val Phe Asp Asn Cys Ser His Thr Val Ser Asp Lys Gly
305   310   315   320

Trp Ala Leu Gly Ile Arg Ser Gly Lys Asp Lys Gly Lys Arg Asp Ala

        325   330   335

Arg Phe Phe Phe Ser Leu Cys Thr Asp Arg Val Lys Lys Ala Thr Ile
        340   345   350

Leu Ile Ser His Ser Arg Tyr Gln Pro Gly Thr Trp Thr His Val Ala
        355   360   365

Ala Thr Tyr Asp Gly Arg His Met Ala Leu Tyr Val Asp Gly Thr Gln
    370   375   380

Val Ala Ser Ser Leu Asp Gln Ser Gly Pro Leu Asn Ser Pro Phe Met
385   390   395   400

Ala Ser Cys Arg Ser Leu Leu Leu Gly Gly Asp Ser Ser Glu Asp Gly
        405   410   415

His Tyr Phe Arg Gly His Leu Gly Thr Leu Val Phe Trp Ser Thr Ala
        420   425   430

Leu Pro Gln Ser His Phe Gln His Ser Ser Gln His Ser Ser Gly Glu
        435   440   445

Glu Glu Ala Thr Asp Leu Val Leu Thr Ala Ser Phe Glu Pro Val Asn
    450   455   460

Thr Glu Trp Val Pro Phe Arg Asp Glu Lys Tyr Pro Arg Leu Glu Val

465   470   475   480

Leu Gln Gly Phe Glu Pro Glu Pro Glu Ile Leu Ser Pro Leu Gln Pro

            485   490   495

Pro Leu Cys Gly Gln Thr Val Cys Asp Asn Val Glu Leu Ile Ser Gln

            500   505   510

Tyr Asn Gly Tyr Trp Pro Leu Arg Gly Glu Lys Val Ile Arg Tyr Gln

            515   520   525

Val Val Asn Ile Cys Asp Asp Glu Gly Leu Asn Pro Ile Val Ser Glu

            530   535   540

Glu Gln Ile Arg Leu Gln His Glu Ala Leu Asn Glu Ala Phe Ser Arg

545   550   555   560

Tyr Asn Ile Ser Trp Gln Leu Ser Val His Gln Val His Asn Ser Thr

            565   570   575

Leu Arg His Arg Val Val Leu Val Asn Cys Glu Pro Ser Lys Ile Gly

            580   585   590

Asn Asp His Cys Asp Pro Glu Cys Glu His Pro Leu Thr Gly Tyr Asp

            595   600   605

Gly Gly Asp Cys Arg Leu Gln Gly Arg Cys Tyr Ser Trp Asn Arg Arg

            610   615   620

Asp Gly Leu Cys His Val Glu Cys Asn Asn Met Leu Asn Asp Phe Asp

625   630   635   640

Asp Gly Asp Cys Cys Asp Pro Gln Val Ala Asp Val Arg Lys Thr Cys

            645   650   655

Phe Asp Pro Asp Ser Pro Lys Arg Ala Tyr Met Ser Val Lys Glu Leu

            660   665   670

Lys Glu Ala Leu Gln Leu Asn Ser Thr His Phe Leu Asn Ile Tyr Phe

            675   680   685

Ala Ser Ser Val Arg Glu Asp Leu Ala Gly Ala Ala Thr Trp Pro Trp

            690   695   700

Asp Lys Asp Ala Val Thr His Leu Gly Gly Ile Val Leu Ser Pro Ala

```
705                 710                 715                 720

Tyr Tyr Gly Met Pro Gly His Thr Asp Thr Met Ile His Glu Val Gly
                    725                 730                 735

His Val Leu Gly Leu Tyr His Val Phe Lys Gly Val Ser Glu Arg Glu
                740                 745                 750

Ser Cys Asn Asp Pro Cys Lys Glu Thr Val Pro Ser Met Glu Thr Gly


            755                 760                 765

Asp Leu Cys Ala Asp Thr Ala Pro Thr Pro Lys Ser Glu Leu Cys Arg
        770                 775                 780

Glu Pro Glu Pro Thr Ser Asp Thr Cys Gly Phe Thr Arg Phe Pro Gly
785                 790                 795                 800

Ala Pro Phe Thr Asn Tyr Met Ser Tyr Thr Asp Asp Asn Cys Thr Asp
                805                 810                 815

Asn Phe Thr Pro Asn Gln Val Ala Arg Met His Cys Tyr Leu Asp Leu
            820                 825                 830


Val Tyr Gln Gln Trp Thr Glu Ser Arg Lys Pro Thr Pro Ile Pro Ile
        835                 840                 845

Pro Pro Met Val Ile Gly Gln Thr Asn Lys Ser Leu Thr Ile His Trp
    850                 855                 860

Leu Pro Pro Ile Ser Gly Val Val Tyr Asp Arg Ala Ser Gly Ser Leu
865                 870                 875                 880

Cys Gly Ala Cys Thr Glu Asp Gly Thr Phe Arg Gln Tyr Val His Thr
                885                 890                 895

Ala Ser Ser Arg Arg Val Cys Asp Ser Ser Gly Tyr Trp Thr Pro Glu


            900                 905                 910

Glu Ala Val Gly Pro Pro Asp Val Asp Gln Pro Cys Glu Pro Ser Leu
            915                 920                 925

Gln Ala Trp Ser Pro Glu Val His Leu Tyr His Met Asn Met Thr Val
        930                 935                 940

Pro Cys Pro Thr Glu Gly Cys Ser Leu Glu Leu Leu Phe Gln His Pro
945                 950                 955                 960

Val Gln Ala Asp Thr Leu Thr Leu Trp Val Thr Ser Phe Phe Met Glu
```

                965   970   975

Ser Ser Gln Val Leu Phe Asp Thr Glu Ile Leu Leu Glu Asn Lys Glu
                980   985   990

Ser Val His Leu Gly Pro Leu Asp Thr Phe Cys Asp Ile Pro Leu Thr
            995   1000   1005

Ile Lys Leu His Val Asp Gly Lys Val Ser Gly Val Lys Val Tyr Thr
        1010   1015   1020

Phe Asp Glu Arg Ile Glu Ile Asp Ala Ala Leu Leu Thr Ser Gln Pro
    1025   1030   1035   1040

His Ser Pro Leu Cys Ser Gly Cys Arg Pro Val Arg Tyr Gln Val Leu

                1045   1050   1055

Arg Asp Pro Pro Phe Ala Ser Gly Leu Pro Val Val Val Thr His Ser
                1060   1065   1070

His Arg Lys Phe Thr Asp Val Glu Val Thr Pro Gly Gln Met Tyr Gln
            1075   1080   1085

Tyr Gln Val Leu Ala Glu Ala Gly Gly Glu Leu Gly Glu Ala Ser Pro
        1090   1095   1100

Pro Leu Asn His Ile His Gly Ala Pro Tyr Cys Gly Asp Gly Lys Val
    1105   1110   1115   1120

Ser Glu Arg Leu Gly Glu Glu Cys Asp Asp Gly Asp Leu Val Ser Gly
                1125   1130   1135

Asp Gly Cys Ser Lys Val Cys Glu Leu Glu Glu Gly Phe Asn Cys Val
                1140   1145   1150

Gly Glu Pro Ser Leu Cys Tyr Met Tyr Glu Gly Asp Gly Ile Cys Glu
            1155   1160   1165

Pro Phe Glu Arg Lys Thr Ser Ile Val Asp Cys Gly Ile Tyr Thr Pro
        1170   1175   1180

Lys Gly Tyr Leu Asp Gln Trp Ala Thr Arg Ala Tyr Ser Ser His Glu

    1185   1190   1195   1200

Asp Lys Lys Lys Cys Pro Val Ser Leu Val Thr Gly Glu Pro His Ser
                1205   1210   1215

Leu Ile Cys Thr Ser Tyr His Pro Asp Leu Pro Asn His Arg Pro Leu
           1220   1225   1230

Thr Gly Trp Phe Pro Cys Val Ala Ser Glu Asn Glu Thr Gln Asp Asp
            1235   1240   1245

Arg Ser Glu Gln Pro Glu Gly Ser Leu Lys Lys Glu Asp Glu Val Trp
        1250   1255   1260

Leu Lys Val Cys Phe Asn Arg Pro Gly Glu Ala Arg Ala Ile Phe Ile
1265   1270   1275   1280

Phe Leu Thr Thr Asp Gly Leu Val Pro Gly Glu His Gln Gln Pro Thr
            1285   1290   1295

Val Thr Leu Tyr Leu Thr Asp Val Arg Gly Ser Asn His Ser Leu Gly
            1300   1305   1310

Thr Tyr Gly Leu Ser Cys Gln His Asn Pro Leu Ile Ile Asn Val Thr
         1315   1320   1325

His His Gln Asn Val Leu Phe His His Thr Thr Ser Val Leu Leu Asn

       1330   1335   1340

Phe Ser Ser Pro Arg Val Gly Ile Ser Ala Val Ala Leu Arg Thr Ser
1345   1350   1355   1360

Ser Arg Ile Gly Leu Ser Ala Pro Ser Asn Cys Ile Ser Glu Asp Glu
            1365   1370   1375

Gly Gln Asn His Gln Gly Gln Ser Cys Ile His Arg Pro Cys Gly Lys
            1380   1385   1390

Gln Asp Ser Cys Pro Ser Leu Leu Leu Asp His Ala Asp Val Val Asn
         1395   1400   1405

Cys Thr Ser Ile Gly Pro Gly Leu Met Lys Cys Ala Ile Thr Cys Gln
        1410   1415   1420

Arg Gly Phe Ala Leu Gln Ala Ser Ser Gly Gln Tyr Ile Arg Pro Met
1425   1430   1435   1440

Gln Lys Glu Ile Leu Leu Thr Cys Ser Ser Gly His Trp Asp Gln Asn
            1445   1450   1455

Val Ser Cys Leu Pro Val Asp Cys Gly Val Pro Asp Pro Ser Leu Val
         1460   1465   1470

Asn Tyr Ala Asn Phe Ser Cys Ser Glu Gly Thr Lys Phe Leu Lys Arg

      1475   1480   1485

Cys Ser Ile Ser Cys Val Pro Pro Ala Lys Leu Gln Gly Leu Ser Pro

    1490   1495   1500

Trp Leu Thr Cys Leu Glu Asp Gly Leu Trp Ser Leu Pro Glu Val Tyr

1505   1510   1515   1520

Cys Lys Leu Glu Cys Asp Ala Pro Pro Ile Ile Leu Asn Ala Asn Leu

        1525   1530   1535

Leu Leu Pro His Cys Leu Gln Asp Asn His Asp Val Gly Thr Ile Cys

      1540   1545   1550

Lys Tyr Glu Cys Lys Pro Gly Tyr Tyr Val Ala Glu Ser Ala Glu Gly

      1555   1560   1565

Lys Val Arg Asn Lys Leu Leu Lys Ile Gln Cys Leu Glu Gly Gly Ile

    1570   1575   1580

Trp Glu Gln Gly Ser Cys Ile Pro Val Val Cys Glu Pro Pro Pro

1585   1590   1595   1600

Val Phe Glu Gly Met Tyr Glu Cys Thr Asn Gly Phe Ser Leu Asp Ser

         1605   1610   1615

Gln Cys Val Leu Asn Cys Asn Gln Glu Arg Glu Lys Leu Pro Ile Leu

      1620   1625   1630

Cys Thr Lys Glu Gly Leu Trp Thr Gln Glu Phe Lys Leu Cys Glu Asn

      1635   1640   1645

Leu Gln Gly Glu Cys Pro Pro Pro Pro Ser Glu Leu Asn Ser Val Glu

    1650   1655   1660

Tyr Lys Cys Glu Gln Gly Tyr Gly Ile Gly Ala Val Cys Ser Pro Leu

1665   1670   1675   1680

Cys Val Ile Pro Pro Ser Asp Pro Val Met Leu Pro Glu Asn Ile Thr

      1685   1690   1695

Ala Asp Thr Leu Glu His Trp Met Glu Pro Val Lys Val Gln Ser Ile

      1700   1705   1710

Val Cys Thr Gly Arg Arg Gln Trp His Pro Asp Pro Val Leu Val His

```
                1715                1720                1725
Cys Ile Gln Ser Cys Glu Pro Phe Gln Ala Asp Gly Trp Cys Asp Thr
        1730                1735                1740
Ile Asn Asn Arg Ala Tyr Cys His Tyr Asp Gly Gly Asp Cys Cys Ser
1745                1750                1755                1760
Ser Thr Leu Ser Ser Lys Lys Val Ile Pro Phe Ala Ala Asp Cys Asp


                1765                1770                1775
Leu Asp Glu Cys Thr Cys Arg Asp Pro Lys Ala Glu Glu Asn Gln
                1780                1785                1790
```

<210> 125

<211> 535

<212> PRT

<213> Homo sapiens

<400> 125

```
Met Ala Trp Ile Leu Asp Cys Leu Phe Ala Ser Ala Phe Glu Pro Arg
 1                 5                10                15
Pro Arg Arg Val Ser Val Leu Gly Gly Ala Pro Gly His Asn Pro Asp
                20                25                30


Arg Arg Thr Lys Met Val Ser Ile His Ser Leu Ser Glu Leu Glu Arg
                35                40                45
Leu Lys Leu Gln Glu Thr Ala Tyr His Glu Leu Val Ala Arg His Phe
        50                55                60
Leu Ser Glu Phe Lys Pro Asp Arg Ala Leu Pro Ile Asp Arg Pro Asn
 65                70                75                80
Thr Leu Asp Lys Trp Phe Leu Ile Leu Arg Gly Gln Gln Arg Ala Val
                85                90                95
Ser His Lys Thr Phe Gly Ile Ser Leu Glu Glu Val Leu Val Asn Glu


                100                105                110
Phe Thr Arg Arg Lys His Leu Glu Leu Thr Ala Thr Met Gln Val Glu
                115                120                125
Glu Ala Thr Gly Gln Ala Ala Gly Arg Arg Arg Gly Asn Val Val Arg
        130                135                140
```

Arg Val Phe Gly Arg Ile Arg Arg Phe Phe Ser Arg Arg Asn Glu
145   150   155   160

Pro Thr Leu Pro Arg Glu Phe Thr Arg Arg Gly Arg Arg Gly Ala Val
                165   170   175

Ser Val Asp Ser Leu Ala Glu Leu Glu Asp Gly Ala Leu Leu Leu Gln
                180   185   190

Thr Leu Gln Leu Ser Lys Ile Ser Phe Pro Ile Gly Gln Arg Leu Leu
                195   200   205

Gly Ser Lys Arg Lys Met Ser Leu Asn Pro Ile Ala Lys Gln Ile Pro
        210   215   220

Gln Val Val Glu Ala Cys Cys Gln Phe Ile Glu Lys His Gly Leu Ser
225   230   235   240

Ala Val Gly Ile Phe Thr Leu Glu Tyr Ser Val Gln Arg Val Arg Gln

                245   250   255

Leu Arg Glu Glu Phe Asp Gln Gly Leu Asp Val Val Leu Asp Asp Asn
                260   265   270

Gln Asn Val His Asp Val Ala Ala Leu Leu Lys Glu Phe Phe Arg Asp
        275   280   285

Met Lys Asp Ser Leu Leu Pro Asp Asp Leu Tyr Met Ser Phe Leu Leu
        290   295   300

Thr Ala Thr Leu Lys Pro Gln Asp Gln Leu Ser Ala Leu Gln Leu Leu
305   310   315   320

Val Tyr Leu Met Pro Pro Cys His Ser Asp Thr Leu Glu Arg Leu Leu
                325   330   335

Lys Ala Leu His Lys Ile Thr Glu Asn Cys Glu Asp Ser Ile Gly Ile
                340   345   350

Asp Gly Gln Leu Val Pro Gly Asn Arg Met Thr Ser Thr Asn Leu Ala
        355   360   365

Leu Val Phe Gly Ser Ala Leu Leu Lys Lys Gly Lys Phe Gly Lys Arg
        370   375   380

Glu Ser Arg Lys Thr Lys Leu Gly Ile Asp His Tyr Val Ala Ser Val

```
            385                 390                 395                 400
Asn Val Val Arg Ala Met Ile Asp Asn Trp Asp Val Leu Phe Gln Val
                          405                 410                 415
Pro Pro His Ile Gln Arg Gln Val Ala Lys Arg Val Trp Lys Ser Ser
                      420                 425                 430
Pro Glu Ala Leu Asp Phe Ile Arg Arg Arg Asn Leu Arg Lys Ile Gln
                  435                 440                 445
Ser Ala Arg Ile Lys Met Glu Glu Asp Ala Leu Leu Ser Asp Pro Val
              450                 455                 460


Glu Thr Ser Ala Glu Ala Arg Ala Ala Val Leu Ala Gln Ser Lys Pro
465                 470                 475                 480
Ser Asp Glu Gly Ser Ser Glu Glu Pro Ala Val Pro Ser Gly Thr Ala
                      485                 490                 495
Arg Ser His Asp Asp Glu Glu Gly Ala Gly Asn Pro Pro Ile Pro Glu
                  500                 505                 510
Gln Asp Arg Pro Leu Leu Arg Val Pro Arg Glu Lys Glu Ala Lys Thr
                  515                 520                 525
Gly Val Ser Tyr Phe Phe Pro
```

```
      530                 535
```

<210>   126

<211>   269

<212>   PRT

<213>   Homo sapiens

<400>   126

```
Met Ser Ala Ala Leu Phe Ser Leu Asp Gly Pro Ala Arg Gly Ala Pro
  1                 5                  10                  15
Trp Pro Ala Glu Pro Ala Pro Phe Tyr Glu Pro Gly Arg Ala Gly Lys
                  20                  25                  30
Pro Gly Arg Gly Ala Glu Pro Gly Ala Leu Gly Glu Pro Gly Ala Ala
                  35                  40                  45
Ala Pro Ala Met Tyr Asp Asp Glu Ser Ala Ile Asp Phe Ser Ala Tyr
```

```
      50                  55                  60
```

Ile Asp Ser Met Ala Ala Val Pro Thr Leu Glu Leu Cys His Asp Glu

65   70   75   80

Leu Phe Ala Asp Leu Phe Asn Ser Asn His Lys Ala Gly Gly Ala Gly

             85   90   95

Pro Leu Glu Leu Leu Pro Gly Gly Pro Ala Arg Pro Leu Gly Pro Gly

          100   105   110

Pro Ala Ala Pro Arg Leu Leu Lys Arg Glu Pro Asp Trp Gly Asp Gly

          115   120   125

Asp Ala Pro Gly Ser Leu Leu Pro Ala Gln Val Ala Ala Cys Ala Gln

          130   135   140

Thr Val Val Ser Leu Ala Ala Ala Gly Gln Pro Thr Pro Pro Thr Ser

145   150   155   160

Pro Glu Pro Pro Arg Ser Ser Pro Arg Gln Thr Pro Ala Pro Gly Pro

          165   170   175

Ala Arg Glu Lys Ser Ala Gly Lys Arg Gly Pro Asp Arg Gly Ser Pro

          180   185   190

Glu Tyr Arg Gln Arg Arg Glu Arg Asn Asn Ile Ala Val Arg Lys Ser

          195   200   205

Arg Asp Lys Ala Lys Arg Arg Asn Gln Glu Met Gln Gln Lys Leu Val

          210   215   220

Glu Leu Ser Ala Glu Asn Glu Lys Leu His Gln Arg Val Glu Gln Leu

225   230   235   240

Thr Arg Asp Leu Ala Gly Leu Arg Gln Phe Phe Lys Gln Leu Pro Ser

          245   250   255

Pro Pro Phe Leu Pro Ala Ala Gly Thr Ala Asp Cys Arg

          260   265

<210>   127
<211>   182
<212>   PRT
<213>   Homo sapiens
<400>   127

Met Lys Ser Phe Leu Leu Val Val Asn Ala Leu Ala Leu Thr Leu Pro

```
       1             5             10            15
Phe Leu Ala Val Glu Val Gln Asn Gln Lys Gln Pro Ala Cys His Glu
                   20            25            30
Asn Asp Glu Arg Pro Phe Tyr Gln Lys Thr Ala Pro Tyr Val Pro Met
          35            40            45
Tyr Tyr Val Pro Asn Ser Tyr Pro Tyr Tyr Gly Thr Asn Leu Tyr Gln


          50            55            60
Arg Arg Pro Ala Ile Ala Ile Asn Asn Pro Tyr Val Pro Arg Thr Tyr
 65             70            75            80
Tyr Ala Asn Pro Ala Val Val Arg Pro His Ala Gln Ile Pro Gln Arg
                   85            90            95
Gln Tyr Leu Pro Asn Ser His Pro Pro Thr Val Val Arg Arg Pro Asn
               100           105           110
Leu His Pro Ser Phe Ile Ala Ile Pro Pro Lys Lys Ile Gln Asp Lys
          115           120           125


Ile Ile Ile Pro Thr Ile Asn Thr Ile Ala Thr Val Glu Pro Thr Pro
          130           135           140
Ala Pro Ala Thr Glu Pro Thr Val Asp Ser Val Val Thr Pro Glu Ala
145           150           155           160
Phe Ser Glu Ser Ile Ile Thr Ser Thr Pro Glu Thr Thr Thr Val Ala
               165           170           175
Val Thr Pro Pro Thr Ala
               180
```

<210> 128
<211> 426
<212> PRT
<213> Homo sapiens
<400> 128

```
Met Trp Pro Leu Thr Ala Leu Leu Leu Leu Val Pro Ser Ser Gly Gln


       1             5             10            15
Ala Ala Thr Leu Glu Lys Pro Ile Leu Ser Leu His Pro Pro Trp Thr
                   20            25            30
```

Thr Ile Phe Lys Gly Glu Arg Val Thr Leu Lys Cys Asp Gly Tyr His
       35   40   45

Pro Leu Leu Leu Glu Leu Gln Pro Ile Ser Thr Leu Trp Tyr Leu Gly
     50   55   60

His Leu Leu Leu Pro Ser His Lys Lys Ser Ile Glu Val Gln Thr Pro
65   70   75   80

Gly Val Tyr Arg Cys Gln Thr Arg Gly Ala Pro Val Ser Asp Pro Ile
           85   90   95

His Leu Ser Val Ser Asn Asp Trp Leu Ile Leu Gln Val Pro Tyr Ala
         100   105   110

Pro Val Phe Glu Gly Glu Pro Leu Val Leu Arg Cys Arg Gly Trp Tyr
     115   120   125

Asp Lys Val Val Tyr Lys Leu His Tyr Tyr His Asp Gly Gln Ala Val
    130   135   140

Arg Tyr Phe His Ser Ser Ala Asn Tyr Thr Val Leu Gln Ala Arg Ala

145   150   155   160

Ser Asp Ser Gly Arg Tyr Gln Cys Ser Gly Thr Met Arg Ile Pro Val
         165   170   175

Glu Ser Ala Pro Met Phe Ser Ala Lys Val Ala Val Thr Val Gln Glu
     180   185   190

Leu Phe Arg Ala Pro Val Leu Arg Val Met Gly Pro Arg Glu Ala Arg
     195   200   205

Gly Ala Ala Leu Gly Gly Val Val Leu Arg Cys Asp Thr Arg Leu His
    210   215   220

Pro Gln Lys Arg Asp Thr Pro Leu Gln Phe Ala Phe Tyr Lys Tyr Ser
225   230   235   240

Arg Ala Val Arg Arg Phe Asp Trp Gly Ala Glu Tyr Thr Val Pro Glu
         245   250   255

Pro Glu Val Glu Glu Leu Glu Ser Tyr Trp Cys Glu Ala Ala Thr Ala
     260   265   270

Thr Arg Ser Val Arg Lys Arg Ser Pro Trp Leu Gln Leu Pro Gly Pro
     275   280   285

Gly Ser Pro Leu Asp Pro Ala Ser Thr Thr Ala Pro Ala Pro Trp Ala

      290   295   300

Ala Ala Leu Ala Pro Gly Asn Arg Pro Leu Ser Phe Arg Lys Pro Pro

305   310   315   320

Val Ser Arg Ser Val Pro Leu Val Thr Ser Val Arg Asn Thr Thr Ser

          325   330   335

Thr Gly Leu Gln Phe Pro Ala Ser Gly Ala Pro Thr Ala Gly Pro Pro

          340   345   350

Ala Cys Ala Pro Pro Thr Pro Leu Glu Gln Ser Ala Gly Ala Leu Lys

          355   360   365

Pro Asp Val Asp Leu Leu Leu Arg Glu Met Gln Leu Leu Lys Gly Leu

          370   375   380

Leu Ser Arg Val Val Leu Glu Leu Lys Glu Pro Gln Ala Leu Arg Glu

385   390   395   400

Leu Arg Gly Thr Pro Glu Thr Pro Thr Ser His Phe Ala Val Ser Pro

          405   410   415

Gly Thr Pro Glu Thr Thr Pro Val Glu Ser

            420   425

<210>   129

<211>   402

<212>   PRT

<213>   Homo sapiens

<400>   129

Met Val Cys Ala Arg Ala Ala Leu Gly Pro Gly Ala Leu Trp Ala Ala

  1   5   10   15

Ala Trp Gly Val Leu Leu Leu Thr Ala Pro Ala Gly Ala Gln Arg Gly

          20   25   30

Arg Lys Lys Val Val His Val Leu Glu Gly Glu Ser Gly Ser Val Val

          35   40   45

Val Gln Thr Ala Pro Gly Gln Val Val Ser His Arg Gly Gly Thr Ile

      50   55   60

Val Leu Pro Cys Arg Tyr His Tyr Glu Ala Ala Ala His Gly His Asp

  65   70   75   80

Gly Val Arg Leu Lys Trp Thr Lys Val Val Asp Pro Leu Ala Phe Thr

                    85   90   95

Asp Val Phe Val Ala Leu Gly Pro Gln His Arg Ala Phe Gly Ser Tyr

              100   105   110

Arg Gly Arg Ala Glu Leu Gln Gly Asp Gly Pro Gly Asp Ala Ser Leu

          115   120   125

Val Leu Arg Asn Val Thr Leu Gln Asp Tyr Gly Arg Tyr Glu Cys Glu

          130   135   140

Val Thr Asn Glu Leu Glu Asp Asp Ala Gly Met Val Lys Leu Asp Leu

145   150   155   160

Glu Gly Val Val Phe Pro Tyr His Pro Arg Gly Gly Arg Tyr Lys Leu

                    165   170   175

Thr Phe Ala Glu Ala Gln Arg Ala Cys Ala Glu Gln Asp Gly Ile Leu

              180   185   190

Ala Ser Ala Glu Gln Leu His Ala Ala Trp Arg Asp Gly Leu Asp Trp

          195   200   205

Cys Asn Ala Gly Trp Leu Arg Asp Gly Ser Val Gln Tyr Pro Val Asn

          210   215   220

Arg Pro Arg Glu Pro Cys Gly Gly Leu Gly Gly Thr Gly Ser Ala Gly

225   230   235   240

Gly Gly Gly Asp Ala Asn Gly Gly Leu Arg Asn Tyr Gly Tyr Arg His

              245   250   255

Asn Ala Glu Glu Arg Tyr Asp Ala Phe Cys Phe Thr Ser Asn Leu Pro

          260   265   270

Gly Arg Val Phe Phe Leu Lys Pro Leu Arg Pro Val Pro Phe Ser Gly

          275   280   285

Ala Ala Arg Ala Cys Ala Ala Arg Gly Ala Ala Val Ala Lys Val Gly

          290   295   300

Gln Leu Phe Ala Ala Trp Lys Leu Gln Leu Leu Asp Arg Cys Thr Ala

305				310					315					320

Gly Trp Leu Ala Asp Gly Ser Ala Arg Tyr Pro Ile Val Asn Pro Arg

			325				330					335		

Ala Arg Cys Gly Gly Arg Arg Pro Gly Val Arg Ser Leu Gly Phe Pro

				340				345					350	

Asp Ala Thr Arg Arg Leu Phe Gly Val Tyr Cys Tyr Arg Ala Pro Gly

			355				360					365		

Ala Pro Asp Pro Ala Pro Gly Gly Trp Gly Trp Gly Trp Ala Gly Gly

		370					375				380			

Gly Gly Trp Ala Gly Gly Ala Arg Asp Pro Ala Ala Trp Thr Pro Leu

385				390					395					400

His Val

<210> 130

<211> 866

<212> PRT

<213> Homo sapiens

<400> 130

Met Gly Phe Pro Pro Leu Leu Lys Gly Gln Ala Ser Ala Thr Arg Ser

1				5					10					15

Ser Leu Ala Ser Cys Ser Trp Val Val Phe Phe Leu Ser Cys Leu Ser

			20				25					30		

Arg His Ala Pro Glu Ile Glu Gly Gly Arg Arg Trp Thr Glu Leu Ile

		35					40				45			

Arg Thr Met Glu Ser Arg Val Leu Leu Arg Thr Phe Cys Leu Ile Phe

	50					55				60				

Gly Leu Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser Leu Gln Ile

65				70					75					80

Asp Val Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr Gly Val Arg

			85				90					95		

Gln Val Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu Phe Gln Asp

			100				105					110		

Thr Pro Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu Gln Phe Phe
      115   120   125

Gln Lys Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val Thr Leu Lys
    130   135   140

Gln Thr His Leu Asn Ser Gly Val Ile Leu Ser Ile His His Leu Asp
145   150   155   160

His Arg Tyr Leu Glu Leu Glu Ser Ser Gly His Arg Asn Glu Val Arg
        165   170   175

Leu His Tyr Arg Ser Gly Ser His Arg Pro His Thr Glu Val Phe Pro
        180   185   190

Tyr Ile Leu Ala Asp Asp Lys Trp His Lys Leu Ser Leu Ala Ile Ser
      195   200   205

Ala Ser His Leu Ile Leu His Ile Asp Cys Asn Lys Ile Tyr Glu Arg
    210   215   220

Val Val Glu Lys Pro Ser Thr Asp Leu Pro Leu Gly Thr Thr Phe Trp
225   230   235   240

Leu Gly Gln Arg Asn Asn Ala His Gly Tyr Phe Lys Gly Ile Met Gln
        245   250   255

Asp Val Gln Leu Leu Val Met Pro Gln Gly Phe Ile Ala Gln Cys Pro
        260   265   270

Asp Leu Asn Arg Thr Cys Pro Thr Cys Asn Asp Phe His Gly Leu Val
      275   280   285

Gln Lys Ile Met Glu Leu Gln Asp Ile Leu Ala Lys Thr Ser Ala Lys
    290   295   300

Leu Ser Arg Ala Glu Gln Arg Met Asn Arg Leu Asp Gln Cys Tyr Cys
305   310   315   320

Glu Arg Thr Cys Thr Met Lys Gly Thr Thr Tyr Arg Glu Phe Glu Ser
        325   330   335

Trp Ile Asp Gly Cys Lys Asn Cys Thr Cys Leu Asn Gly Thr Ile Gln
        340   345   350

Cys Glu Thr Leu Ile Cys Pro Asn Pro Asp Cys Pro Leu Lys Ser Ala
      355   360   365

Leu Ala Tyr Val Asp Gly Lys Cys Cys Lys Glu Cys Lys Ser Ile Cys

          370   375   380
Gln Phe Gln Gly Arg Thr Tyr Phe Glu Gly Glu Arg Asn Thr Val Tyr
385   390   395   400
Ser Ser Ser Gly Val Cys Val Leu Tyr Glu Cys Lys Asp Gln Thr Met
                  405   410   415
Lys Leu Val Glu Ser Ser Gly Cys Pro Ala Leu Asp Cys Pro Glu Ser
                  420   425   430
His Gln Ile Thr Leu Ser His Ser Cys Cys Lys Val Cys Lys Gly Tyr
              435   440   445

Asp Phe Cys Ser Glu Arg His Asn Cys Met Glu Asn Ser Ile Cys Arg
          450   455   460
Asn Leu Asn Asp Arg Ala Val Cys Ser Cys Arg Asp Gly Phe Arg Ala
465   470   475   480
Leu Arg Glu Asp Asn Ala Tyr Cys Glu Asp Ile Asp Glu Cys Ala Glu
                  485   490   495
Gly Arg His Tyr Cys Arg Glu Asn Thr Met Cys Val Asn Thr Pro Gly
              500   505   510
Ser Phe Met Cys Ile Cys Lys Thr Gly Tyr Ile Arg Ile Asp Asp Tyr

          515   520   525
Ser Cys Thr Glu His Asp Glu Cys Ile Thr Asn Gln His Asn Cys Asp
          530   535   540
Glu Asn Ala Leu Cys Phe Asn Thr Val Gly Gly His Asn Cys Val Cys
545   550   555   560
Lys Pro Gly Tyr Thr Gly Asn Gly Thr Thr Cys Lys Ala Phe Cys Lys
                  565   570   575
Asp Gly Cys Arg Asn Gly Gly Ala Cys Ile Ala Ala Asn Val Cys Ala
              580   585   590

Cys Pro Gln Gly Phe Thr Gly Pro Ser Cys Glu Thr Asp Ile Asp Glu
              595   600   605
Cys Ser Asp Gly Phe Val Gln Cys Asp Ser Arg Ala Asn Cys Ile Asn

- 270 -

```
                610                   615                   620
Leu Pro Gly Trp Tyr His Cys Glu Cys Arg Asp Gly Tyr His Asp Asn
625                   630                   635                   640
Gly Met Phe Ser Pro Ser Gly Glu Ser Cys Glu Asp Ile Asp Glu Cys
                      645                   650                   655
Gly Thr Gly Arg His Ser Cys Ala Asn Asp Thr Ile Cys Phe Asn Leu


                660                   665                   670
Asp Gly Gly Tyr Asp Cys Arg Cys Pro His Gly Lys Asn Cys Thr Gly
                675                   680                   685
Asp Cys Ile His Asp Gly Lys Val Lys His Asn Gly Gln Ile Trp Val
    690                   695                   700
Leu Glu Asn Asp Arg Cys Ser Val Cys Ser Cys Gln Asn Gly Phe Val
705                   710                   715                   720
Met Cys Arg Arg Met Val Cys Asp Cys Glu Asn Pro Thr Val Asp Leu
                725                   730                   735


Phe Cys Cys Pro Glu Cys Asp Pro Arg Leu Ser Ser Gln Cys Leu His
                740                   745                   750
Gln Asn Gly Glu Thr Leu Tyr Asn Ser Gly Asp Thr Trp Val Gln Asn
            755                   760                   765
Cys Gln Gln Cys Arg Cys Leu Gln Gly Glu Val Asp Cys Trp Pro Leu
    770                   775                   780
Pro Cys Pro Asp Val Glu Cys Glu Phe Ser Ile Leu Pro Glu Asn Glu
785                   790                   795                   800
Cys Cys Pro Arg Cys Val Thr Asp Pro Cys Gln Ala Asp Thr Ile Arg


                805                   810                   815
Asn Asp Ile Thr Lys Thr Cys Leu Asp Glu Met Asn Val Val Arg Phe
                820                   825                   830
Thr Gly Ser Ser Trp Ile Lys His Gly Thr Glu Cys Thr Leu Cys Gln
            835                   840                   845
Cys Lys Asn Gly His Ile Cys Cys Ser Val Asp Pro Gln Cys Leu Gln
    850                   855                   860
Glu Leu
```

865

<210> 131

<211> 619

<212> PRT

<213> Homo sapiens

<400

> 131

Met Val Pro His Ala Ile Leu Ala Arg Gly Arg Asp Val Cys Arg Arg

1   5   10   15

Asn Gly Leu Leu Ile Leu Ser Val Leu Ser Val Ile Val Gly Cys Leu

                20   25   30

Leu Gly Phe Phe Leu Arg Thr Arg Arg Leu Ser Pro Gln Glu Ile Ser

        35   40   45

Tyr Phe Gln Phe Pro Gly Glu Leu Leu Met Arg Met Leu Lys Met Met

    50   55   60

Ile Leu Pro Leu Val Val Ser Ser Leu Met Ser Gly Leu Ala Ser Leu

65   70   75   80

Asp Ala Lys Thr Ser Ser Arg Leu Gly Val Leu Thr Val Ala Tyr Tyr

                85   90   95

Leu Trp Thr Thr Phe Met Ala Val Ile Val Gly Ile Phe Met Val Ser

        100   105   110

Ile Ile His Pro Gly Ser Ala Ala Gln Lys Glu Thr Thr Glu Gln Ser

        115   120   125

Gly Lys Pro Ile Met Ser Ser Ala Asp Ala Leu Leu Asp Leu Ile Arg

    130   135   140

Asn Met Phe Pro Ala Asn Leu Val Glu Ala Thr Phe Lys Gln Tyr Arg

145   150   155   160

Thr Lys Thr Thr Pro Val Val Lys Ser Pro Lys Val Ala Pro Glu Glu

                165   170   175

Ala Pro Pro Arg Arg Ile Leu Ile Tyr Gly Val Gln Glu Glu Asn Gly

            180   185   190

Ser His Val Gln Asn Phe Ala Leu Asp Leu Thr Pro Pro Glu Val

    195   200   205

Val Tyr Lys Ser Glu Pro Gly Thr Ser Asp Gly Met Asn Val Leu Gly

    210   215   220

Ile Val Phe Phe Ser Ala Thr Met Gly Ile Met Leu Gly Arg Met Gly

225   230   235   240

Asp Ser Gly Ala Pro Leu Val Ser Phe Cys Gln Cys Leu Asn Glu Ser

            245   250   255

Val Met Lys Ile Val Ala Val Ala Val Trp Tyr Phe Pro Phe Gly Ile

            260   265   270

Val Phe Leu Ile Ala Gly Lys Ile Leu Glu Met Asp Asp Pro Arg Ala

        275   280   285

Val Gly Lys Lys Leu Gly Phe Tyr Ser Val Thr Val Val Cys Gly Leu

    290   295   300

Val Leu His Gly Leu Phe Ile Leu Pro Leu Leu Tyr Phe Phe Ile Thr

305   310   315   320

Lys Lys Asn Pro Ile Val Phe Ile Arg Gly Ile Leu Gln Ala Leu Leu

            325   330   335

Ile Ala Leu Ala Thr Ser Ser Arg Lys Asn Gln Val Arg Ala Leu Gln

            340   345   350

Cys Pro Arg Ser Leu Pro Pro Ala Gly Ala Ala Leu Gln Arg His Lys

        355   360   365

His Ser Trp Arg Gly Gly Cys Leu Gly Arg Gly Glu Leu Pro Asp Arg

        370   375   380

Gly Pro Ser His Pro Gly Gly Gly Cys Trp Ala Asp Thr Gly Pro Ser

385   390   395   400

Asn Arg Ser Ser Ala Thr Leu Pro Ile Thr Phe Lys Cys Leu Leu Glu

            405   410   415

Asn Asn His Ile Asp Arg Arg Ile Ala Arg Phe Val Leu Pro Val Gly

        420   425   430

Ala Thr Ile Asn Met Asp Gly Thr Ala Leu Tyr Glu Ala Val Ala Ala

        435   440   445

Ile Phe Ile Ala Gln Val Asn Asn Tyr Glu Leu Asp Phe Gly Gln Ile

```
                450                 455                 460
Ile Thr Ile Ser Ile Thr Ala Thr Ala Ala Ser Ile Gly Ala Ala Gly
465                 470                 475                 480
Ile Pro Gln Ala Gly Leu Val Thr Met Val Ile Val Leu Thr Ser Val
                    485                 490                 495
Gly Leu Pro Thr Asp Asp Ile Thr Leu Ile Ile Ala Val Asp Trp Ala


                    500                 505                 510
Leu Asp Arg Phe Arg Thr Met Ile Asn Val Leu Gly Asp Ala Leu Ala
            515                 520                 525
Ala Gly Ile Met Ala His Ile Cys Arg Lys Asp Phe Ala Arg Asp Thr
    530                 535                 540
Gly Thr Glu Lys Leu Leu Pro Cys Glu Thr Lys Pro Val Ser Leu Gln
545                 550                 555                 560
Glu Ile Val Ala Ala Gln Gln Asn Gly Cys Val Lys Ser Val Ala Glu
                565                 570                 575


Ala Ser Glu Leu Thr Leu Gly Pro Thr Cys Pro His His Val Pro Val
            580                 585                 590
Gln Val Glu Gln Asp Glu Glu Leu Pro Ala Ala Ser Leu Asn His Cys
            595                 600                 605
Thr Ile Gln Ile Ser Glu Leu Glu Thr Asn Val
    610                 615
```

<210>   132

<211>   686

<212>   PRT

<213>   Homo sapiens

<400>   132

```
Met Lys Pro Ser Trp Leu Gln Cys Arg Lys Val Thr Ser Ala Gly Gly
 1                   5                   10                  15


Leu Gly Gly Pro Leu Pro Gly Ser Ser Pro Ala Arg Gly Ala Gly Ala
                20                  25                  30
Ala Leu Arg Ala Leu Val Val Pro Gly Pro Arg Gly Gly Leu Gly Gly
        35                  40                  45
```

Arg Gly Cys Arg Ala Leu Ser Ser Gly Ser Gly Ser Glu Tyr Lys Thr

     50   55   60

His Phe Ala Ala Ser Val Thr Asp Pro Glu Arg Phe Trp Gly Lys Ala

 65   70   75   80

Ala Glu Gln Ile Ser Trp Tyr Lys Pro Trp Thr Lys Thr Leu Glu Asn

               85   90   95

Lys His Ser Pro Ser Thr Arg Trp Phe Val Glu Gly Met Leu Asn Ile

           100   105   110

Cys Tyr Asn Ala Val Asp Arg His Ile Glu Asn Gly Lys Gly Asp Lys

         115   120   125

Ile Ala Ile Ile Tyr Asp Ser Pro Val Thr Asn Thr Lys Ala Thr Phe

         130   135   140

Thr Tyr Lys Glu Val Leu Glu Gln Val Ser Lys Leu Ala Gly Val Leu

145   150   155   160

Val Lys His Gly Ile Lys Lys Gly Asp Thr Val Val Ile Tyr Met Pro

           165   170   175

Met Ile Pro Gln Ala Met Tyr Thr Met Leu Ala Cys Ala Arg Ile Gly

         180   185   190

Ala Ile His Ser Leu Ile Phe Gly Gly Phe Ala Ser Lys Glu Leu Ser

         195   200   205

Ser Arg Ile Asp His Val Lys Pro Lys Val Val Val Thr Ala Ser Phe

     210   215   220

Gly Ile Glu Pro Gly Arg Arg Val Glu Tyr Val Pro Leu Val Glu Glu

225   230   235   240

Ala Leu Lys Ile Gly Gln His Lys Pro Asp Lys Ile Leu Ile Tyr Asn

         245   250   255

Arg Pro Asn Met Glu Ala Val Pro Leu Ala Pro Gly Arg Asp Leu Asp

         260   265   270

Trp Asp Glu Glu Met Ala Lys Ala Gln Ser His Asp Cys Val Pro Val

         275   280   285

Leu Ser Glu His Pro Leu Tyr Ile Leu Tyr Thr Ser Gly Thr Thr Gly

```
              290                   295                   300
```

```
Leu Pro Lys Gly Val Ile Arg Pro Thr Gly Gly Tyr Ala Val Met Leu
305                   310                   315                   320
His Trp Ser Met Ser Ser Ile Tyr Gly Leu Gln Pro Gly Glu Val Trp
                  325                   330                   335
Trp Ala Ala Ser Asp Leu Gly Trp Val Val Gly His Ser Tyr Ile Cys
                  340                   345                   350
Tyr Gly Pro Leu Leu His Gly Asn Thr Thr Val Leu Tyr Glu Gly Lys
              355                   360                   365
Pro Val Gly Thr Pro Asp Ala Gly Ala Tyr Phe Arg Val Leu Ala Glu
```

```
              370                   375                   380
His Gly Val Ala Ala Leu Phe Thr Ala Pro Thr Ala Ile Arg Ala Ile
385                   390                   395                   400
Arg Gln Gln Asp Pro Gly Ala Ala Leu Gly Lys Gln Tyr Ser Leu Thr
                  405                   410                   415
Arg Phe Lys Thr Leu Phe Val Ala Gly Glu Arg Cys Asp Val Glu Thr
                  420                   425                   430
Leu Glu Trp Ser Lys Asn Val Phe Arg Val Pro Val Leu Asp His Trp
              435                   440                   445
```

```
Trp Gln Thr Glu Thr Gly Ser Pro Ile Thr Ala Ser Cys Val Gly Leu
              450                   455                   460
Gly Asn Ser Lys Thr Pro Pro Pro Gly Gln Ala Gly Lys Ser Val Pro
465                   470                   475                   480
Gly Tyr Asn Val Met Ile Leu Asp Asp Asn Met Gln Lys Leu Lys Ala
                  485                   490                   495
Arg Cys Leu Gly Asn Ile Val Val Lys Leu Pro Leu Pro Pro Gly Ala
                  500                   505                   510
Phe Ser Gly Leu Trp Lys Asn Gln Glu Ala Phe Lys His Leu Tyr Phe
```

```
              515                   520                   525
Glu Lys Phe Pro Gly Tyr Tyr Asp Thr Met Asp Ala Gly Tyr Met Asp
              530                   535                   540
```

Glu Glu Gly Tyr Leu Tyr Val Met Ser Arg Val Asp Asp Val Ile Asn
545   550   555   560

Val Ala Gly His Arg Ile Ser Ala Gly Ala Ile Glu Glu Ser Ile Leu
                565   570   575

Ser His Gly Thr Val Ala Asp Cys Ala Val Val Gly Lys Glu Asp Pro
            580   585   590

Leu Lys Gly His Val Pro Leu Ala Leu Cys Val Leu Arg Lys Asp Ile
            595   600   605

Asn Ala Thr Glu Glu Gln Val Leu Glu Glu Ile Val Lys His Val Arg
        610   615   620

Gln Asn Ile Gly Pro Val Ala Ala Phe Arg Asn Ala Val Phe Val Lys
625   630   635   640

Gln Leu Pro Lys Thr Arg Ser Gly Lys Ile Pro Arg Ser Ala Leu Ser
                645   650   655

Ala Ile Val Asn Gly Lys Pro Tyr Lys Ile Thr Ser Thr Ile Glu Asp

                660   665   670
Pro Ser Ile Phe Gly His Val Glu Glu Met Leu Lys Gln Ala
                675   680   685

<210>   133
<211>   1556
<212>   PRT
<213>   Homo sapiens
<400>   133

Met Pro Leu Leu His Arg Lys Pro Phe Val Arg Gln Lys Pro Pro Ala
 1   5   10   15

Asp Leu Arg Pro Asp Glu Glu Val Phe Tyr Cys Lys Val Thr Asn Glu
                20   25   30

Ile Phe Arg His Tyr Asp Asp Phe Phe Glu Arg Thr Ile Leu Cys Asn

        35   40   45
Ser Leu Val Trp Ser Cys Ala Val Thr Gly Arg Pro Gly Leu Thr Tyr
        50   55   60

Gln Glu Ala Leu Glu Ser Glu Lys Lys Ala Arg Gln Asn Leu Gln Ser

```
        65              70              75              80

Phe Pro Glu Pro Leu Ile Ile Pro Val Leu Tyr Leu Thr Ser Leu Thr
                    85              90              95

His Arg Ser Arg Leu His Glu Ile Cys Asp Asp Ile Phe Ala Tyr Val
                100             105             110


Lys Asp Arg Tyr Phe Val Glu Glu Thr Val Glu Val Ile Arg Asn Asn
            115             120             125

Gly Ala Arg Leu Gln Cys Arg Ile Leu Glu Val Leu Pro Pro Ser His
        130             135             140

Gln Asn Gly Phe Ala Asn Gly His Val Asn Ser Val Asp Gly Glu Thr
    145             150             155             160

Ile Ile Ile Ser Asp Ser Asp Asp Ser Glu Thr Gln Ser Cys Ser Phe
                165             170             175

Gln Asn Gly Lys Lys Lys Asp Ala Ile Asp Pro Leu Leu Phe Lys Tyr


                180             185             190

Lys Val Gln Pro Thr Lys Lys Glu Leu His Glu Ser Ala Ile Val Lys
            195             200             205

Ala Thr Gln Ile Ser Arg Arg Lys His Leu Phe Ser Arg Asp Lys Leu
        210             215             220

Lys Leu Phe Leu Lys Gln His Cys Glu Pro Gln Asp Gly Val Ile Lys
    225             230             235             240

Ile Lys Ala Ser Ser Leu Ser Thr Tyr Lys Ile Ala Glu Gln Asp Phe
                245             250             255


Ser Tyr Phe Phe Pro Asp Asp Pro Thr Phe Ile Phe Ser Pro Ala
                260             265             270

Asn Arg Arg Arg Gly Arg Pro Pro Lys Arg Ile His Ile Ser Gln Glu
            275             280             285

Asp Asn Val Ala Asn Lys Gln Thr Leu Ala Ser Tyr Arg Ser Lys Ala
        290             295             300

Thr Lys Glu Arg Asp Lys Leu Leu Lys Gln Glu Glu Met Lys Ser Leu
    305             310             315             320
```

Ala Phe Glu Lys Ala Lys Leu Lys Arg Glu Lys Ala Asp Ala Leu Glu

325   330   335

Ala Lys Lys Lys Glu Lys Glu Asp Lys Glu Lys Lys Arg Glu Glu Leu

340   345   350

Lys Lys Ile Val Glu Glu Glu Arg Leu Lys Lys Lys Glu Glu Lys Glu

355   360   365

Arg Leu Lys Val Glu Arg Glu Lys Glu Arg Glu Lys Leu Arg Glu Glu

370   375   380

Lys Arg Lys Tyr Val Glu Tyr Leu Lys Gln Trp Ser Lys Pro Arg Glu

385   390   395   400

Asp Met Glu Cys Asp Asp Leu Lys Glu Leu Pro Glu Pro Thr Pro Val

405   410   415

Lys Thr Arg Leu Pro Pro Glu Ile Phe Gly Asp Ala Leu Met Val Leu

420   425   430

Glu Phe Leu Asn Ala Phe Gly Glu Leu Phe Asp Leu Gln Asp Glu Phe

435   440   445

Pro Asp Gly Val Thr Leu Glu Val Leu Glu Glu Ala Leu Val Gly Asn

450   455   460

Asp Ser Glu Gly Pro Leu Cys Glu Leu Leu Phe Phe Phe Leu Thr Ala

465   470   475   480

Ile Phe Gln Ala Ile Ala Glu Glu Glu Glu Glu Val Ala Lys Glu Gln

485   490   495

Leu Thr Asp Ala Asp Thr Lys Asp Leu Thr Glu Ala Leu Asp Glu Asp

500   505   510

Ala Asp Pro Thr Lys Ser Ala Leu Ser Ala Val Ala Ser Leu Ala Ala

515   520   525

Ala Trp Pro Gln Leu His Gln Gly Cys Ser Leu Lys Ser Leu Asp Leu

530   535   540

Asp Ser Cys Thr Leu Ser Glu Ile Leu Arg Leu His Ile Leu Ala Ser

545   550   555   560

Gly Ala Asp Val Thr Ser Ala Asn Ala Lys Tyr Arg Tyr Gln Lys Arg

```
                565               570               575
Gly Gly Phe Asp Ala Thr Asp Asp Ala Cys Met Glu Leu Arg Leu Ser
            580               585               590
Asn Pro Ser Leu Val Lys Lys Leu Ser Ser Thr Ser Val Tyr Asp Leu
        595               600               605
Thr Pro Gly Glu Lys Met Lys Ile Leu His Ala Leu Cys Gly Lys Leu


    610               615               620
Leu Thr Leu Val Ser Thr Arg Asp Phe Ile Glu Asp Tyr Val Asp Ile
625               630               635               640
Leu Arg Gln Ala Lys Gln Glu Phe Arg Glu Leu Lys Ala Glu Gln His
            645               650               655
Arg Lys Glu Arg Glu Glu Ala Ala Ala Arg Ile Arg Lys Arg Lys Glu
        660               665               670
Glu Lys Leu Lys Glu Gln Glu Gln Lys Met Lys Glu Lys Gln Glu Lys
            675               680               685


Leu Lys Glu Asp Glu Gln Arg Asn Ser Thr Ala Asp Ile Ser Ile Gly
        690               695               700
Glu Glu Glu Arg Glu Asp Phe Asp Thr Ser Ile Glu Ser Lys Asp Thr
705               710               715               720
Glu Gln Lys Glu Leu Asp Gln Asp Met Val Thr Glu Asp Glu Asp Asp
            725               730               735
Pro Gly Ser His Lys Arg Gly Arg Arg Gly Lys Arg Gly Gln Asn Gly
            740               745               750
Phe Lys Glu Phe Thr Arg Gln Glu Gln Ile Asn Cys Val Thr Arg Glu


        755               760               765
Pro Leu Thr Ala Asp Glu Glu Glu Ala Leu Lys Gln Glu His Gln Arg
        770               775               780
Lys Glu Lys Glu Leu Leu Glu Lys Ile Gln Ser Ala Ile Ala Cys Thr
785               790               795               800
Asn Ile Phe Pro Leu Gly Arg Asp Arg Met Tyr Arg Arg Tyr Trp Ile
                805               810               815
Phe Pro Ser Ile Pro Gly Leu Phe Ile Glu Glu Asp Tyr Ser Gly Leu
```

```
                820                825                830

Thr Glu Asp Met Leu Leu Pro Arg Pro Ser Ser Phe Gln Asn Asn Val
          835                840                845

Gln Ser Gln Asp Pro Gln Val Ser Thr Lys Thr Gly Glu Pro Leu Met
     850                855                860

Ser Glu Ser Thr Ser Asn Ile Asp Gln Gly Pro Arg Asp His Ser Val
865                870                875                880

Gln Leu Pro Lys Pro Val His Lys Pro Asn Arg Trp Cys Phe Tyr Ser
               885                890                895

Ser Cys Glu Gln Leu Asp Gln Leu Ile Glu Ala Leu Asn Ser Arg Gly


                900                905                910

His Arg Glu Ser Ala Leu Lys Glu Thr Leu Leu Gln Glu Lys Ser Arg
          915                920                925

Ile Cys Ala Gln Leu Ala Arg Phe Ser Glu Glu Lys Phe His Phe Ser
     930                935                940

Asp Lys Pro Gln Pro Asp Ser Lys Pro Thr Tyr Ser Arg Gly Arg Ser
945                950                955                960

Ser Asn Ala Tyr Asp Pro Ser Gln Met Cys Ala Glu Lys Gln Leu Glu
               965                970                975


Leu Arg Leu Arg Asp Phe Leu Leu Asp Ile Glu Asp Arg Ile Tyr Gln
          980                985                990

Gly Thr Leu Gly Ala Ile Lys Val Thr Asp Arg His Ile Trp Arg Ser
          995                1000                1005

Ala Leu Glu Ser Gly Arg Tyr Glu Leu Leu Ser Glu Glu Asn Lys Glu
     1010                1015                1020

Asn Gly Ile Ile Lys Thr Val Asn Glu Asp Val Glu Glu Met Glu Ile
1025                1030                1035                1040

Asp Glu Gln Thr Lys Val Ile Val Lys Asp Arg Leu Leu Gly Ile Lys


                1045                1050                1055

Thr Glu Thr Pro Ser Thr Val Ser Thr Asn Ala Ser Thr Pro Gln Ser
          1060                1065                1070
```

Val Ser Ser Val Val His Tyr Leu Ala Met Ala Leu Phe Gln Ile Glu
       1075   1080   1085

Gln Gly Ile Glu Arg Arg Phe Leu Lys Ala Pro Leu Asp Ala Ser Asp
     1090   1095   1100

Ser Gly Arg Ser Tyr Lys Thr Val Leu Asp Arg Trp Arg Glu Ser Leu
1105   1110   1115   1120

Leu Ser Ser Ala Ser Leu Ser Gln Val Phe Leu His Leu Ser Thr Leu
        1125   1130   1135

Asp Arg Ser Val Ile Trp Ser Lys Ser Ile Leu Asn Ala Arg Cys Lys
        1140   1145   1150

Ile Cys Arg Lys Lys Gly Asp Ala Glu Asn Met Val Leu Cys Asp Gly
        1155   1160   1165

Cys Asp Arg Gly His His Thr Tyr Cys Val Arg Pro Lys Leu Lys Thr
      1170   1175   1180

Val Pro Glu Gly Asp Trp Phe Cys Pro Glu Cys Arg Pro Lys Gln Arg

1185   1190   1195   1200

Ser Arg Arg Leu Ser Ser Arg Gln Arg Pro Ser Leu Glu Ser Asp Glu
          1205   1210   1215

Asp Val Glu Asp Ser Met Gly Gly Glu Asp Asp Glu Val Asp Gly Asp
        1220   1225   1230

Glu Glu Glu Gly Gln Ser Glu Glu Glu Glu Tyr Glu Val Glu Gln Asp
        1235   1240   1245

Glu Asp Asp Ser Gln Glu Glu Glu Glu Val Ser Leu Pro Lys Arg Gly
       1250   1255   1260

Arg Pro Gln Val Arg Leu Pro Val Lys Thr Arg Gly Lys Leu Ser Ser
1265   1270   1275   1280

Ser Phe Ser Ser Arg Gly Gln Gln Gln Glu Pro Gly Arg Tyr Pro Ser
         1285   1290   1295

Arg Ser Gln Gln Ser Thr Pro Lys Thr Thr Val Ser Ser Lys Thr Gly
       1300   1305   1310

Arg Ser Leu Arg Lys Ile Asn Ser Ala Pro Pro Thr Glu Thr Lys Ser
      1315   1320   1325

Leu Arg Ile Ala Ser Arg Ser Thr Arg His Ser His Gly Pro Leu Gln

        1330   1335   1340

Ala Asp Val Phe Val Glu Leu Leu Ser Pro Arg Arg Lys Arg Arg Gly

1345   1350   1355   1360

Arg Lys Ser Ala Asn Asn Thr Pro Glu Asn Ser Pro Asn Phe Pro Asn

                1365   1370   1375

Phe Arg Val Ile Ala Thr Lys Ser Ser Glu Gln Ser Arg Ser Val Asn

                1380   1385   1390

Ile Ala Ser Lys Leu Ser Leu Gln Glu Ser Glu Ser Lys Arg Arg Cys

        1395   1400   1405

Arg Lys Arg Gln Ser Pro Glu Pro Ser Pro Val Thr Leu Gly Arg Arg

        1410   1415   1420

Ser Ser Gly Arg Gln Gly Gly Val His Glu Leu Ser Ala Phe Glu Gln

1425   1430   1435   1440

Leu Val Val Glu Leu Val Arg His Asp Asp Ser Trp Pro Phe Leu Lys

                1445   1450   1455

Leu Val Ser Lys Ile Gln Val Pro Asp Tyr Tyr Asp Ile Ile Lys Lys

                1460   1465   1470

Pro Ile Ala Leu Asn Ile Ile Arg Glu Lys Val Asn Lys Cys Glu Tyr

        1475   1480   1485

Lys Leu Ala Ser Glu Phe Ile Asp Asp Ile Glu Leu Met Phe Ser Asn

        1490   1495   1500

Cys Phe Glu Tyr Asn Pro Arg Asn Thr Ser Glu Ala Lys Ala Gly Thr

1505   1510   1515   1520

Arg Leu Gln Ala Phe Phe His Ile Gln Ala Gln Lys Leu Gly Leu His

                1525   1530   1535

Val Thr Pro Ser Asn Val Asp Gln Val Ser Thr Pro Pro Ala Ala Lys

        1540   1545   1550

Lys Ser Arg Ile

        1555

<210>   134

<211>   1670

<212>   PRT

<213>   Homo sapiens

<400>   134

Met Ser Ala Arg Thr Ala Pro Arg Pro Gln Val Leu Leu Leu Pro Leu
1   5   10   15

Leu Leu Val Leu Leu Ala Ala Ala Pro Ala Ala Ser Lys Gly Cys Val
                20   25   30

Cys Lys Asp Lys Gly Gln Cys Phe Cys Asp Gly Ala Lys Gly Glu Lys
            35   40   45

Gly Glu Lys Gly Phe Pro Gly Pro Pro Gly Ser Pro Gly Gln Lys Gly

        50   55   60

Phe Thr Gly Pro Glu Gly Leu Pro Gly Pro Gln Gly Pro Lys Gly Phe
65   70   75   80

Pro Gly Leu Pro Gly Leu Thr Gly Ser Lys Gly Val Arg Gly Ile Ser
                85   90   95

Gly Leu Pro Gly Phe Ser Gly Ser Pro Gly Leu Pro Gly Thr Pro Gly
                100   105   110

Asn Thr Gly Pro Tyr Gly Leu Val Gly Val Pro Gly Cys Ser Gly Ser
            115   120   125

Lys Gly Glu Gln Gly Phe Pro Gly Leu Pro Gly Thr Leu Gly Tyr Pro
        130   135   140

Gly Ile Pro Gly Ala Ala Gly Leu Lys Gly Gln Lys Gly Ala Pro Ala
145   150   155   160

Lys Glu Glu Asp Ile Glu Leu Asp Ala Lys Gly Asp Pro Gly Leu Pro
                165   170   175

Gly Ala Pro Gly Pro Gln Gly Leu Pro Gly Pro Pro Gly Phe Pro Gly
                180   185   190

Pro Val Gly Pro Pro Gly Pro Pro Gly Phe Phe Gly Phe Pro Gly Ala

        195   200   205

Met Gly Pro Arg Gly Pro Lys Gly His Met Gly Glu Arg Val Ile Gly
        210   215   220

His Lys Gly Glu Arg Gly Val Lys Gly Leu Thr Gly Pro Pro Gly Pro
225   230   235   240

Pro Gly Thr Val Ile Val Thr Leu Thr Gly Pro Asp Asn Arg Thr Asp
                 245   250   255

Leu Lys Gly Glu Lys Gly Asp Lys Gly Ala Met Gly Glu Pro Gly Pro
             260   265   270

Pro Gly Pro Ser Gly Leu Pro Gly Glu Ser Tyr Gly Ser Glu Lys Gly
             275   280   285

Ala Pro Gly Asp Pro Gly Leu Gln Gly Lys Pro Gly Lys Asp Gly Val
         290   295   300

Pro Gly Phe Pro Gly Ser Glu Gly Val Lys Gly Asn Arg Gly Phe Pro
305   310   315   320

Gly Leu Met Gly Glu Asp Gly Ile Lys Gly Gln Lys Gly Asp Ile Gly
                 325   330   335

Pro Pro Gly Phe Arg Gly Pro Thr Glu Tyr Tyr Asp Thr Tyr Gln Glu

             340   345   350

Lys Gly Asp Glu Gly Thr Pro Gly Pro Pro Gly Pro Arg Gly Ala Arg
             355   360   365

Gly Pro Gln Gly Pro Ser Gly Pro Pro Gly Val Pro Gly Ser Pro Gly
         370   375   380

Ser Ser Arg Pro Gly Leu Arg Gly Ala Pro Gly Trp Pro Gly Leu Lys
385   390   395   400

Gly Ser Lys Gly Glu Arg Gly Arg Pro Gly Lys Asp Ala Met Gly Thr
                 405   410   415

Pro Gly Ser Pro Gly Cys Ala Gly Ser Pro Gly Leu Pro Gly Ser Pro
             420   425   430

Gly Pro Pro Gly Pro Pro Gly Asp Ile Val Phe Arg Lys Gly Pro Pro
         435   440   445

Gly Asp His Gly Leu Pro Gly Tyr Leu Gly Ser Pro Gly Ile Pro Gly
         450   455   460

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

Tyr Ile Pro Gly Pro Pro Gly Leu Pro Gly Leu Pro Gly Leu His Gly

                  485   490   495

Val Lys Gly Ile Pro Gly Arg Gln Gly Ala Ala Gly Leu Lys Gly Ser

        500   505   510

Pro Gly Ser Pro Gly Asn Thr Gly Leu Pro Gly Phe Pro Gly Phe Pro

     515   520   525

Gly Ala Gln Gly Asp Pro Gly Leu Lys Gly Glu Lys Gly Glu Thr Leu

   530   535   540

Gln Pro Glu Gly Gln Val Gly Val Pro Gly Asp Pro Gly Leu Arg Gly

545   550   555   560

Gln Pro Gly Arg Lys Gly Leu Asp Gly Ile Pro Gly Thr Pro Gly Val

        565   570   575

Lys Gly Leu Pro Gly Pro Lys Gly Glu Leu Ala Leu Ser Gly Glu Lys

        580   585   590

Gly Asp Gln Gly Pro Pro Gly Asp Pro Gly Ser Pro Gly Ser Pro Gly

     595   600   605

Pro Ala Gly Pro Ala Gly Pro Pro Gly Tyr Gly Pro Gln Gly Glu Pro

   610   615   620

Gly Leu Gln Gly Thr Gln Gly Val Pro Gly Ala Pro Gly Pro Pro Gly

625   630   635   640

Glu Ala Gly Pro Arg Gly Glu Leu Ser Val Ser Thr Pro Val Pro Gly

        645   650   655

Pro Pro Gly Pro Pro Gly Pro Pro Gly His Pro Gly Pro Gln Gly Pro

        660   665   670

Pro Gly Ile Pro Gly Ser Leu Gly Lys Cys Gly Asp Pro Gly Leu Pro

     675   680   685

Gly Pro Asp Gly Glu Pro Gly Ile Pro Gly Ile Gly Phe Pro Gly Pro

   690   695   700

Pro Gly Pro Lys Gly Asp Gln Gly Phe Pro Gly Thr Lys Gly Ser Leu

705   710   715   720

Gly Cys Pro Gly Lys Met Gly Glu Pro Gly Leu Pro Gly Lys Pro Gly

```
                725              730              735
Leu Pro Gly Ala Lys Gly Glu Pro Ala Val Ala Met Pro Gly Gly Pro
          740              745              750
Gly Thr Pro Gly Phe Pro Gly Glu Arg Gly Asn Ser Gly Glu His Gly
      755              760              765
Glu Ile Gly Leu Pro Gly Leu Pro Gly Leu Pro Gly Thr Pro Gly Asn


      770              775              780
Glu Gly Leu Asp Gly Pro Arg Gly Asp Pro Gly Gln Pro Gly Pro Pro
785              790              795              800
Gly Glu Gln Gly Pro Pro Gly Arg Cys Ile Glu Gly Pro Arg Gly Ala
              805              810              815
Gln Gly Leu Pro Gly Leu Asn Gly Leu Lys Gly Gln Gln Gly Arg Arg
          820              825              830
Gly Lys Thr Gly Pro Lys Gly Asp Pro Gly Ile Pro Gly Leu Asp Arg
          835              840              845


Ser Gly Phe Pro Gly Glu Thr Gly Ser Pro Gly Ile Pro Gly His Gln
      850              855              860
Gly Glu Met Gly Pro Leu Gly Gln Arg Gly Tyr Pro Gly Asn Pro Gly
865              870              875              880
Ile Leu Gly Pro Pro Gly Glu Asp Gly Val Ile Gly Met Met Gly Phe
              885              890              895
Pro Gly Ala Ile Gly Pro Pro Gly Pro Pro Gly Asn Pro Gly Thr Pro
          900              905              910
Gly Gln Arg Gly Ser Pro Gly Ile Pro Gly Val Lys Gly Gln Arg Gly


      915              920              925
Thr Pro Gly Ala Lys Gly Glu Gln Gly Asp Lys Gly Asn Pro Gly Pro
      930              935              940
Ser Glu Ile Ser His Val Ile Gly Asp Lys Gly Glu Pro Gly Leu Lys
945              950              955              960
Gly Phe Ala Gly Asn Pro Gly Glu Lys Gly Asn Arg Gly Val Pro Gly
              965              970              975
Met Pro Gly Leu Lys Gly Leu Lys Gly Leu Pro Gly Pro Ala Gly Pro
```

                    980   985   990

Pro Gly Pro Arg Gly Asp Leu Gly Ser Thr Gly Asn Pro Gly Glu Pro
            995   1000   1005

Gly Leu Arg Gly Ile Pro Gly Ser Met Gly Asn Met Gly Met Pro Gly
        1010   1015   1020

Ser Lys Gly Lys Arg Gly Thr Leu Gly Phe Pro Gly Arg Ala Gly Arg
1025   1030   1035   1040

Pro Gly Leu Pro Gly Ile His Gly Leu Gln Gly Asp Lys Gly Glu Pro
                1045   1050   1055

Gly Tyr Ser Glu Gly Thr Arg Pro Gly Pro Pro Gly Pro Thr Gly Asp

                    1060   1065   1070

Pro Gly Leu Pro Gly Asp Met Gly Lys Lys Gly Glu Met Gly Gln Pro
            1075   1080   1085

Gly Pro Pro Gly His Leu Gly Pro Ala Gly Pro Glu Gly Ala Pro Gly
        1090   1095   1100

Ser Pro Gly Ser Pro Gly Leu Pro Gly Lys Pro Gly Pro His Gly Asp
1105   1110   1115   1120

Leu Gly Phe Lys Gly Ile Lys Gly Leu Leu Gly Pro Pro Gly Ile Arg
                1125   1130   1135

Gly Pro Pro Gly Leu Pro Gly Phe Pro Gly Ser Pro Gly Pro Met Gly
            1140   1145   1150

Ile Arg Gly Asp Gln Gly Arg Asp Gly Ile Pro Gly Pro Ala Gly Glu
            1155   1160   1165

Lys Gly Glu Thr Gly Leu Leu Arg Ala Pro Pro Gly Pro Arg Gly Asn
    1170   1175   1180

Pro Gly Ala Gln Gly Ala Lys Gly Asp Arg Gly Ala Pro Gly Phe Pro
1185   1190   1195   1200

Gly Leu Pro Gly Arg Lys Gly Ala Met Gly Asp Ala Gly Pro Arg Gly

                    1205   1210   1215

Pro Thr Gly Ile Glu Gly Phe Pro Gly Pro Pro Gly Leu Pro Gly Ala
            1220   1225   1230

Ile Ile Pro Gly Gln Thr Gly Asn Arg Gly Pro Pro Gly Ser Arg Gly
     1235   1240   1245

Ser Pro Gly Ala Pro Gly Pro Pro Gly Pro Pro Gly Ser His Val Ile
    1250   1255   1260

Gly Ile Lys Gly Asp Lys Gly Ser Met Gly His Pro Gly Pro Lys Gly
1265   1270   1275   1280

Pro Pro Gly Thr Ala Gly Asp Met Gly Pro Pro Gly Arg Leu Gly Ala
        1285   1290   1295

Pro Gly Thr Pro Gly Leu Pro Gly Pro Arg Gly Asp Pro Gly Phe Gln
      1300   1305   1310

Gly Phe Pro Gly Val Lys Gly Glu Lys Gly Asn Pro Gly Phe Leu Gly
      1315   1320   1325

Ser Ile Gly Pro Pro Gly Pro Ile Gly Pro Lys Gly Pro Pro Gly Val
    1330   1335   1340

Arg Gly Asp Pro Gly Thr Leu Lys Ile Ile Ser Leu Pro Gly Ser Pro

1345   1350   1355   1360

Gly Pro Pro Gly Thr Pro Gly Glu Pro Gly Met Gln Gly Glu Pro Gly
        1365   1370   1375

Pro Pro Gly Pro Pro Gly Asn Leu Gly Pro Cys Gly Pro Arg Gly Lys
      1380   1385   1390

Pro Gly Lys Asp Gly Lys Pro Gly Thr Pro Gly Pro Ala Gly Glu Lys
      1395   1400   1405

Gly Asn Lys Gly Ser Lys Gly Glu Pro Gly Pro Ala Gly Ser Asp Gly
    1410   1415   1420

Leu Pro Gly Leu Lys Gly Lys Arg Gly Asp Ser Gly Ser Pro Ala Thr
1425   1430   1435   1440

Trp Thr Thr Arg Gly Phe Val Phe Thr Arg His Ser Gln Thr Thr Ala
      1445   1450   1455

Ile Pro Ser Cys Pro Glu Gly Thr Val Pro Leu Tyr Ser Gly Phe Ser
      1460   1465   1470

Phe Leu Phe Val Gln Gly Asn Gln Arg Ala His Gly Gln Asp Leu Gly
      1475   1480   1485

Thr Leu Gly Ser Cys Leu Gln Arg Phe Thr Thr Met Pro Phe Leu Phe

     1490   1495   1500

Cys Asn Val Asn Asp Val Cys Asn Phe Ala Ser Arg Asn Asp Tyr Ser

1505   1510   1515   1520

Tyr Trp Leu Ser Thr Pro Ala Leu Met Pro Met Asn Met Ala Pro Ile

           1525   1530   1535

Thr Gly Arg Ala Leu Glu Pro Tyr Ile Ser Arg Cys Thr Val Cys Glu

          1540   1545   1550

Gly Pro Ala Ile Ala Ile Ala Val His Ser Gln Thr Thr Asp Ile Pro

          1555   1560   1565

Pro Cys Pro His Gly Trp Ile Ser Leu Trp Lys Gly Phe Ser Phe Ile

     1570   1575   1580

Met Phe Thr Ser Ala Gly Ser Glu Gly Thr Gly Gln Ala Leu Ala Ser

1585   1590   1595   1600

Pro Gly Ser Cys Leu Glu Glu Phe Arg Ala Ser Pro Phe Leu Glu Cys

          1605   1610   1615

His Gly Arg Gly Thr Cys Asn Tyr Tyr Ser Asn Ser Tyr Ser Phe Trp

          1620   1625   1630

Leu Ala Ser Leu Asn Pro Glu Arg Met Phe Arg Lys Pro Ile Pro Ser

          1635   1640   1645

Thr Val Lys Ala Gly Glu Leu Glu Lys Ile Ile Ser Arg Cys Gln Val

     1650   1655   1660

Cys Met Lys Lys Arg His

1665   1670

<210>   135

<211>   670

<212>   PRT

<213>   Homo sapiens

<400>   135

Met Ala Phe Pro Val Asp Met Leu Glu Asn Cys Ser His Glu Glu Leu

 1   5   10   15

Glu Asn Ser Ala Glu Asp Tyr Met Ser Asp Leu Arg Cys Gly Asp Pro

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


                100                 105                 110
Arg Val Val Leu Tyr Val Leu Asn Arg Ile Ile Tyr Arg Lys Gln Glu
          115                 120                 125
Met Glu Arg Asn Glu Ile Pro Phe Leu Cys His Ser Ser Thr Asp Tyr
       130                 135                 140
Ala Lys Ile Leu Trp Lys Lys Gly Glu Ala Ile Gly Phe Tyr Ser Val
145                 150                 155                 160
Lys Pro Thr Gly Ser Ile Cys Ala Ser Phe Leu Thr Gln Ser Tyr Gln
                165                 170                 175


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


                245                 250                 255
Ala Leu Gln Arg Glu Ala Leu Lys Ile Leu Ala Leu Ser Gln Asn Glu
          260                 265                 270
```

Pro Lys Arg Pro Met Ser Gly Glu Tyr Gly Pro Ala Ser Val Pro Glu
       275   280   285

Tyr Glu Ala Arg Thr Glu Asp Asn Gln Ser Ser Glu Met Gln Leu Thr
   290   295   300

Ile Asp Ser Leu Lys Asp Ala Phe Ala Ser Thr Ser Glu Gly His Asp
305   310   315   320

Lys Thr Ser Val Ser Thr His Thr Arg Ser Gly Asn Leu Lys Arg Pro
       325   330   335

Lys Ile Gly Lys Arg Phe Gln Asp Ser Glu Phe Ser Ser Ser Gln Gly
       340   345   350

Glu Asp Glu Lys Thr Ser Gln Thr Ser Leu Thr Ala Ser Ile Asn Lys
      355   360   365

Leu Glu Ser Thr Ala Arg Pro Ser Glu Ser Ser Glu Glu Phe Leu Glu
    370   375   380

Glu Glu Pro Glu Gln Arg Gly Ile Glu Phe Glu Asp Glu Ser Ser Asp

385   390   395   400

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

Asp Gly Glu Lys Glu Ser Glu Leu Glu Pro Met Asn Gly Glu Ile Met
       420   425   430

Asp Asp Ser Leu Lys Thr Ser Leu Ile Thr Glu Glu Glu Asp Ser Thr
       435   440   445

Ser Glu Val Leu Asp Glu Glu Leu Lys Leu Gln Pro Phe Asn Ser Ser
    450   455   460

Glu Asp Ser Thr Asn Leu Val Pro Leu Val Val Glu Ser Ser Lys Pro
465   470   475   480

Pro Glu Val Asp Ala Pro Asp Lys Thr Pro Arg Ile Pro Asp Ser Glu
           485   490   495

Met Leu Met Asp Glu Gly Thr Ser Asp Glu Lys Gly His Met Glu Glu
       500   505   510

Lys Leu Ser Leu Leu Pro Arg Lys Lys Ala His Leu Gly Ser Ser Asp
      515   520   525

Asn Val Ala Thr Met Ser Asn Glu Glu Arg Ser Asp Gly Gly Phe Pro

    530   535   540

Asn Ser Val Ile Ala Glu Phe Ser Glu Glu Pro Val Ser Glu Asn Leu

545   550   555   560

Ser Pro Asn Thr Thr Ser Ser Leu Glu Asp Gln Gly Glu Glu Gly Val

        565   570   575

Ser Glu Pro Gln Glu Thr Ser Thr Ala Leu Pro Gln Ser Ser Leu Ile

        580   585   590

Glu Val Glu Leu Glu Asp Val Pro Phe Ser Gln Asn Ala Gly Gln Lys

      595   600   605

Asn Gln Ser Glu Glu Gln Ser Glu Ala Ser Ser Glu Gln Leu Asp Gln

      610   615   620

Phe Thr Gln Ser Ala Glu Lys Ala Val Asp Ser Ser Ser Glu Glu Ile

625   630   635   640

Glu Val Glu Val Pro Val Val Asp Arg Arg Asn Leu Arg Arg Lys Ala

        645   650   655

Lys Gly His Lys Gly Pro Ala Lys Lys Lys Ala Lys Leu Thr

          660   665   670

<210> 136

<211> 474

<212> PRT

<213> Homo sapiens

<400> 136

Met Trp Arg Val Arg Lys Arg Gly Tyr Phe Gly Ile Trp Ser Phe Pro

  1   5   10   15

Leu Ile Ile Ala Ala Val Cys Ala Gln Ser Val Asn Asp Pro Ser Asn

        20   25   30

Met Ser Leu Val Lys Glu Thr Val Asp Arg Leu Leu Lys Gly Tyr Asp

      35   40   45

Ile Arg Leu Arg Pro Asp Phe Gly Gly Pro Pro Val Ala Val Gly Met

    50   55   60

Asn Ile Asp Ile Ala Ser Ile Asp Met Val Ser Glu Val Asn Met Asp
65   70   75   80

Tyr Thr Leu Thr Met Tyr Phe Gln Gln Ala Trp Arg Asp Lys Arg Leu
                    85   90   95

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

Asp Gln Leu Trp Val Pro Asp Thr Tyr Phe Leu Asn Asp Lys Lys Ser
            115   120   125

Phe Val His Gly Val Thr Val Lys Asn Arg Met Ile Arg Leu His Pro

        130   135   140

Asp Gly Thr Val Leu Tyr Gly Leu Arg Ile Thr Thr Thr Ala Ala Cys
145   150   155   160

Met Met Asp Leu Arg Arg Tyr Pro Leu Asp Glu Gln Asn Cys Thr Leu
                    165   170   175

Glu Ile Glu Ser Tyr Gly Tyr Thr Thr Asp Asp Ile Glu Phe Tyr Trp
                    180   185   190

Arg Gly Asp Asp Asn Ala Val Thr Gly Val Thr Lys Ile Glu Leu Pro
            195   200   205

Gln Phe Ser Ile Val Asp Tyr Lys Leu Ile Thr Lys Lys Val Val Phe
            210   215   220

Ser Thr Gly Ser Tyr Pro Arg Leu Ser Leu Ser Phe Lys Leu Lys Arg
225   230   235   240

Asn Ile Gly Tyr Phe Ile Leu Gln Thr Tyr Met Pro Ser Ile Leu Ile
                    245   250   255

Thr Ile Leu Ser Trp Val Ser Phe Trp Ile Asn Tyr Asp Ala Ser Ala
                    260   265   270

Ala Arg Val Ala Leu Gly Ile Thr Thr Val Leu Thr Met Thr Thr Ile

        275   280   285

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

Ile Asp Met Tyr Leu Met Gly Cys Phe Val Phe Val Phe Met Ala Leu
305   310   315   320

Leu Glu Tyr Ala Leu Val Asn Tyr Ile Phe Phe Gly Arg Gly Pro Gln
                325   330   335

Arg Gln Lys Lys Ala Ala Glu Lys Ala Ala Ser Ala Asn Asn Glu Lys
            340   345   350

Met Arg Leu Asp Val Asn Lys Met Asp Pro His Glu Asn Ile Leu Leu
        355   360   365

Ser Thr Leu Glu Ile Lys Asn Glu Met Ala Thr Ser Glu Ala Val Met
    370   375   380

Gly Leu Gly Asp Pro Arg Ser Thr Met Leu Ala Tyr Asp Ala Ser Ser
385   390   395   400

Ile Gln Tyr Arg Lys Ala Gly Leu Pro Arg His Ser Phe Gly Arg Asn
                405   410   415

Ala Leu Glu Arg His Val Ala Gln Lys Lys Ser Arg Leu Arg Arg Arg

                420   425   430

Ala Ser Gln Leu Lys Ile Thr Ile Pro Asp Leu Thr Asp Val Asn Ala
            435   440   445

Ile Asp Arg Trp Ser Arg Ile Phe Phe Pro Val Val Phe Ser Phe Phe
    450   455   460

Asn Ile Val Tyr Trp Leu Tyr Tyr Val Asn
465   470

<210>   137

<211>   328

<212>   PRT

<213>   Homo sapiens

<400>   137

Met Ala Asn Ser Ala Ser Pro Glu Gln Asn Gln Asn His Cys Ser Ala

    1   5   10   15

Ile Asn Asn Ser Ile Pro Leu Met Gln Gly Asn Leu Pro Thr Leu Thr
                20   25   30

Leu Ser Gly Lys Ile Arg Val Thr Val Thr Phe Phe Leu Phe Leu Leu
            35   40   45

Ser Ala Thr Phe Asn Ala Ser Phe Leu Leu Lys Leu Gln Lys Trp Thr

```
          50                    55                    60
Gln Lys Lys Glu Lys Gly Lys Lys Leu Ser Arg Met Lys Leu Leu Leu
  65                    70                    75                    80


Lys His Leu Thr Leu Ala Asn Leu Leu Glu Thr Leu Ile Val Met Pro
                      85                    90                    95
Leu Asp Gly Met Trp Asn Ile Thr Val Gln Trp Tyr Ala Gly Glu Leu
                      100                   105                   110
Leu Cys Lys Val Leu Ser Tyr Leu Lys Leu Phe Ser Met Tyr Ala Pro
                      115                   120                   125
Ala Phe Met Met Val Val Ile Ser Leu Asp Arg Ser Leu Ala Ile Thr
                      130                   135                   140
Arg Pro Leu Ala Leu Lys Ser Asn Ser Lys Val Gly Gln Ser Met Val


145                   150                   155                   160
Gly Leu Ala Trp Ile Leu Ser Ser Val Phe Ala Gly Pro Gln Leu Tyr
                      165                   170                   175
Ile Phe Arg Met Ile His Leu Ala Asp Ser Ser Gly Gln Thr Lys Val
                      180                   185                   190
Phe Ser Gln Cys Val Thr His Cys Ser Phe Ser Gln Trp Trp His Gln
                      195                   200                   205
Ala Phe Tyr Asn Phe Phe Thr Phe Ser Cys Leu Phe Ile Ile Pro Leu
                      210                   215                   220


Phe Ile Met Leu Ile Cys Asn Ala Lys Ile Ile Phe Thr Leu Thr Arg
225                   230                   235                   240
Val Leu His Gln Asp Pro His Glu Leu Gln Leu Asn Gln Ser Lys Asn
                      245                   250                   255
Asn Ile Pro Arg Ala Arg Leu Lys Thr Leu Lys Met Thr Val Ala Phe
                      260                   265                   270
Ala Thr Ser Phe Thr Val Cys Trp Thr Pro Tyr Tyr Val Leu Gly Ile
                      275                   280                   285
Trp Tyr Trp Phe Asp Pro Glu Met Leu Asn Arg Leu Ser Asp Pro Val


          290                   295                   300
```

Asn His Phe Phe Phe Leu Phe Ala Phe Leu Asn Pro Cys Phe Asp Pro

305   310   315   320

Leu Ile Tyr Gly Tyr Phe Ser Leu

                325

<210>   138

<211>   887

<212>   PRT

<213>   Homo sapiens

<400>   138

Met Met Ser Asp Glu Lys Asn Leu Gly Val Ser Gln Lys Leu Val Ser

  1   5   10   15

Pro Ser Arg Ser Thr Ser Ser Cys Ser Ser Lys Gln Gly Ser Arg Gln

                20   25   30

Asp Ser Trp Glu Val Val Glu Gly Leu Arg Gly Glu Met Asn Tyr Thr

                35   40   45

Gln Glu Pro Pro Val Gln Lys Gly Phe Leu Leu Lys Lys Arg Lys Trp

     50   55   60

Pro Leu Lys Gly Trp His Lys Arg Phe Phe Tyr Leu Asp Lys Gly Ile

 65   70   75   80

Leu Lys Tyr Ala Lys Ser Gln Thr Asp Ile Glu Arg Glu Lys Leu His

                85   90   95

Gly Cys Ile Asp Val Gly Leu Ser Val Met Ser Val Lys Lys Ser Ser

                100   105   110

Lys Cys Ile Asp Leu Asp Thr Glu Glu His Ile Tyr His Leu Lys Val

                115   120   125

Lys Ser Glu Glu Val Phe Asp Glu Trp Val Ser Lys Leu Arg His His

     130   135   140

Arg Met Tyr Arg Gln Asn Glu Ile Ala Met Phe Pro His Glu Val Asn

145   150   155   160

His Phe Phe Ser Gly Ser Thr Ile Thr Asp Ser Ser Ser Gly Val Phe

                165   170   175

Asp Ser Ile Ser Ser Arg Lys Arg Ser Ser Ile Ser Lys Gln Asn Leu

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


Gln Ser Met Asp Val Leu His Arg Thr Tyr Ser Ala Pro Ala Ile Asn
                245                 250                 255
Ala Ile Gln Gly Gly Ser Phe Glu Ser Pro Lys Lys Glu Lys Arg Ser
                260                 265                 270
His Arg Arg Trp Arg Ser Arg Ala Ile Gly Lys Asp Ala Lys Gly Thr
            275                 280                 285
Leu Gln Val Pro Lys Pro Phe Ser Gly Pro Val Arg Leu His Ser Ser
        290                 295                 300
Asn Pro Asn Leu Ser Thr Leu Asp Phe Gly Glu Glu Lys Asn Tyr Ser


305                 310                 315                 320
Asp Gly Ser Glu Thr Ser Ser Glu Phe Ser Lys Met Gln Glu Asp Leu
                325                 330                 335
Cys His Ile Ala His Lys Val Tyr Phe Thr Leu Arg Ser Ala Phe Asn
            340                 345                 350
Ile Met Ser Ala Glu Arg Glu Lys Leu Lys Gln Leu Met Glu Gln Asp
            355                 360                 365
Ala Ser Ser Ser Pro Ser Ala Gln Val Ile Gly Leu Lys Asn Ala Leu
        370                 375                 380


Ser Ser Ala Leu Ala Gln Asn Thr Asp Leu Lys Glu Arg Leu Arg Arg
385                 390                 395                 400
Ile His Ala Glu Ser Leu Leu Leu Asp Ser Pro Ala Val Ala Lys Ser
                405                 410                 415
Gly Asp Asn Leu Ala Glu Glu Asn Ser Arg Asp Glu Asn Arg Ala Leu
            420                 425                 430
Val His Gln Leu Ser Asn Glu Ser Arg Leu Ser Ile Thr Asp Ser Leu
```

435   440   445

Ser Glu Phe Phe Asp Ala Gln Glu Val Leu Leu Ser Pro Ser Ser Ser

450   455   460

Glu Asn Glu Ile Ser Asp Asp Asp Ser Tyr Val Ser Asp Ile Ser Asp
465   470   475   480

Asn Leu Ser Leu Asp Asn Leu Ser Asn Asp Leu Asp Asn Glu Arg Gln
                485   490   495

Thr Leu Gly Pro Val Leu Asp Ser Gly Arg Glu Ala Lys Ser Arg Arg
                500   505   510

Arg Thr Cys Leu Pro Ala Pro Cys Pro Ser Ser Ser Asn Ile Ser Leu
                515   520   525

Trp Asn Ile Leu Arg Asn Asn Ile Gly Lys Asp Leu Ser Lys Val Ala
                530   535   540

Met Pro Val Glu Leu Asn Glu Pro Leu Asn Thr Leu Gln Arg Leu Cys
545   550   555   560

Glu Glu Leu Glu Tyr Ser Glu Leu Leu Asp Lys Ala Ala Gln Ile Pro
                565   570   575

Ser Pro Leu Glu Arg Met Val Tyr Val Ala Ala Phe Ala Ile Ser Ala
                580   585   590

Tyr Ala Ser Ser Tyr Tyr Arg Ala Gly Ser Lys Pro Phe Asn Pro Val

595   600   605

Leu Gly Glu Thr Tyr Glu Cys Ile Arg Glu Asp Lys Gly Phe Gln Phe
                610   615   620

Phe Ser Glu Gln Val Ser His His Pro Pro Ile Ser Ala Cys His Ala
625   630   635   640

Glu Ser Arg Asn Phe Val Phe Trp Gln Asp Val Arg Trp Lys Asn Lys
                645   650   655

Phe Trp Gly Lys Ser Met Glu Ile Val Pro Ile Gly Thr Thr His Val
                660   665   670

Thr Leu Pro Val Phe Gly Asp His Phe Glu Trp Asn Lys Val Thr Ser
                675   680   685

Cys Ile His Asn Ile Leu Ser Gly Gln Arg Trp Ile Glu His Tyr Gly
   690   695   700

Glu Ile Val Ile Lys Asn Leu His Asp Asp Ser Cys Tyr Cys Lys Val
705   710   715   720

Asn Phe Ile Lys Ala Lys Tyr Trp Ser Thr Asn Ala His Glu Ile Glu
           725   730   735

Gly Thr Val Phe Asp Arg Ser Gly Lys Ala Val His Arg Leu Phe Gly

          740   745   750

Lys Trp His Glu Ser Ile Tyr Cys Gly Gly Gly Ser Ser Ser Ala Cys
       755   760   765

Val Trp Arg Ala Asn Pro Met Pro Lys Gly Tyr Glu Gln Tyr Tyr Ser
   770   775   780

Phe Thr Gln Phe Ala Leu Glu Leu Asn Glu Met Asp Pro Ser Ser Lys
785   790   795   800

Ser Leu Leu Pro Pro Thr Asp Thr Arg Phe Arg Pro Asp Gln Arg Phe
          805   810   815

Leu Glu Glu Gly Asn Leu Glu Glu Ala Glu Ile Gln Lys Gln Arg Ile
        820   825   830

Glu Gln Leu Gln Arg Glu Arg Arg Val Leu Glu Glu Asn His Val
        835   840   845

Glu His Gln Pro Arg Phe Phe Arg Lys Ser Asp Asp Asp Ser Trp Val
   850   855   860

Ser Asn Gly Thr Tyr Leu Glu Leu Arg Lys Asp Leu Gly Phe Ser Lys
865   870   875   880

Leu Asp His Pro Val Leu Trp

          885

<210> 139

<211> 1324

<212> PRT

<213> Homo sapiens

<400> 139

Met Leu Leu Ser Pro Ser Leu Leu Leu Leu Leu Leu Leu Gly Ala Pro

```
    1                5                10               15
Arg Gly Cys Ala Glu Gly Val Ala Ala Ala Leu Thr Pro Glu Arg Leu
                20               25               30
Leu Glu Trp Gln Asp Lys Gly Ile Phe Val Ile Gln Ser Glu Ser Leu
            35               40               45
Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu Asn Cys


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


Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr
        130              135              140
Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Asp Ile Cys Glu
  145              150              155              160
Tyr Leu His Lys Asp Leu His Thr Ile Lys Gly Asn Thr His Gly Met
            165              170              175
Pro Cys Met Phe Pro Phe Gln Tyr Asn His Gln Trp His His Glu Cys
            180              185              190
Thr Arg Glu Gly Arg Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser


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

```
                260              265                270
```

Glu Thr Glu Glu Asn Phe Ile Arg Glu His Met Ser Ser Lys Thr Val

```
           275              280              285
```

Glu Val Trp Met Gly Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln

```
       290              295              300
```

Trp Ser Asp Gly Thr Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val

```
   305              310              315              320
```

Asn Phe Glu Pro Phe Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe

```
              325              330              335
```

Met Pro Ser Ala Trp Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr

```
           340              345              350
```

Ile Cys Lys Lys Tyr Leu Asn His Ile Asp His Glu Ile Val Glu Lys

```
           355              360              365
```

Asp Ala Trp Lys Tyr Tyr Ala Thr His Cys Glu Pro Gly Trp Asn Pro

```
       370              375              380
```

Tyr Asn Arg Asn Cys Tyr Lys Leu Gln Lys Glu Glu Lys Thr Trp His

```
   385              390              395              400
```

Glu Ala Leu Arg Ser Cys Gln Ala Asp Asn Ser Ala Leu Ile Asp Ile

```
              405              410              415
```

Thr Ser Leu Ala Glu Val Glu Phe Leu Val Thr Leu Leu Gly Asp Glu

```
           420              425              430
```

Asn Ala Ser Glu Thr Trp Ile Gly Leu Ser Ser Asn Lys Ile Pro Val

```
           435              440              445
```

Ser Phe Glu Trp Ser Asn Asp Ser Ser Val Ile Phe Thr Asn Trp His

```
       450              455              460
```

Thr Leu Glu Pro His Ile Phe Pro Asn Arg Ser Gln Leu Cys Val Ser

```
   465              470              475              480
```

Ala Glu Gln Ser Glu Gly His Trp Lys Val Lys Asn Cys Glu Glu Arg

```
           485              490              495
```

Leu Phe Tyr Ile Cys Lys Lys Ala Gly His Val Leu Ser Asp Ala Glu

```
       500              505              510
```

Ser Gly Cys Gln Glu Gly Trp Glu Arg His Gly Gly Phe Cys Tyr Lys
      515   520   525

Ile Asp Thr Val Leu Arg Ser Phe Asp Gln Ala Ser Ser Gly Tyr Tyr
     530   535   540

Cys Pro Pro Ala Leu Val Thr Ile Thr Asn Arg Phe Glu Gln Ala Phe
545   550   555   560

Ile Thr Ser Leu Ile Ser Ser Val Val Lys Met Lys Asp Ser Tyr Phe
        565   570   575

Trp Ile Ala Leu Gln Asp Gln Asn Asp Thr Gly Glu Tyr Thr Trp Lys
       580   585   590

Pro Val Gly Gln Lys Pro Glu Pro Val Gln Tyr Thr His Trp Asn Thr
      595   600   605

His Gln Pro Arg Tyr Ser Gly Gly Cys Val Ala Met Arg Gly Arg His
    610   615   620

Pro Leu Gly Arg Trp Glu Val Lys His Cys Arg His Phe Lys Ala Met

625   630   635   640

Ser Leu Cys Lys Gln Pro Val Glu Asn Gln Glu Lys Ala Glu Tyr Glu
        645   650   655

Glu Arg Trp Pro Phe His Pro Cys Tyr Leu Asp Trp Glu Ser Glu Pro
       660   665   670

Gly Leu Ala Ser Cys Phe Lys Val Phe His Ser Glu Lys Val Leu Met
      675   680   685

Lys Arg Thr Trp Arg Glu Ala Glu Ala Phe Cys Glu Glu Phe Gly Ala
    690   695   700

His Leu Ala Ser Phe Ala His Ile Glu Glu Glu Asn Phe Val Asn Glu
705   710   715   720

Leu Leu His Ser Lys Phe Asn Trp Thr Glu Glu Arg Gln Phe Trp Ile
       725   730   735

Gly Phe Asn Lys Arg Asn Pro Leu Asn Ala Gly Ser Trp Glu Trp Ser
      740   745   750

Asp Arg Thr Pro Val Val Ser Ser Phe Leu Asp Asn Thr Tyr Phe Gly
      755   760   765

Glu Asp Ala Arg Asn Cys Ala Val Tyr Lys Ala Asn Lys Thr Leu Leu

    770   775   780

Pro Leu His Cys Gly Ser Lys Arg Glu Trp Ile Cys Lys Ile Pro Arg

785   790   795   800

Asp Val Lys Pro Lys Ile Pro Phe Trp Tyr Gln Tyr Asp Val Pro Trp

         805   810   815

Leu Phe Tyr Gln Asp Ala Glu Tyr Leu Phe His Thr Phe Ala Ser Glu

         820   825   830

Trp Leu Asn Phe Glu Phe Val Cys Ser Trp Leu His Ser Asp Leu Leu

        835   840   845

Thr Ile His Ser Ala His Glu Gln Glu Phe Ile His Ser Lys Ile Lys

     850   855   860

Ala Leu Ser Lys Tyr Gly Ala Ser Trp Trp Ile Gly Leu Gln Glu Glu

865   870   875   880

Arg Ala Asn Asp Glu Phe Arg Trp Arg Asp Gly Thr Pro Val Ile Tyr

        885   890   895

Gln Asn Trp Asp Thr Gly Arg Glu Arg Thr Val Asn Asn Gln Ser Gln

        900   905   910

Arg Cys Gly Phe Ile Ser Ser Ile Thr Gly Leu Trp Gly Ser Glu Glu

        915   920   925

Cys Ser Val Ser Met Pro Ser Ile Cys Lys Arg Lys Lys Val Trp Leu

     930   935   940

Ile Glu Lys Lys Lys Asp Thr Pro Lys Gln His Gly Thr Cys Pro Lys

945   950   955   960

Gly Trp Leu Tyr Phe Asn Tyr Lys Cys Leu Leu Leu Asn Ile Pro Lys

        965   970   975

Asp Pro Ser Ser Trp Lys Asn Trp Thr His Ala Gln His Phe Cys Ala

        980   985   990

Glu Glu Gly Gly Thr Leu Val Ala Ile Glu Ser Glu Val Glu Gln Ala

        995   1000   1005

Phe Ile Thr Met Asn Leu Phe Gly Gln Thr Thr Ser Val Trp Ile Gly

       1010   1015   1020

Leu Gln Asn Asp Asp Tyr Glu Thr Trp Leu Asn Gly Lys Pro Val Val

1025   1030   1035   1040

Tyr Ser Asn Trp Ser Pro Phe Asp Ile Ile Asn Ile Pro Ser His Asn

               1045   1050   1055

Thr Thr Glu Val Gln Lys His Ile Pro Leu Cys Ala Leu Leu Ser Ser

            1060   1065   1070

Asn Pro Asn Phe His Phe Thr Gly Lys Trp Tyr Phe Glu Asp Cys Gly

           1075   1080   1085

Lys Glu Gly Tyr Gly Phe Val Cys Glu Lys Met Gln Asp Thr Ser Gly

         1090   1095   1100

His Gly Val Asn Thr Ser Asp Met Tyr Pro Met Pro Asn Thr Leu Glu

1105   1110   1115   1120

Tyr Gly Asn Arg Thr Tyr Lys Ile Ile Asn Ala Asn Met Thr Trp Tyr

             1125   1130   1135

Ala Ala Ile Lys Thr Cys Leu Met His Lys Ala Gln Leu Val Ser Ile

              1140   1145   1150

Thr Asp Gln Tyr His Gln Ser Phe Leu Thr Val Val Leu Asn Arg Leu

           1155   1160   1165

Gly Tyr Ala His Trp Ile Gly Leu Phe Thr Thr Asp Asn Gly Leu Asn

         1170   1175   1180

Phe Asp Trp Ser Asp Gly Thr Lys Ser Ser Phe Thr Phe Trp Lys Asp

1185   1190   1195   1200

Glu Glu Ser Ser Leu Leu Gly Asp Cys Val Phe Ala Asp Ser Asn Gly

            1205   1210   1215

Arg Trp His Ser Thr Ala Cys Glu Ser Phe Leu Gln Gly Ala Ile Cys

             1220   1225   1230

His Val Pro Pro Glu Thr Arg Gln Ser Glu His Pro Glu Leu Cys Ser

           1235   1240   1245

Glu Thr Ser Ile Pro Trp Ile Lys Phe Lys Ser Asn Cys Tyr Ser Phe

         1250   1255   1260

Ser Thr Val Leu Asp Ser Met Ser Phe Glu Ala Ala His Glu Phe Cys

```
        1265              1270              1275              1280


Lys Lys Glu Gly Ser Asn Leu Leu Thr Ile Lys Asp Glu Ala Glu Asn
                  1285              1290              1295

Ala Phe Leu Leu Glu Glu Leu Phe Ala Phe Gly Ser Ser Val Gln Met
              1300              1305              1310

Val Trp Leu Asn Ala Gln Phe Asp Gly Asn Ser Lys
          1315              1320
```

<210>   140
<211>   497
<212>   PRT
<213>   Homo sapiens
<400>   140

```
Met Thr Lys Ser Asn Gly Glu Glu Pro Lys Met Gly Gly Arg Met Glu
 1                5                10               15


Arg Phe Gln Gln Gly Val Arg Lys Arg Thr Leu Leu Ala Lys Lys Lys
                  20               25               30

Val Gln Asn Ile Thr Lys Glu Asp Val Lys Ser Tyr Leu Phe Arg Asn
          35               40               45

Ala Phe Val Leu Leu Thr Val Thr Ala Val Ile Val Gly Thr Ile Leu
      50               55               60

Gly Phe Thr Leu Arg Pro Tyr Arg Met Ser Tyr Arg Glu Val Lys Tyr
 65               70               75               80

Phe Ser Phe Pro Gly Glu Leu Leu Met Arg Met Leu Gln Met Leu Val


                  85               90               95

Leu Pro Leu Ile Ile Ser Ser Leu Val Thr Gly Met Ala Ala Leu Asp
                  100              105              110

Ser Lys Ala Ser Gly Lys Met Gly Met Arg Ala Val Val Tyr Tyr Met
              115              120              125

Thr Thr Thr Ile Ile Ala Val Val Ile Gly Ile Ile Ile Val Ile Ile
          130              135              140

Ile His Pro Gly Lys Gly Thr Lys Glu Asn Met His Arg Glu Gly Lys
```

```
                 145                     150                     155                     160



Ile Val Arg Val Thr Ala Ala Asp Ala Phe Leu Asp Leu Ile Arg Asn
                         165                     170                     175
Met Phe Pro Pro Asn Leu Val Glu Ala Cys Phe Lys Gln Phe Lys Thr
                     180                     185                     190
Asn Tyr Glu Lys Arg Ser Phe Lys Val Pro Ile Gln Ala Asn Glu Thr
                 195                     200                     205
Leu Val Gly Ala Val Ile Asn Asn Val Ser Glu Ala Met Glu Thr Leu
             210                     215                     220
Thr Arg Ile Thr Glu Glu Leu Val Pro Val Pro Gly Ser Val Asn Gly



                 225                     230                     235                     240
Val Asn Ala Leu Gly Leu Val Val Phe Ser Met Cys Phe Gly Phe Val
                         245                     250                     255
Ile Gly Asn Met Lys Glu Gln Gly Gln Ala Leu Arg Glu Phe Phe Asp
                         260                     265                     270
Ser Leu Asn Glu Ala Ile Met Arg Leu Val Ala Val Ile Met Trp Tyr
                 275                     280                     285
Ala Pro Val Gly Ile Leu Phe Leu Ile Ala Gly Lys Ile Val Glu Met
             290                     295                     300



Glu Asp Met Gly Val Ile Gly Gly Gln Leu Ala Met Tyr Thr Val Thr
         305                     310                     315                     320
Val Ile Val Gly Leu Leu Ile His Ala Val Ile Val Leu Pro Leu Leu
                     325                     330                     335
Tyr Phe Leu Val Thr Arg Lys Asn Pro Trp Val Phe Ile Gly Gly Leu
                 340                     345                     350
Leu Gln Ala Leu Ile Thr Ala Leu Gly Thr Ser Ser Ser Ser Ala Thr
             355                     360                     365
Leu Pro Ile Thr Phe Lys Cys Leu Glu Glu Asn Asn Gly Val Asp Lys



                 370                     375                     380
Arg Val Thr Arg Phe Val Leu Pro Val Gly Ala Thr Ile Asn Met Asp
         385                     390                     395                     400
```

Gly Thr Ala Leu Tyr Glu Ala Leu Ala Ala Ile Phe Ile Ala Gln Val

                405   410   415

Asn Asn Phe Glu Leu Asn Phe Gly Gln Ile Ile Thr Ile Arg Asp Arg

                420   425   430

Leu Arg Thr Thr Thr Asn Val Leu Gly Asp Ser Leu Gly Ala Gly Ile

            435   440   445

Val Glu His Leu Ser Arg His Glu Leu Lys Asn Arg Asp Val Glu Met

        450   455   460

Gly Asn Ser Val Ile Glu Glu Asn Glu Met Lys Lys Pro Tyr Gln Leu

465   470   475   480

Ile Ala Gln Asp Asn Glu Thr Glu Lys Pro Ile Asp Ser Glu Thr Lys

                485   490   495

Met

<210>   141

<211>   1444

<212>   PRT

<213>   Homo sapiens

<400>   141

Met Lys Ser Cys Ala Val Ser Leu Thr Thr Ala Ala Val Ala Phe Gly

  1   5   10   15

Asp Glu Ala Lys Lys Met Ala Glu Gly Lys Ala Ser Arg Glu Ser Glu

                20   25   30

Glu Glu Ser Val Ser Leu Thr Val Glu Glu Arg Glu Ala Leu Gly Gly

            35   40   45

Met Asp Ser Arg Leu Phe Gly Phe Val Arg Leu His Glu Asp Gly Ala

        50   55   60

Arg Thr Lys Thr Leu Leu Gly Lys Ala Val Arg Cys Tyr Glu Ser Leu

65   70   75   80

Ile Leu Lys Ala Glu Gly Lys Val Glu Ser Asp Phe Phe Cys Gln Leu

                85   90   95

Gly His Phe Asn Leu Leu Leu Glu Asp Tyr Ser Lys Ala Leu Ser Ala

```
                100                   105                   110
Tyr Gln Arg Tyr Tyr Ser Leu Gln Ala Asp Tyr Trp Lys Asn Ala Ala
            115                   120                   125
Phe Leu Tyr Gly Leu Gly Leu Val Tyr Phe Tyr Tyr Asn Ala Phe His
        130                   135                   140
Trp Ala Ile Lys Ala Phe Gln Asp Val Leu Tyr Val Asp Pro Ser Phe


145                   150                   155                   160
Cys Arg Ala Lys Glu Ile His Leu Arg Leu Gly Leu Met Phe Lys Val
                    165                   170                   175
Asn Thr Asp Tyr Lys Ser Ser Leu Lys His Phe Gln Leu Ala Leu Ile
                180                   185                   190
Asp Cys Asn Pro Cys Thr Leu Ser Asn Ala Glu Ile Gln Phe His Ile
            195                   200                   205
Ala His Leu Tyr Glu Thr Gln Arg Lys Tyr His Ser Ala Lys Glu Ala
        210                   215                   220


Tyr Glu Gln Leu Leu Gln Thr Glu Asn Leu Pro Ala Gln Val Lys Ala
225                   230                   235                   240
Thr Val Leu Gln Gln Leu Gly Trp Met His His Asn Met Asp Leu Val
                    245                   250                   255
Gly Asp Lys Ala Thr Lys Glu Ser Tyr Ala Ile Gln Tyr Leu Gln Lys
                260                   265                   270
Ser Leu Glu Ala Asp Pro Asn Ser Gly Gln Ser Trp Tyr Phe Leu Gly
            275                   280                   285
Arg Cys Tyr Ser Ser Ile Gly Lys Val Gln Asp Ala Phe Ile Ser Tyr


        290                   295                   300
Arg Gln Ser Ile Asp Lys Ser Glu Ala Ser Ala Asp Thr Trp Cys Ser
305                   310                   315                   320
Ile Gly Val Leu Tyr Gln Gln Gln Asn Gln Pro Met Asp Ala Leu Gln
                    325                   330                   335
Ala Tyr Ile Cys Ala Val Gln Leu Asp His Gly His Ala Ala Ala Trp
                340                   345                   350
Met Asp Leu Gly Thr Leu Tyr Glu Ser Cys Asn Gln Pro Gln Asp Ala
```

```
                355                 360                 365


Ile Lys Cys Tyr Leu Asn Ala Ala Arg Ser Lys Arg Cys Ser Asn Thr
      370                 375                 380
Ser Thr Leu Ala Ala Arg Ile Lys Phe Leu Gln Ala Gln Leu Cys Asn
385                 390                 395                 400
Leu Pro Gln Ser Ser Leu Gln Asn Lys Thr Lys Leu Leu Pro Ser Ile
                405                 410                 415
Glu Glu Ala Trp Ser Leu Pro Ile Pro Ala Glu Leu Thr Ser Arg Gln
                420                 425                 430
Gly Ala Met Asn Thr Ala Gln Gln Ala Tyr Arg Ala His Asp Pro Asn


                435                 440                 445
Thr Glu His Val Leu Asn His Ser Gln Thr Pro Ile Leu Gln Gln Ser
      450                 455                 460
Leu Ser Leu His Met Ile Thr Ser Ser Gln Val Glu Gly Leu Ser Ser
465                 470                 475                 480
Pro Ala Lys Lys Lys Arg Thr Ser Ser Pro Thr Lys Asn Gly Ser Asp
                485                 490                 495
Asn Trp Asn Gly Gly Gln Ser Leu Ser His His Pro Val Gln Gln Val
                500                 505                 510


Tyr Ser Leu Cys Leu Thr Pro Gln Lys Leu Gln His Leu Glu Gln Leu
      515                 520                 525
Arg Ala Asn Arg Asp Asn Leu Asn Pro Ala Gln Lys His Gln Leu Glu
      530                 535                 540
Gln Leu Glu Ser Gln Phe Val Leu Met Gln Gln Met Arg His Lys Glu
545                 550                 555                 560
Val Ala Gln Val Arg Thr Thr Gly Ile His Asn Gly Ala Ile Thr Asp
                565                 570                 575
Ser Ser Leu Pro Thr Asn Ser Val Ser Asn Arg Gln Pro His Gly Ala


                580                 585                 590
Leu Thr Arg Val Ser Ser Val Ser Gln Pro Gly Val Arg Pro Ala Cys
      595                 600                 605
```

Val Glu Lys Leu Leu Ser Ser Gly Ala Phe Ser Ala Gly Cys Ile Pro
  610   615   620

Cys Gly Thr Ser Lys Ile Leu Gly Ser Thr Asp Thr Ile Leu Leu Gly
625   630   635   640

Ser Asn Cys Ile Ala Gly Ser Glu Ser Asn Gly Asn Val Pro Tyr Leu
     645   650   655

Gln Gln Asn Thr His Thr Leu Pro His Asn His Thr Asp Leu Asn Ser
     660   665   670

Ser Thr Glu Glu Pro Trp Arg Lys Gln Leu Ser Asn Ser Ala Gln Gly
     675   680   685

Leu His Lys Ser Gln Ser Ser Cys Leu Ser Gly Pro Asn Glu Glu Gln
  690   695   700

Pro Leu Phe Ser Thr Gly Ser Ala Gln Tyr His Gln Ala Thr Ser Thr
705   710   715   720

Gly Ile Lys Lys Ala Asn Glu His Leu Thr Leu Pro Ser Asn Ser Val

     725   730   735

Pro Gln Gly Asp Ala Asp Ser His Leu Ser Cys His Thr Ala Thr Ser
     740   745   750

Gly Gly Gln Gln Gly Ile Met Phe Thr Lys Glu Ser Lys Pro Ser Lys
     755   760   765

Asn Arg Ser Leu Val Pro Glu Thr Ser Arg His Thr Gly Asp Thr Ser
  770   775   780

Asn Gly Cys Ala Asp Val Lys Gly Leu Ser Asn His Val His Gln Leu
785   790   795   800

Ile Ala Asp Ala Val Ser Ser Pro Asn His Gly Asp Ser Pro Asn Leu
     805   810   815

Leu Ile Ala Asp Asn Pro Gln Leu Ser Ala Leu Leu Ile Gly Lys Ala
     820   825   830

Asn Gly Asn Val Gly Thr Gly Thr Cys Asp Lys Val Asn Asn Ile His
     835   840   845

Pro Ala Val His Thr Lys Thr Asp His Ser Val Ala Ser Ser Pro Ser
  850   855   860

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

865   870   875   880

Ser Ile Asn Ser Val Thr Ser Leu Asn Ser Pro His Ser Gly Leu His
                885   890   895

Thr Val Asn Gly Glu Gly Leu Gly Lys Ser Gln Ser Ser Thr Lys Val
                900   905   910

Asp Leu Pro Leu Ala Ser His Arg Ser Thr Ser Gln Ile Leu Pro Ser
            915   920   925

Met Ser Val Ser Ile Cys Pro Ser Ser Thr Glu Val Leu Lys Ala Cys
            930   935   940

Arg Asn Pro Gly Lys Asn Gly Leu Ser Asn Ser Cys Ile Leu Leu Asp
945   950   955   960

Lys Cys Pro Pro Pro Arg Pro Pro Thr Ser Pro Tyr Pro Pro Leu Pro
                965   970   975

Lys Asp Lys Leu Asn Pro Pro Thr Pro Ser Ile Tyr Leu Glu Asn Lys
                980   985   990

Arg Asp Ala Phe Phe Pro Pro Leu His Gln Phe Cys Thr Asn Pro Lys
            995   1000   1005

Asn Pro Val Thr Val Ile Arg Gly Leu Ala Gly Ala Leu Lys Leu Asp

            1010   1015   1020

Leu Gly Leu Phe Ser Thr Lys Thr Leu Val Glu Ala Asn Asn Glu His
1025   1030   1035   1040

Met Val Glu Val Arg Thr Gln Leu Leu Gln Pro Ala Asp Glu Asn Trp
                1045   1050   1055

Asp Pro Thr Gly Thr Lys Lys Ile Trp Arg Cys Glu Ser Asn Arg Ser
                1060   1065   1070

His Thr Thr Ile Ala Lys Tyr Ala Gln Tyr Gln Ala Ser Ser Phe Gln
            1075   1080   1085

Glu Ser Leu Arg Glu Glu Asn Glu Lys Arg Thr Gln His Lys Asp His
        1090   1095   1100

Ser Asp Asn Glu Ser Thr Ser Ser Glu Asn Ser Gly Arg Arg Arg Lys

```
     1105                1110                1115                1120
Gly Pro Phe Lys Thr Ile Lys Phe Gly Thr Asn Ile Asp Leu Ser Asp

          1125                1130                1135
Asn Lys Lys Trp Lys Leu Gln Leu His Glu Leu Thr Lys Leu Pro Ala

          1140                1145                1150
Phe Ala Arg Val Val Ser Ala Gly Asn Leu Leu Thr His Val Gly His


          1155                1160                1165
Thr Ile Leu Gly Met Asn Thr Val Gln Leu Tyr Met Lys Val Pro Gly

     1170                1175                1180
Ser Arg Thr Pro Gly His Gln Glu Asn Asn Asn Phe Cys Ser Val Asn

1185                1190                1195                1200
Ile Asn Ile Gly Pro Gly Asp Cys Glu Trp Phe Val Val Pro Glu Asp

          1205                1210                1215
Tyr Trp Gly Val Leu Asn Asp Phe Cys Glu Lys Asn Asn Leu Asn Phe

          1220                1225                1230
Leu Met Ser Ser Trp Trp Pro Asn Leu Glu Asp Leu Tyr Glu Ala Asn

          1235                1240                1245
Val Pro Val Tyr Arg Phe Ile Gln Arg Pro Gly Asp Leu Val Trp Ile

     1250                1255                1260
Asn Ala Gly Thr Val His Trp Val Gln Ala Val Gly Trp Cys Asn Asn

1265                1270                1275                1280
Ile Ala Trp Asn Val Gly Pro Leu Thr Ala Cys Gln Tyr Lys Leu Ala

               1285                1290                1295
Val Glu Arg Tyr Glu Trp Asn Lys Leu Lys Ser Val Lys Ser Pro Val


          1300                1305                1310
Pro Met Val His Leu Ser Trp Asn Met Ala Arg Asn Ile Lys Val Ser

          1315                1320                1325
Asp Pro Lys Leu Phe Glu Met Ile Lys Tyr Cys Leu Leu Lys Ile Leu

          1330                1335                1340
Lys Gln Tyr Gln Thr Leu Arg Glu Ala Leu Val Ala Ala Gly Lys Glu

1345                1350                1355                1360
Val Ile Trp His Gly Arg Thr Asn Asp Glu Pro Ala His Tyr Cys Ser
```

                    1365   1370   1375

Ile Cys Glu Val Glu Val Phe Asn Leu Leu Phe Val Thr Asn Glu Ser
            1380   1385   1390

Asn Thr Gln Lys Thr Tyr Ile Val His Cys His Asp Cys Ala Arg Lys
             1395   1400   1405

Thr Ser Lys Ser Leu Glu Asn Phe Val Val Leu Glu Gln Tyr Lys Met
        1410   1415   1420

Glu Asp Leu Ile Gln Val Tyr Asp Gln Phe Thr Leu Ala Leu Ser Leu
1425   1430   1435   1440

Ser Ser Ser Ser

<210>   142
<211>   359
<212>   PRT
<213>   Homo sapiens
<400>   142

Met Ala Leu Asn Ser Ser Thr Glu Asp Gly Ile Lys Arg Ile Gln Asp
  1   5   10   15

Asp Cys Pro Arg Ala Gly Arg His Ser Tyr Ile Phe Val Met Ile Pro
                20   25   30

Thr Leu Tyr Ser Ile Ile Phe Val Val Gly Ile Phe Gly Asn Ser Leu
             35   40   45

Val Val Ile Val Ile Tyr Phe Tyr Met Lys Leu Lys Thr Val Ala Ser

          50   55   60

Val Phe Leu Leu Asn Leu Ala Leu Ala Asp Leu Cys Phe Leu Leu Thr
 65   70   75   80

Leu Pro Leu Trp Ala Val Tyr Thr Ala Met Glu Tyr Arg Trp Pro Phe
                85   90   95

Gly Asn His Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Asn Leu
                100   105   110

Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg Tyr Leu

```
                115                 120                 125

Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Thr Met Leu Val
    130                 135                 140
Ala Lys Val Thr Cys Ile Ile Ile Trp Leu Met Ala Gly Leu Ala Ser
145                 150                 155                 160
Leu Pro Ala Val Ile His Arg Asn Val Tyr Phe Ile Glu Asn Thr Asn
                165                 170                 175
Ile Thr Val Cys Ala Phe His Tyr Glu Ser Arg Asn Ser Thr Leu Pro
                180                 185                 190
Ile Gly Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe


                195                 200                 205
Leu Ile Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Ala Leu Lys Lys
    210                 215                 220
Ala Tyr Glu Ile Gln Lys Asn Lys Pro Arg Asn Asp Asp Ile Phe Arg
225                 230                 235                 240
Ile Ile Met Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Val Pro His
                245                 250                 255
Gln Ile Phe Thr Phe Leu Asp Val Leu Ile Gln Leu Gly Val Ile His
                260                 265                 270


Asp Cys Lys Ile Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile
                275                 280                 285
Cys Ile Ala Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly Phe
    290                 295                 300
Leu Gly Lys Lys Phe Lys Lys Tyr Phe Leu Gln Leu Leu Lys Tyr Ile
305                 310                 315                 320
Pro Pro Lys Ala Lys Ser His Ser Ser Leu Ser Thr Lys Met Ser Thr
                325                 330                 335
Leu Ser Tyr Arg Pro Ser Asp Asn Met Ser Ser Ala Ala Lys Lys Pro


                340                 345                 350
Ala Ser Cys Ser Glu Val Glu
    355
```