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(54) Título: **Método para predecir la respuesta al tratamiento con quimioterapia en pacientes de cáncer colorrectal**

(57) Resumen:

Método para predecir la respuesta al tratamiento con quimioterapia en pacientes de cáncer colorrectal.
Método de obtención de datos útiles para predecir la respuesta al tratamiento con quimioterapia en pacientes con cáncer colorrectal, kit, dispositivo y microarray para llevar a cabo dicho método.

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Aviso: Se puede realizar consulta prevista por el art. 37.3.8 LP.

DESCRIPCIÓN

Método para predecir la respuesta al tratamiento con quimioterapia en pacientes de cáncer colorrectal.

CAMPO DE LA INVENCIÓN

La presente invención se encuentra dentro del campo de la Biología Molecular y la Medicina. Específicamente se refiere a un método de obtención de datos útiles para predecir la respuesta al tratamiento con quimioterapia en pacientes con cáncer colorrectal, que permite el establecimiento de un patrón individual de reconocimiento cuantitativo específico, que se puede modificar con el tratamiento, permitiendo el establecimiento de grupos de pacientes con el mismo diagnóstico pero distinto comportamiento clínico, pudiendo seleccionar así, el tratamiento más adecuado para cada paciente. La predicción de respuesta al tratamiento se realiza mediante el análisis del perfil de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1.*

ANTECEDENTES DE LA INVENCIÓN

El cáncer colorrectal (CCR) es el tercer tumor más común en el mundo, con más de 1.2 millones de nuevos casos diagnosticados cada año, y es responsable de alrededor del 8% de las muertes relacionadas con cáncer (http://globocan.iarc.fr). Aproximadamente dos tercios de los pacientes se diagnostican en estadíos precoces de la enfermedad (I-III), potencialmente curables mediante tratamiento quirúrgico seguido o no de quimioterapia adyuvante. No obstante, un 40% de estos pacientes eventualmente recidivan tras la cirugía. El tratamiento con quimioterapia adyuvante postquirúrgica reduce el riesgo de recidiva tumoral en un 10-20%. Globalmente, por lo tanto, se estima que aproximadamente un 80% de los pacientes no se benefician de un tratamiento quimioterápico complementario a la cirugía, bien por estar curados con tratamiento quirúrgico únicamente, bien por ser refractarios al tratamiento quimioterápico. Los tumores no subsidiarios de resección quirúrgica completa se consideran incurables. La quimioterapia en este contexto ha demostrado mejorar de manera modesta aunque significativa la calidad y esperanza de vida de los pacientes, si bien a expensas de un considerable coste económico y de una no desdeñable toxicidad. El tratamiento estándar en el cáncer colorrectal avanzado consiste en distintas combinaciones de fluoropirimidinas con oxaliplatino o irinotecan. Estos esquemas terapéuticos inducen respuestas tumorales objetivas en un 40-60% de los pacientes con medianas de supervivencia en torno a los 20 meses. A lo largo de la última década, diversos fármacos, entre los que se encuentran fármacos dirigidos frente al factor de crecimiento endotelial o VEGF (bevacizumab, aflibercept) o el receptor del factor de crecimiento epidérmico o EGFR (cetuximab, panitumumab), han sido incorporados al arsenal terapéutico con resultados prometedores. A pesar de estos avances, no obstante, la mayoría de los pacientes con enfermedad irresecable eventualmente fallece por progresión tumoral, con una mediana de supervivencia de 20-24 meses en el mejor de los casos (Vieitz *et al.*, 2011. *Clin. Transl. Oncol.* 13(11), 798–804; García-Carbonero *et al. 2010. Clin. Transl. Oncol., 12(11), 729–734*).

Los factores pronósticos tradicionales empleados en los sistemas de estadiaje convencionales como el TNM, fundamentalmente basados en las características histopatológicas del tumor y en su grado de extensión en el organismo, clasifican a los pacientes con carcinoma colorrectal en cuatro grandes grupos o estadíos de la enfermedad: tumores limitados a la mucosa colorrectal o estadío I, tumores que infiltran toda la pared intestinal o estadío II, tumores que invaden los ganglios linfáticos regionales o estadío III, y tumores con metástasis en órganos a distancia o estadío IV. Si bien estas clasificaciones tradicionales permiten diferenciar de una manera grosera subgrupos de pacientes con distinto pronóstico a largo plazo, existe una enorme heterogeneidad biológica dentro de dichos subgrupos tanto en términos de supervivencia como en términos de potencial respuesta tumoral al tratamiento con quimioterapia. En este contexto resulta fundamental el desarrollo de nuevos marcadores biológicos que nos permitan mejorar nuestra habilidad de clasificar a los pacientes en subgrupos pronósticos/predictivos.

La elaboración de perfiles de expresión génica usando la tecnología microarray muestra un alto potencial en la investigación del cáncer, ya que permite el análisis simultáneo y comparado de miles de genes en diversas muestras biológicas (p.ej. muestras tumorales) de pacientes afectos de la misma enfermedad pero con distinto comportamiento clínico (Nannini *et al.* 2009. *Cancer Treat. Rev.* 35(3), 201-209). El análisis del patrón de expresión génica ha demostrado mejorar el diagnóstico, pronóstico y la precisión predictiva en diferentes tipos de cáncer (Liang *et al.* 2003. *Nat. Rev. Cancer*, 3, 869-876). Por ejemplo, varios estudios han mostrando como los perfiles de expresión génica discriminan entre cáncer de mama con o sin receptores de estrógenos, o entre cáncer de mama familiar o esporádico. Además, de esta manera han sido descritos subgrupos moleculares antes desconocidos, como el subgrupo de células basales o luminales de cáncer de mama, y han dado lugar a nuevas propuestas de clasificación en tumores del sistema nervioso central o en sarcomas de partes blandas. Pero la aplicación más atractiva desde el punto de visto clínico, es la posibilidad de diferenciación entre subgrupos de pacientes con diferentes probabilidades de recurrencia o muerte por cáncer (Rosenwald *et al.*, 2002. *N. Engl. J. Med.* 246, 1937-1947; van de Vijver He Y.D. *et al.*, 2002. *N. Engl. J. Med.* 247, 1999-2009; Beer D.G. *et al.*, 2002. *Nat. Med.* 8, 816-824), o con diferentes probabilidades de responder a un determinado agente antineoplásico (Staunton J.E. *et al.*, 2001. *Proc. Natl. Acad. Sci* 98,10787-10792; Pusztai L. *et al.*, 2003. *The Oncologist*, 8, 252-258).

En las 2 últimas décadas, se ha demostrado que el perfil de expresión génica puede diferenciar entre tejido colónico normal, adenomas benignos y adenocarcinomas en distintos estadíos de extensión de la enfermedad, y se puede determinar también el riesgo de desarrollar CCR dependiente del análisis de tejido colónico normal, así como la probabilidad de recurrencia después de la resección quirúrgica de un CCR (Bertucci *et al.,* 2004. *Oncogene* 23, 1377-1391; Bandrés *et al.,* 2007. *Oncology Reports* 17, 1089-1094). Sin embargo, el valor de esta tecnología como un predictor de la respuesta del cáncer de colon a la quimioterapia, ha sido poco investigado.

Los tratamientos para el CCR avanzado tienen una eficacia limitada, son costosos y no están exentos de riesgos para el paciente. Por todo ello, resulta fundamental desarrollar biomarcadores que permitan predecir prospectivamente qué pacientes van a responder al tratamiento. Por un lado, el disponer de herramientas que permitan identificar *a priori* aquellos pacientes que no se van a beneficiar de un determinado tratamiento médico evitaría al paciente la toxicidad, el gasto y el tiempo que conlleva recibir dicho tratamiento, a la vez que le posibilitaría recibir un tratamiento alternativo con mayores posibilidades de éxito. Por otro lado, la identificación de marcadores biológicos predictivos de respuesta tumoral puede aportar información fundamental acerca de los mecanismos moleculares que determinan y regulan dicha respuesta y facilitar el descubrimiento de vías de manipulación de la misma que permitan maximizar el efecto terapéutico. En este contexto, el estudio mediante microarrays del patrón de expresión génica en pacientes con CCR avanzado tratados con quimioterapia, en función de su respuesta a la misma, podría facilitar el desarrollo de una firma genética de una incuestionable utilidad clínica.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

Un primer aspecto de la invención se refiere al uso de cualquiera de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2,*

VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1, o cualquiera de sus combinaciones, para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal.

Otro aspecto de la invención se refiere a un método de obtención de datos útiles para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, que comprende:

a) obtener una muestra biológica aislada que comprende células tumorales del individuo, y

b) detectar la cantidad de producto de expresión de cualquiera de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1,* o cualquiera de sus combinaciones en la muestra aislada de (a).

En una realización preferida el primer método de la invención comprende además:

c) comparar los niveles de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, en la muestra obtenida en (a), con la cantidad de expresión detectada para dichos genes en una población de individuos de referencia de respuesta patológica conocida.

Otro aspecto de la invención se refiere a un método para predecir o pronosticar la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, que comprende los pasos (a)-(c) del primer método de la invención, y además comprende:

d) incluir al individuo que presentan un nivel de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2,*

VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1 significativamente superior a los niveles de expresión de los mismos genes en una población de referencia, en el grupo de individuos respondedores a la terapia del cáncer colorrectal.

En una realización preferida de este aspecto de la invención la muestra biológica aislada de un individuo del paso (a) empleada para la determinación de los niveles de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se obtiene del tejido tumoral colorrectal del paciente.

En otra realización preferida de la invención la determinación del nivel de expresión de los genes no necesita limitarse de manera particular y se puede seleccionar a partir de un procedimiento de perfilado génico, tal como una micromatriz y/o un procedimiento que comprenda la PCR (reacción en cadena de la polimerasa), tal como la PCR en tiempo real; y/o la transferencia Northern.

Más preferentemente, la detección del producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se realiza mediante PCR cuantitativa a tiempo real.

En otra realización aun mas preferida de este aspecto de la invención la detección del producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se realiza mediante microarrays.

En una realización preferida de este aspecto de la invención el tratamiento quimioterápico comprende el uso de compuestos basados en platino, compuestos inhibidores de la topoisomerasa I, compuestos análogos de las pirimidinas, o cualquiera de sus combinaciones. Más preferiblemente el compuesto basado en platino es el oxaliplatino, el inhibidor de la topoisomerasa I es el irinotecan, y el análogo de pirimidina es el 5-fluorouracilo.

Una realización preferida de este aspecto de la invención, comprende realizar al menos dos veces la secuencia de pasos (a) – (b) del método de la invención, en muestras biológicas procedentes de un mismo individuo, y aisladas en momentos diferentes. Más preferiblemente, las muestras se obtienen antes y después del tratamiento, o de un ciclo de tratamiento con quimioterapia.

Otro aspecto de la presente invención se refiere a un kit o dispositivo, de ahora en adelante kit o dispositivo de la invención, que comprende los elementos necesarios para analizar la cantidad del producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1.*

Otro aspecto de la invención se refiere a un microarray, de ahora en adelante microarray de la invención, que comprende oligonucleótidos o microarreglos de canal único diseñados a partir de una secuencia conocida o un ARNm de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1.*

Más preferiblemente, la secuencia de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* es la secuencia nucleotídica correspondiente que se selecciona de la SEQ ID NO: 1 a la SEQ ID NO: 82.

Otro aspecto de la invención se refiere al uso del kit o dispositivo de la invención, o del microarray para la obtención de datos útiles para predecir o pronosticar la respuesta al tratamiento en pacientes con cáncer colorrectal.

DESCRIPCIÓN DE LA INVENCIÓN

La presente invención proporciona un método de obtención de datos útiles para predecir la respuesta de un sujeto humano con cáncer colorrectal al tratamiento de quimioterapia, permitiendo el establecimiento de grupos de pacientes afectos de la misma enfermedad pero con distinto comportamiento clínico. Se trata de un procedimiento fácil y fiable *in vitro* y herramientas útiles para este objetivo, tales como kits, dispositivos o sistemas de detección que puedan emplearse para llevar a cabo los métodos de la invención. Un objetivo adicional de la presente invencion, radica en proporcionar la medicación apropiada para un paciente individual que padezca de cáncer colorrectal basándose en la predicción del éxito del tratamiento.

El tratamiento de quimioterapia del cáncer colorrectal puede consistir, pero no está restringido, a la administración combinada o no de medicamentos como son capecitabina, floxuridina, fluorouracilo, oxaliplatino, irinotecán, etc.

Por tanto, un primer aspecto de la invención se refiere al uso de cualquiera de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, o cualquiera de sus combinaciones, para predecir o pronosticar la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal.

Otro aspecto de la invención se refiere al uso simultáneo de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal. Sin embargo, el uso independiente de cualquiera de ellos o cualquiera de sus combinaciones podrían ser suficientes para evaluar la respuesta y/o el seguimiento de dicha enfermedad.

En una realización preferida de este aspecto de la invención, la respuesta al tratamiento es una respuesta a la reducción de la carga tumoral. En una realización alternativa, la respuesta al tratamiento es una mejora o ausencia de deterioro del estado del tumor. En otra realización, la respuesta al tratamiento es un resultado clínico, tal como la supervivencia exenta de progresión o la supervivencia global.

MÉTODO DE OBTENCIÓN DE DATOS ÚTILES Y MÉTODO PARA PREDECIR LA RESPUESTA AL TRATAMIENTO DEL CÁNCER COLORRECTAL

Otro aspecto de la invención se refiere a un método de obtención de datos útiles, de ahora en adelante primer método de la invención, para predecir o pronosticar la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, que comprende:

a) obtener una muestra biológica aislada que comprende células tumorales del individuo, y

b) detectar la cantidad de producto de expresión de cualquiera de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1,* o cualquiera de sus combinaciones en la muestra aislada de (a).

Aunque la detección de la cantidad de producto de expresión de cualquiera de los genes, o de cualquiera de sus combinaciones, puede servir para predecir o pronosticar la respuesta al tratamiento con quimioterapia, en una realización preferida, la detección de la cantidad de producto de expresión de los genes del paso (b) se hace de manera simultánea.
En otra realización preferida el primer método de la invención además comprende:

c) comparar los niveles de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, en la muestra obtenida en (a), con la cantidad de expresión detectada para dichos genes en una población de individuos de referencia de respuesta patológica conocida.

Otro aspecto de la invención se refiere a un método para predecir o pronosticar la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, de ahora en adelante segundo método de la invención, que comprende los pasos (a)-(c) del primer método de la invención, y además comprende:

d) incluir al individuo que presentan un nivel de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* significativamente superior a los niveles de expresión de los mismos genes en una población de referencia, en el grupo de individuos respondedores a la quimioterapia del cáncer colorrectal.

La Tabla1 muestra los niveles de expresión obtenidos para dichos genes:

Tabla 1. Niveles de expresión en células tumorales de pacientes respondedores con cáncer colorrectal.

Nombre del Gen	Veces de cambio en su nivel de expresión (Fold change)	Descripción	Gene ID	Secuencias nucleotídicas	Secuencias aminoacídicas
AQP1	2,30	aquaporin 1	358	SEQ ID NO:1 - SEQ ID NO:4	SEQ ID NO:83 - SEQ ID NO:86
CLEC3B	3,06	C-type lectin domain family 3, member B	7123	SEQ ID NO:5	SEQ ID NO:87
DCK	1,85	deoxycytidine kinase	1633	SEQ ID NO:6 - SEQ ID NO:7	SEQ ID NO:88 - SEQ ID NO:89
DEFA5	3,03	defensin, alpha 5, Paneth cell-specific	1670	SEQ ID NO:49	SEQ ID NO:131
DNAJC3	2,68	DnaJ (Hsp40) homolog, subfamily C, member 3	5611	SEQ ID NO:50	SEQ ID NO:132
FBLIM1	1,93	filamin binding LIM protein 1	54751	SEQ ID NO:13 - SEQ ID NO:15	SEQ ID NO:95 - SEQ ID NO:97
GAS7	2,00	growth arrest-specific 7	8522	SEQ ID NO:16 - SEQ ID NO:19	SEQ ID NO:98 - SEQ ID NO:101
IGFBP4	1,74	insulin-like growth factor binding protein 4	3487	SEQ ID NO:20	SEQ ID NO:102
KSR1	2,00	kinase suppressor of ras 1	8844	SEQ ID NO:51	SEQ ID NO:133

Nombre del Gen	Veces de cambio en su nivel de expresión (Fold change)	Descripción	Gene ID	Secuencias nucleotídicas	Secuencias aminoacídicas
LONP1	1,74	lon peptidase 1, mitochondrial	9361	SEQ ID NO:52	SEQ ID NO:134
MTHFD1L	1,89	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	25902	SEQ ID NO:53 - SEQ ID NO:56	SEQ ID NO:135 - SEQ ID NO:138
NAV1	1,84	neuron navigator 1	89796	SEQ ID NO:21 - SEQ ID NO:22	SEQ ID NO:103 - SEQ ID NO:104
NIPBL	2,07	Nipped-B homolog	25836	SEQ ID NO:57 - SEQ ID NO:58	SEQ ID NO:139 - SEQ ID NO:140
PALM2	2,30	PALM2-AKAP2 readthrough	445815	SEQ ID NO:59 - SEQ ID NO:60	SEQ ID NO:141 - SEQ ID NO:142
PCDHGC3	1,99	protocadherin gamma subfamily C, 3	5098	SEQ ID NO:23 - SEQ ID NO:39	SEQ ID NO:105 - SEQ ID NO:121
PROS1	2,09	protein S (alpha)	5627	SEQ ID NO:8	SEQ ID NO:90
RARA	1,95	retinoic acid receptor, alpha	5914	SEQ ID NO:40 - SEQ ID NO:43	SEQ ID NO:122 - SEQ ID NO:125
RSF1	1,74	remodeling and spacing factor 1	51773	SEQ ID NO:44	SEQ ID NO:126
TENC1	1,92	tensin like C1 domain containing phosphatase (tensin 2)	23371	SEQ ID NO:45 - SEQ ID NO:47	SEQ ID NO:127 - SEQ ID NO:129
TGFBR3	2,22	transforming growth factor, beta receptor III	7049	SEQ ID NO:10 - SEQ ID NO:12	SEQ ID NO:92 - SEQ ID NO:94
TRAK2	2,33	trafficking protein, kinesin binding 2	66008	SEQ ID NO:48	SEQ ID NO:130
VSNL1	1,95	visinin-like 1	7447	SEQ ID NO:61	SEQ ID NO:143
WHSC1L1	2,17	Wolf-Hirschhorn syndrome candidate 1-like 1	54904	SEQ ID NO:9	SEQ ID NO:91
WWC2	1,91	WW and C2 domain	80014	SEQ ID NO:62	SEQ ID NO:144

Nombre del Gen	Veces de cambio en su nivel de expresión (Fold change)	Descripción	Gene ID	Secuencias nucleotídicas	Secuencias aminoacídicas
		containing 2			
FAF1	-1,01	Fas (TNFRSF6) associated factor	11124	SEQ ID NO:63	SEQ ID NO:145
FBXO9	-1,08	F-box protein 9	26268	SEQ ID NO:64 - SEQ ID NO:66	SEQ ID NO:146 - SEQ ID NO:148
KIAA1033	-1,11	WASH complex subunit 7	23325	SEQ ID NO:67	SEQ ID NO:149
N4BP2L1	-1,02	NEDD4 binding protein 2-like 1	90634	SEQ ID NO:68 - SEQ ID NO:69	SEQ ID NO:150 - SEQ ID NO:151
SLC12A	-1,03	Solute carrier family 12 (sodium/potassium/chloride transporters), member 2	6558	SEQ ID NO:70 - SEQ ID NO:74	SEQ ID NO:152 - SEQ ID NO:156
STARD13	-1,72	StAR-related lipid transfer (START) domain containing 13	90627	SEQ ID NO:75 - SEQ ID NO:80	SEQ ID NO:157 - SEQ ID NO:162
RB1CC1	-1,04	RB1-inducible coiled-coil 1	9821	SEQ ID NO:81 - SEQ ID NO:82	SEQ ID NO: 162 - SEQ ID NO:164

En el contexto de la presente invención, los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se definen también por una secuencia de nucleótidos o polinucleótido, que constituye la secuencia codificante de las proteínas recogidas respectivamente en las SEQ ID recogidas en la Tabla 1, y que comprendería a diversas variantes procedentes de:

a) moléculas de ácido nucleico que codifican un polipéptido que comprende la secuencia aminoacídica de la SEQ ID recogidas en la Tabla 1,

b) moléculas de ácido nucleico cuya cadena complementaria híbrida con la secuencia polinucleotídica de a),

c) moléculas de ácido nucleico cuya secuencia difiere de a) y/o b) debido a la degeneración del código genético,

d) moléculas de ácido nucleico que codifican un polipéptido que comprende la secuencia aminoacídica con una identidad de al menos un 80%, un 90%, un 95%, un 98% o un 99% con las SEQ ID recogidas en la Tabla 1, respectivamente, y en las que el polipéptido codificado por dichos ácidos nucleicos posee la actividad y las características estructurales de las proteínas *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*. Entre dichas moléculas de ácido nucleico se encuentra la recogida en las SEQ ID indicada en la Tabla1.

Los sujetos cuya respuesta se predice son sujetos humanos que se sospecha que padecen y/o que preferiblemente han sido diagnosticados con cáncer colorrectal preferentemente pero no limitado a estadíos avanzados de la enfermedad (estadío IV de la clasificación TNM). Los términos “individuo”, “sujeto humano”, “sujeto” y “paciente” se usan por tanto de manera indistinta en esta memoria descriptiva. El término “individuo”, tal y como se utiliza en la descripción, se refiere a animales, preferiblemente mamíferos, y más preferiblemente, humanos. El término “individuo” no pretende ser limitativo en ningún aspecto, pudiendo ser éste de cualquier edad, sexo y condición física.

“Uno o más” tal como se usa también en la presente memoria descriptiva incluye uno y la especificación individualizada de cualquier número que sea más de uno, tal como dos, tres, cuatro, cinco, seis, etc. “Más de uno” o “algunos” tal como se usa en la presente memoria descriptiva incluye la especificación individualizada de cualquier número que sea más de uno, tal como dos, tres, cuatro, cinco, seis, etc.

Los pasos (b) y/o (c) de los métodos descritos anteriormente pueden ser total o parcialmente automatizados, por ejemplo, por medio de un equipo robótico sensor para la detección de la cantidad de producto de la expresión de los genes en el paso (b) o la comparación computarizada en el paso (c). Además de los pasos especificados anteriormente puede comprender otros pasos adicionales, por ejemplo relacionados con el pre-tratamiento de la muestra o la evaluación de los resultados obtenidos mediante estos métodos. Por ejemplo, el método para predecir la respuesta al tratamiento de un paciente con cáncer colorrectal, puede incluir un paso adicional consistente en la generación de un informe sobre los resultados del perfil génico del paciente, que incluya la probabilidad de respuesta al tratamiento de dicho paciente diagnosticado de cáncer colorrectal.

En una realización preferida de este aspecto de la invención la muestra biológica aislada de un individuo del paso (a) empleada para la determinación de los niveles de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se obtiene del tejido tumoral colorrectal del paciente.

Los estudios de los autores de la presente invención han permitido obtener información sobre los patrones de expresión de genes en pacientes afectos de cáncer colorrectal respondedores al tratamiento frente a sujetos no respondedores. Esto ha permitido obtener un modelo de las modificaciones significativas que definen la sensibilidad al tratamiento de quimioterapia en este tipo de patología.

La detección de la cantidad del producto de expresión de los genes puede realizarse por cualquier medio conocido en el estado de la técnica. Los autores de la presente invención han demostrado que la detección de la cantidad o la concentración de estos productos de expresión de manera semicuantitativa o cuantitativa permiten diferenciar entre el individuo con cáncer colorrectal respondedor y el individuo no respondedor. La cantidad del producto de expresión de los genes detectada podría establecer un perfil diferencial en individuos afectados por cáncer de colorrectal, que permite subclasificarlos en función de su sensibilidad a la quimioterapia.

La medida de la cantidad o la concentración, preferiblemente de manera semicuantitativa o cuantitativa, puede ser llevada a cabo de manera directa o indirecta. La medida directa se refiere a la medida de la cantidad o la concentración del producto de expresión de los genes, basada en una señal que se obtiene directamente de los transcritos de dichos genes, o de las proteínas a las que se traducen, y que está correlacionada directamente con el número de moléculas de RNA o de proteínas producidas por los genes. Dicha señal a la que también podemos referirnos como señal de intensidad – puede obtenerse, por ejemplo, midiendo un valor de intensidad de una propiedad química o física de dichos productos. La medida indirecta incluye la medida obtenida de un componente secundario o un sistema de medida biológica (por ejemplo la medida de respuestas celulares, ligandos, “etiquetas” o productos de reacción enzimática).

El término “cantidad”, tal y como se utiliza en la descripción, se refiere pero no se limita, a la cantidad absoluta o relativa de los productos de expresión de los genes, así como a cualquier otro valor o parámetro relacionado con los mismos o que pueda derivarse de éstos. Dichos valores o parámetros comprenden valores de intensidad de la señal obtenidos a partir de cualquiera de las propiedades físicas o químicas de dichos productos de expresión obtenidos mediante medida directa. Adicionalmente, dichos valores o parámetros incluyen todos aquellos obtenidos mediante medida indirecta, por ejemplo, cualquiera de los sistemas de medida descritos en otra parte del presente documento.

El término “comparación”, tal y como se utiliza en la descripción, se refiere pero no se limita, a la comparación de la cantidad de los productos de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* de la muestra biológica a analizar, también llamada muestra biológica problema, con una cantidad de los productos de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* de una o varias muestras de referencia deseable descrita en otra parte de la presente descripción. La muestra de referencia puede ser analizada, por ejemplo, simultánea o consecutivamente, junto con la muestra biológica problema. La comparación descrita en el apartado (c) del método de la presente invención puede ser realizada manualmente o asistida por ordenador.

Los productos de expresión de los genes van a dar un determinado perfil de expresión génica. Se entiende por “perfil de expresión génica” el perfil génico obtenido tras la cuantificación del ARNm y/o de proteína producida por los genes de interés o biomarcadores, es decir, por los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, en una muestra biológica aislada. El perfil de expresión de los genes se realiza, preferiblemente, determinando el nivel de ARNm derivado de su transcripción, previa extracción del ARN total presente en la muestra biológica aislada, lo cual puede realizarse mediante protocolos conocidos en el estado de la técnica. La determinación del nivel de ARNm derivado de la transcripción de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L,*

NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1, puede realizarse, por ejemplo, aunque sin limitarnos, mediante amplificación por reacción en cadena de la polimerasa (PCR), retrotranscripción en combinación con la reacción en cadena de la polimerasa (RT-PCR), RT-PCR cuantitativa, retrotranscripción en combinación con la reacción en cadena de la ligasa (RT-LCR), o cualquier otro método de amplificación de ácidos nucleicos; análisis en serie de la expresión génica (SAGE, SuperSAGE); chips de ADN elaborados con oligonucleótidos depositados por cualquier mecanismo; microarrays de ADN elaborados con oligonucleótidos sintetizados *in situ* mediante fotolitografía o por cualquier otro mecanismo; hibridación in situ utilizando sondas específicas marcadas con cualquier método de marcaje; mediante geles de electroforesis; mediante transferencia a membrana e hibridación con una sonda específica; mediante resonancia magnética nuclear o cualquier otra técnica de diagnóstico por imagen utilizando nanopartículas paramagnéticas o cualquier otro tipo de nanopartículas detectables funcionalizadas con anticuerpos o por cualquier otro medio. El perfil de expresión génica también podría obtenerse mediante la detección y/o cuantificación de las proteínas producto de la traducción del ARNm derivado de la transcripción de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, mediante por ejemplo, pero sin limitarnos, inmunodetección por western blot. La detección cuantitativa de la expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* y puede realizarse más preferiblemente mediante PCR en tiempo real (RT-PCR ó RTqPCR). La detección en tiempo real de los productos amplificados puede llevarse a cabo mediante la utilización de moléculas fluorescentes que se intercalan en el ADN de cadena doble o mediante hibridación con diferentes tipos de sondas.

Por tanto, en otra realización preferida de la invención la determinación del nivel de expresión de los genes no necesita limitarse de manera particular y se puede seleccionar a partir de un procedimiento de perfilado génico, tal como una micromatriz y/o un procedimiento que comprenda la PCR (reacción en cadena de la polimerasa), tal como la PCR en tiempo real; y/o la transferencia Northern.

Más preferentemente, la detección del producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se realiza mediante PCR cuantitativa a tiempo real y se expresa como -ΔΔCt. La PCR cuantitativa en tiempo real (RQ-PCR) es una técnica de cuantificación de la expresión génica sensible y reproducible que se puede usar de manera particular para la expresión del perfil génico en células y tejidos. Se puede usar cualquier procedimiento para la evaluación de los resultados de la RT-PCR y se puede preferir el procedimiento ΔΔCt. El procedimiento ΔΔCt se describe en detalle en Livak *y col.* (*Methods* 2001, 25, 402-408). (Ct = Valores umbral del ciclo). Cuando se lleva la presente invención a la práctica, se deberá usar preferiblemente el procedimiento ΔΔCt tal como describen Livak *y col.* (Methods 2001, 25:402-408). El procedimiento ΔΔCt implicará una "muestra del control" y una "muestra del sujeto". La "muestra del sujeto" es una muestra procedente del sujeto que se va a analizar. Por cada muestra, se incluyen un gen diana (aquí: el gen de interés) y un gen endógeno del control (tal como se describe a continuación) para la amplificación de la PCR a partir de alícuotas (normalmente diluciones en serie). Normalmente se usan varias réplicas de cada concentración diluida para derivar la eficacia de la amplificación. La eficacia de la amplificación de la PCR se puede definir como el porcentaje de amplificación (de 0 a 1). Durante la reacción de la qPCR, un software mide normalmente el número de ciclos de cada muestra en el cual la fluorescencia cruza una línea arbitraria (indicadora de la amplificación de la PCR), el umbral. Este punto de cruce es el valor Ct. Muestras más diluidas cruzarán a valores Ct posteriores. Para cuantificar la expresión génica de un gen particular, se resta el Ct de un ácido nucleico procedente del gen de interés al Ct del ácido nucleico procedente del control endógeno en la misma muestra para normalizar la variación en la cantidad y calidad del ARN entre diferentes muestras y obtener la expresión relativa (con respecto al control endógeno) de cada una de las muestras, la "muestra del sujeto" y la "muestra del control". Opcionalmente, esto se lleva a cabo por duplicado, triplicado, cuadriplicado y de manera similar, respectivamente. Se puede obtener de manera adecuada un valor ΔCt del control calculando el promedio de los valores ΔCt obtenidos a partir de muestras de un grupo del control de varios individuos con los cuales se van a comparar los valores de la "muestra del sujeto". El grupo del control (del cual se calcula el valor promedio) consiste en los individuos adecuados a los respectivos fines (de comparación). La persona experta aprenderá de esta divulgación que un grupo de control adecuado es para un fin concreto. En una realización particular, la presente invención se puede llevar a la práctica omitiendo la determinación del valor ΔCt del grupo del control, es decir, determinar (solo) el valor ΔCt de la "muestra del sujeto" y a continuación comparando posteriormente este con el respectivo valor ΔCt promedio del control indicado en los ejemplos.

En otra realización aun mas preferida de este aspecto de la invención la detección del producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se realiza mediante microarrays.

La cantidad de referencia se obtiene a partir de los valores de expresión constitutiva de los genes, en un grupo de individuos sanos, o de la expresión de los genes en el grupo de individuos antes de ser sometidos al tratamiento.

La cantidad de referencia será, por ejemplo, en el caso de la diferenciación entre los pacientes afectados por cáncer colorrectal respondedores al tratamiento, la expresión constitutiva del gen en un grupo control de individuos no respondedores.

Por otro lado, la muestra o muestras de referencia pueden ser, por ejemplo, obtenidas a partir de tejido tumoral de un paciente con cáncer colorrectal que no respondió al tratamiento.

En otra realización preferida de este aspecto de la presente invención, la cantidad de referencia se obtiene a partir de una muestra de referencia. La cantidad de referencia puede obtenerse también, por ejemplo, de los límites de distribución normal de una cantidad encontrada en muestras obtenidas de una población de individuos con cáncer colorrectal no respondedores, mediante técnicas estadísticas bien conocidas. En otra realización preferida, la muestra de referencia se obtiene de los pacientes antes y después del tratamiento. Por tanto, una realización preferida de este aspecto de la invención, comprende realizar al menos dos veces la secuencia de pasos (a) – (b) del método de la invención, en muestras biológicas procedentes de un mismo individuo, y aisladas en momentos diferentes. Más preferiblemente, las muestras se obtienen antes y después del tratamiento.

Los inventores han demostrado que los niveles de expresión de uno o más de estos genes pueden ser indicativos de la respuesta de un sujeto al tratamiento. En una realización preferida de este aspecto de la invención, la respuesta es una reducción significativa de la carga tumoral evaluada por criterios radiológicos objetivos estándar universales (criterios

RECIST). En una realización alternativa, la respuesta es un resultado clínico, tal como la supervivencia exenta de progresión tumoral.

La evaluación de la respuesta completa y/o la respuesta parcial es un factor importante para determinar el estado de un paciente individual. De esta manera, es necesario estimar la carga total del tumor en el valor inicial y usar ésta como elemento comparador para las posteriores medidas que se llevan a cabo normalmente de acuerdo a los criterios RECIST (versión 1.1), Eisenhauer *et al.*, 2009. *Eur. J. Cancer*, 45 (228–247), definidos de la siguiente manera:

1. Respuesta Completa (RC): Desaparición de todas las evidencias medibles y evaluables de la enfermedad
2. Respuesta Parcial (RP): Al menos una disminución del 30% en la suma de diámetros de las lesiones diana, tomando como referencia el valor inicial de la suma de diámetros.
3. Enfermedad Progresiva (EP): Al menos un aumento del 20% en la suma de diámetros de las lesiones diana, tomando como referencia la suma más pequeña en el estudio (esto incluye el valor inicial de la suma si este es el más pequeño del estudio). Además del aumento relativo del 20%, la suma debe también demostrar un aumento absoluto de al menos 5 mm. (Nota: la aparición de una o más nuevas lesiones se considera también progresión).
4. Enfermedad Estable (EE): Ni una disminución suficiente para calificarla como RP ni un aumento suficiente para calificarla como EP.

A lo largo de la presente invención, los términos RC, RP, EP y EE se definen de acuerdos con las definiciones 1 a 4 anteriores tomadas de las Directrices RECIST revisadas de Eisenhauer *et al.*, 2009. *Eur. J. Cancer*, 45 228–247.

En otra realización preferida, el tratamiento neoadyuvante comprende el uso de radioterapia. En otra realización aun más preferida, dicho tratamiento comprende la administración de quimioterapia con compuestos de tipo fluoropirimidina y un agente adicional.

La quimioterapia, la respuesta a la cual se va a prever, comprende esquemas de quimioterapia estándar en el tratamiento del cáncer colorrectal, esquemas basados en fluoropirimidinas. Se entiende la quimioterapia como el tratamiento del cáncer con un fármaco antineoplásico o con una combinación de dichos fármacos. Sin pretender estar vinculado a ninguna teoría particular, se entiende que la quimioterapia actúa normalmente eliminando células que se dividen rápidamente, lo que es una de las propiedades principales de la mayor parte de células cancerosas. Para el tratamiento de los pacientes de cáncer colorrectal, la quimioterapia comprende preferiblemente la administración de fluoropirimidinas, que se piensa que actúan como antimetabolitos. Los ejemplos de compuestos de fluoropirimidina son la capecitabina, la floxuridina, y el fluorouracilo (5-FU), que es el más preferido en la presente invención. Dicha fluoropirimidina se puede administrar sola o en combinación con un agente adicional, siendo la poliquimioterapia en general más eficaz aunque también más tóxica. El agente adicional puede ser una molécula capaz de interactuar con el ADN, tal como en la inhibición de la síntesis de ADN y/o en prevenir el desenrollado del ADN. En una realización preferida de la presente invención, la quimioterapia puede comprender la administración de oxaliplatino y fluoropirimidina, o de irinotecán y fluoropirimidina. Se piensa que la citotoxicidad del oxaliplatino (documento US 4.169.846) da como resultado la inhibición de la síntesis del ADN en células cancerosas. Los estudios *in vivo* han mostrado que oxaliplatino presenta actividad antitumoral frente al carcinoma de colon por su efecto citotóxico (no dirigidos). Irinotecán por otra parte es un análogo semisintético del alcaloide natural camptotecina, que se piensa que actúa evitando el desenrollado del ADN mediante la inhibición de la topoisomerasa 1. De esta manera, oxaliplatino e irinotecán se piensa que ejercen su función interviniendo con el ADN.

Por lo tanto, en una realización aún mas preferida, la quimioterapia es una terapia que comprende la administración de compuestos basados en platino, compuestos inhibidores de la topoisomerasa I, un compuesto análogo de pirimidina, o cualquiera de sus combinaciones. Más preferiblemente, el compuesto basado en platino es el oxaliplatino, el inhibidor de la topoisomerasa I es el irinotecan, y el análogo de pirimidina es el 5-fluorouracilo.

Otro aspecto de la invención se refiere a un método para el seguimiento de la evolución del cáncer colorrectal en un individuo, de ahora en adelante tercer método de la invención, que comprende realizar al menos dos veces la secuencia de pasos (a) – (b) según el primer o el segundo método de la invención, en muestras biológicas procedentes de un mismo individuo, y aisladas en momentos diferentes.

KIT DE LA INVENCIÓN

Otro aspecto de la presente invención se refiere a un kit o dispositivo, de aquí en adelante kit o dispositivo de la invención, que comprende los elementos necesarios para analizar la cantidad del producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1.*

El kit se basa en el poder predictivo del procedimiento de la presente invención. Tal como se ha mencionado anteriormente, el valor indicador de referencia para la falta de respuesta de cada gen concreto se puede determinar antes de llevar a cabo el procedimiento de la presente invención. En el caso particular del kit, se pueden proporcionar con el valor indicador de referencia para la falta de respuesta (y/o un valor de referencia indicador para la respuesta). Con la ayuda del kit, se puede calcular la expresión de cada gen, es decir, con respecto a las muestras de control ejemplificadas anteriormente. El control puede de esta manera estar comprendido también en el kit.

El kit de la invención más preferiblemente comprende los medios necesarios para comparar la cantidad detectada en el paso (b) con una cantidad de referencia. Dicho kit puede contener todos aquellos reactivos necesarios para analizar la cantidad del producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* por medio de cualquiera de los métodos descritos anteriormente en este documento. El kit además puede incluir, sin ningún tipo de limitación, tampones, agentes para prevenir la contaminación, inhibidores de la degradación de las proteínas, etc. Por otro lado el kit puede incluir todos los soportes y recipientes necesarios para su puesta en marcha y optimización. Preferiblemente, el kit comprende además las instrucciones para llevar a cabo cualquiera de los métodos de la invención.

Más preferiblemente, el kit o dispositivo de la invención comprende los cebadores y sondas obtenidos de las secuencias de los genes de la invención, tal y como también se encuentran en la Tabla 1. Puesto que un solo gen puede ser útil para predecir o pronosticar la respuesta al tratamiento en pacientes con cáncer colorrectal, el kit puede contener la/s sonda/s y cebadores útiles para cuantificar la expresión de dicho gen, o cualquiera de las combinaciones de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1.*

En realizaciones particulares, el kit se selecciona entre (a) un kit adecuado para la PCR, (b) un kit adecuado para la Transferencia Northern Blot y (c) un kit adecuado para los análisis de micromatriz. Se pueden combinar cualquiera de dos o más de estas realizaciones, de tal manera que el kit puede comprender, por ejemplo, ambos de (a) y (c).

En el caso de (a) un kit adecuado para la PCR, esta PCR es normalmente la PCR cuantitativa en tiempo real PCR (RQ-PCR), una técnica de cuantificación de la expresión génica sensible y reproducible. En este caso se desea que el kit comprenda adicionalmente cebadores y sondas y oligonucleótido(s) del kit. Estos reactivos pueden estar comprendidos opcionalmente en el kit.

Una Transferencia Northern implica el uso de electroforesis para separar las muestras de ARN por tamaño y la posterior detección con un(os) oligonucleótido(s) (sonda de hibridación) complementaria con (parte de) la secuencia diana del ARN de interés.

Es también posible que el(los) oligonucleótido(s) estén inmovilizados en manchas sobre una superficie (preferiblemente sólida). En una de sus realizaciones, el kit comprende una micromatriz. Una micromatriz de ARN es una matriz sobre un sustrato sólido (normalmente un porta de vidrio o una celda de una película fina de silicio) que evalúa grandes cantidades de diferentes ARN que son detectables mediante sondas específicas inmovilizadas sobre manchas sobre un sustrato sólido. Cada mancha contiene una secuencia específica de ácido nucleico, normalmente una secuencia de ADN, como sondas (o indicadores). Aunque el número de manchas no está limitado de manera alguna, existe una realización preferida en la que la micromatriz se personaliza para los procedimientos de la invención. En una realización, dicha matriz personalizada comprende cincuenta manchas o menos, tal como treinta manchas o menos, incluyendo veinte manchas o menos.

MICROARRAY DE LA INVENCIÓN

Por tanto, otro aspecto de la invención se refiere a un microarray, de ahora en adelante microarray de la invención, que comprende oligonucleótidos o microarreglos de canal único diseñados a partir de una secuencia conocida o un ARNm de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1.* Más preferiblemente, la secuencia de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1,*

RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1 es la secuencia nucleotídica indicada para cada uno de ellos en la Tabla 1, respectivamente.

El uso del kit no está particularmente limitado, aunque se prefiere su uso en cualquiera de los métodos de la invención o en cualquiera de sus realizaciones. Así pues, otro aspecto de la invención se refiere al uso del kit o dispositivo de la invención para la obtención de datos útiles para el pronóstico o la predicción de la respuesta a la quimioterapia neoadyuvante en individuos con cáncer colorrectal.

Otro aspecto de la invención se refiere a un medio de almacenamiento legible por un ordenador que comprende instrucciones de programa capaces de hacer que un ordenador lleve a cabo los pasos de cualquiera de los métodos de la invención (del primer, el segundo o el tercer método de la invención).

Otro aspecto de la invención se refiere a una señal transmisible que comprende instrucciones de programa capaces de hacer que un ordenador lleve a cabo los pasos de cualquiera de los métodos de la invención.
Los términos “polinucleótido” y “ácido nucleico” se usan aquí de manera intercambiable, refiriéndose a formas poliméricas de nucleótidos de cualquier longitud, tanto ribonucleótidos (ARN ó RNA) como desoxiribonucleótidos (ADN ó DNA). Los términos “secuencia aminoacídica”, “péptido”, “oligopéptido”, “polipéptido” y “proteína” se usan aquí de manera intercambiable, y se refieren a una forma polimérica de aminoácidos de cualquier longitud, que pueden ser codificantes o no codificantes, química o bioquímicamente modificados.

A lo largo de la descripción y las reivindicaciones la palabra "comprende" y sus variantes no pretenden excluir otras características técnicas, aditivos, componentes o pasos. Para los expertos en la materia, otros objetos, ventajas y características de la invención se desprenderán en parte de la descripción y en parte de la práctica de la invención. Los siguientes ejemplos y dibujos se proporcionan a modo de ilustración, y no se pretende que sean limitativos de la presente invención.

BREVE DESCRIPCIÓN DE LAS FIGURAS

Con objeto de ayudar a una mejor comprensión de las características del invento de acuerdo con un ejemplo preferente de realización práctica del mismo y para complementar esta descripción, se acompaña como parte integrante de la misma un juego de dibujos, cuyo carácter es ilustrativo y no limitativo. En estas figuras:

Figura 1. Análisis cluster jerárquico supervisado que muestra los genes diferencialmente expresados en pacientes que lograron una respuesta objetiva a la quimioterapia (Si: RC y RP; azul) frente a pacientes que no responden a la quimioterapia (No: EE o EP; rojo). Los genes en rojo indican sobreexpresión, verde indica infraexpresión.

Figura 2. Análisis cluster jerárquico supervisado que muestra los genes expresados diferencialmente en paciente que lograron una supervivencia libre de progresión (SLP) mayor que la media de tiempo de SLP (Si; azul) frente a pacientes SLP menor que la media (No; rojo). Los genes en rojo indican sobreexpresión, verde indica infraexpresión.

Figura 3. Valores medios ΔCt de genes validados en pacientes con respuesta objetiva a la quimioterapia (si) frente a no respondedores (No). *valor de $p<0.05$. **valor de $p<0.01$. ***valor de $p<0.001$. Los datos derivados de RT-qPCR son presentados como valores ΔCt con valores más altos para la menor expresión de ARN.

Figura 4. El resultado clínico considerando la supervivencia libre de progresión (SLP) de pacientes por los niveles de expresión génica. La línea negra sólida representa a los pacientes con mayor nivel de expresión génica (sobre la media). La línea negra discontinua representa a los pacientes con menos niveles de expresión génica.

Figura 5. Los valores medios ΔCt de genes validados en pacientes con supervivencia libre de progresión (SLP) mayor que la media (11.53 meses) [Si] comparados con los pacientes con menor SLP [No]. *valor-p <0.05; **valor $p<0.01$; ***valor-$p<0.001$. Los datos derivados de la RT-qPCR están representados como valores ΔCt, con mayores valores para menos expresión de ARN.

EJEMPLOS DE LA INVENCIÓN

A continuación se ilustrará la invención mediante unos ensayos realizados por los inventores, que pone de manifiesto la especificidad y efectividad de los métodos de la invención para obtener datos útiles en la predicción de la respuesta al tratamiento de dicha enfermedad.

Materiales y métodos

El protocolo del estudio ha sido aprobado por los comités éticos de los centros participantes y con un formulario de consentimiento por escrito de todos los pacientes. Se utilizaron un total de 159 tumores de pacientes diagnosticados con CCR avanzado, como *training* (formación) (n=40) y validación (n=119). Las muestras que cumplían los siguientes criterios fueron incluidas en el estudio: (1) diagnóstico primario confirmado de CCR; (2) los pacientes fueron tratados con al menos una línea de quimioterapia para la enfermedad avanzada y la respuesta fue evaluada; (3) tejidos adecuados congelados disponibles para ensayos moleculares (se requiere una proporción de células tumorales >50%). El conjunto de formación consistía en 40 muestras de CCR procedentes del Hospital Marqués de Valdecilla, Santander, España. El conjunto de validación consistía en 119 muestras procedentes de 4 hospitales diferentes (Hospital Virgen del Rocío de Sevilla (España), Hospital Virgen de la Victoria de Málaga (España), Hospital Virgen de la Merced de Osuna (España) y Hospital Marqués de Valdelcilla de Santander (España), y se incluyeron 86 muestra tumorales (40 procedentes del conjunto de formación y 46 de pacientes de CCR recién tratados) y 33 muestras de tejido normal de pacientes con CCR fueron usadas como controles. La distribución de las características demográficas y clínico-patológicas de las cohortes iniciales y de validación se presenta en la Tabla 2, y las características histológicas de las muestras tumorales están esbozadas en la Tabla 3. No se encontraron diferencias significativas entre ambos grupos.

Tabla 2. Datos demográficos, características clínicas y tratamiento en los conjuntos de formación y validación.

	Conjunto de Formación (n=40)	**Conjunto de Validación (n=86)**	
Características	**N (%)**	**N (%)**	**P**
Edad (años)			0,417
- Mediana (rango)	61 (47-79)	65 (42-80)	
Sexo			1,00
- Femenino	16 (40)	33 (38,4)	
- Masculino	24 (60)	53 (61,6)	
Metástasis en el diagnóstico			0,625
- Sí	34 (85)	69 (80.3)	
- No	6 (15)	17 (19.7)	
Metástasis / enfermedad avanzada			
Estado funcional			0,306
- 0-1	40 (100)	82 (95,3)	
- 2	0 (0)	4 (4,7)	
Parámetros de laboratorio (Mediana (rango))			
- CEA (ng/mL)	62,5 (1-4007)	28 (1-1448)	
- Hemoglobina (g/dL)	12 (2-15)	12 (2-15)	
- Alcalinofosfatasa (UI/L)	107 (48-620)	96 (43-16189)	
- Lactatodehidrogenasa (UI/L)	441 (273-2692)	355 (109-2692)	
Regímenes de quimioterapia (CT) iniciales			
Quimioterapia basada en Oxaliplatino			
- Oxaliplatino+FP	18 (45)	39 (45,4)	
- Oxaliplatino+FP+AntiEGFR	8 (20)	14 (16,3)	
- Oxaliplatino+FP+AntiEGFR/AntiVEGFR	9 (22,5)	14 (16,3)	
Quimioterapia basada en Irinotecan			
- Irinotecan+FP	0 (0)	9 (10,5)	
- Irinotecan+FP+AntiEGFR	0 (0)	1 (1,2)	

	Conjunto de Formación (n=40)	**Conjunto de Validación (n=86)**	
• Irinotecan+FP+AntiEGFR+AntiEGFR/AntiVEGFR	0 (0)	1 (1,2)	
Triple (Oxaliplatino+ Irinotecan+FP)	5 (12,5)	4 (4,6)	
Sólo FP	0 (0)	3 (3,4)	
Respuesta			
Respuesta del tumor a la CT inicial			0,441
• Sí (CR+PR)	25 (62,5)	46 (53,5)	
• No (SD+PD)	15 (37,5)	40 (46,5)	
Progresión del tumor después de la CT inicial			0,068
• Sí	27 (67.5)	71 (82.6)	
• No	13 (32.5)	15 (17.4)	
Tratamiento quirúrgico de la recidiva o metástasis con resección completa			0,378
• Sí	12 (30)	19 (22,1)	
• No	28 (70)	67 (77,9)	
Resultado			
Seguimiento de los pacientes vivo (meses)			0,586
• Mediana (rango)	31.9 (12.9-77-57)	30.8 (5.50-77.57)	
Estado del paciente en el último contacto			
• Muerto	17 (42,5)	49 (57)	
• Vivo con tumor	22 (55)	31 (36)	
• Vivo sin tumor	1 (2.5)	6 (7)	

CEA: antígeno carcinoembrionario; EGFR: receptor del factor de crecimiento epidermal; VEGF: factor de crecimiento endotelial vascular; VEGFR: receptor del factor de crecimiento endotelial vascular; FP: fluoropirimidinas; CR: respuesta completa; PR: respuesta parcial; SD: estabilidad de la enfermedad; PD: progresión de la enfermedad.

Tabla 3. Características de los tumores en los conjuntos de formación y validación.

	Conjunto de Formación (n=40)	**Conjunto de Validación (n=86)**	
Características	**N (%)**	**N (%)**	**P**
Tipo de muestra			
- Pieza quirúrgica	38 (95)	85 (98,8)	
- Biopsia endoscópica	1 (2.5)	1 (1,2)	
- Otros	1 (2.5)	0 (0)	
Localización del tumor			
Ubicación del tumor primario			0,834
- Colon	28 (70)	62 (72,1)	
- Recto	12 (30)	24 (27,9)	
Ubicación de la metástasis			
- Hígado	33 (82,5)	57 (66,3)	0,062
- Pulmón	12 (30)	22 (25,6)	0,668
- Carcinomatosis peritoneal	6 (15)	16 (18,6)	0,802
- Otros	1 (2,5)	24 (27,9)	
Características histológicas			
Histología			0,306
- Adenocarcinoma	40 (100)	82 (95,3)	
- Mucino carcinoma		4 (4,7)	
Diferenciación del tumor			
- Bien diferenciado	14 (35)	38 (44,2)	
- Moderadamente diferenciado	8 (20)	28 (32,6)	
- Poco diferenciado	15 (37,5)	15 (17,4)	
- Desconocido	3 (7,5)	5 (5,8)	
Invasión Linfovascular			
- Sí	23 (57,5)	30 (34,9)	
- No	3 (7,5)	15 (17,4)	
- Desonocida	14 (35)	41 (47,7)	
Estado de K-ras			0,338
- Silvestre	25 (62,5)	45 (52,3)	
- Mutado	15 (37,5)	41 (47,7)	

Muestras de ARN

Las muestras de tejido tumoral fueron molidas hasta un polvo fino bajo nitrógeno líquido usando un mortero. La homogenización fue lograda usando homogeneizadores QIAashredder y el ARN total fue extraído usando el mini kit RNeasy (ambos kits de QiagenInc; Valencia, CA, USA). La cantidad y calidad del ARN fueron estimadas mediante gel de agarosa y medidas espectrofotométricas. Cuando no fue posible debido a la escasa cantidad de ARN, fueron estimados usando el Bioanalyzer 2100 (Eukaryote total RNA Nano o Pico kit: Agilent Technologies; Santa Clara, CA, USA). De las 40 muestras iniciales, podríamos obtener ARN adecuado en calidad y cantidad en 37 casos (93%).

Microarray de perfiles de expresión génica

Los experimentos de microarray fueron desarrollados usando el *Human Whole Genome* U133 Plus 2.0 array (Affymetrix; Santa Clara, CA, USA), que contiene 54675 sondas de genes humanos. El AND de doble hebra fue sintetizado usando One-Cycle cDNA Synthesis kit (Affymetrix), de acuerdo a las recomendaciones del fabricante. El ARN total (2 µg) fue primero transcrito a la inversa usando un promotor de cebador T-7 Oligo (dT) para obtener ADNc de primera hebra y después ADNc de segunda hebra que fue purificado con GeneChip Cleanup Module (Affymetrix) y usado como una plantilla en la posterior reacción de transcripción *in vitro*. El ARNc marcado fue purificado también con GeneChip Cleanup Module y cuantificado espectrofotométricamente. El ARNc purificado fue fragmentado in buffer de fragmentación (5x buffer: 200 mMTris-acetate (pH 8.1) + 500 mMKOAc + 150 mMMgOAc) e hibridizado al microarray en 200 µl de solución de hibridación que contiene 15 µg de diana marcada en 1x Mes buffer (0.1 M Mes + 1.0 M NaCl + 20mM ETA + 0.01% Tween 20) y 0.1 mg/ml de ADN de esperma de arenque, 10% DMSO, 0.5 mg/ml BSA, 50 pM del oligonucleótido control B2 y 1x controles de hibridación eucariota (nioB, bioC, bioD, cre). Tanto el oligonucleótido control B2 como los controles de hibridación eucariota fueron obtenidos de Affymetrix. La mezcla de hibridación fue aplicada a Human Genome U133 Plus 2.0 array (Affymetrix), el cual incluye el total del genoma humano con 54613 conjuntos de sondas. Los arrays se situaron en el horno de hibridación 640 (Affymetrix) a 45 °C durante 16 horas, girando a 60 rpm. Tras la hibridación, los arrays fueron lavados con 6x SSPE-T (0.9 M NaCl + 60 mM NaH_2PO_4 + 6 mM AEDT + 0.01 % Tween 20) a 30 °C sobre una superficie fluida (FS400 Affymetrix) en 10 ciclos de 2 mezclas por ciclo, y posteriormente con 0.1 M Mes + 0.1 M NaCl + 0.01% Tween 20 a 50°C en 6 ciclos de 15 mezclas por ciclo. Los arrays fueron teñidos después durante 5 minutos a 35°C con un conjugado Estreptavidina-Phycoeritrina (sondas moleculares), seguido de 10 ciclos de lavado de 4 mezclas por ciclo con 6x SSPE-T. Para aumentar las señales, los arrays fueron teñidos complementariamente con una solución de anticuerpos anti-estreptavidina durante 5 minutos, seguido por 5 minutos de tinción con un conjugado de estreptavidina-phycoeritrina. Después de 15 ciclos de lavado de 4 mezclas por ciclo, los arrays fueron escaneados usando GC300 laser confocal scanner (Affymetrix).

Validación de los genes expresados diferencialmente en CCR.

El ARN total fue extraído de las muestras de tejidos tumorales con mirVanaRNA isolation kit (Ambion, Austin, TX, USA), de acuerdo a las instrucciones del fabricante. El ARN total recogido, fue determinado usando el Nanodrop ND-100025 spectrophotometer (Nanodrop Tech, DE, USA). Los arrays de baja densidad Taqman® de diseño personalizado (TLDA) 7900 HT con tarjetas de microfluidos que cuentan con 161 ensayos individuales fueron ordenados a partir de Applied Biosystems (Applied Biosystems; Carlsbad, CA, USA) (*utilizar los términos correctos en castellano).

Los TLDAs fueron desarrollados en un proceso de 2 pasos: brevemente durante el primer paso, 800 ng (50 ng/16 µl) del ARN total fueron transcritos a la inversa usando Megaplex RT primers y TaqManRNA reverse trancription kit en un volumen total de 20 µl. Las reacciones fueron incubadas en un GStormThermal Cycler (Gene Technologies, Essex, UK) durante 5 minutos a 25°C, 30 minutos a 42°C, y un minuto a 50°C durante 40 ciclos, mantenido durante 5 minutos a 85°C y después a 4°C. En el segundo paso, 450 µL de la muestra de ADNc y 450 mL de la Taqman Universal PCR master mix, fueron cargados en puertos llenos, sobre la tarjeta microfluídica TLDA. La tarjeta fue brevemente centrifugada durante 1 minutos a (280 gramos *utilizar el término correcto) para distribuir las muestras en los múltiples pozos conectados a los puertos llenos y después sellados para prevenir la contaminación entre pozos. Las tarjetas TLDA fueron manejadas y analizadas por el ABI PRISM® 7900HT sequence detection protocol (Applied Biosystems). Las reacciones fueron incubadas a 95°C durante 10 minutos, seguido de 40 ciclos de 15 segundos a 95°C y un minuto a 60°C.

Análisis estadístico

Variables de resultado clínico. Las estadísticas fueron usadas para caracterizar los parámetros clínicos más relevantes. La asociación de las variables categóricas, fue explorada por el test del chi-cuadrado, o la prueba exacta de Fisher. Para evaluar la distribución de las variables continuas entre los grupos de estudio, fueron usados los tests paramétricos (t-test) y no-paramétrico (Kruskal-Wallis) cuando era apropiado.

La respuesta tumoral fue evaluada por métodos convencionales de acuerdo a los criterios estándar RECIST 1.0: Una respuesta completa (RC) fue definida como la desaparición de todas las evidencias medibles y evaluables de la enfermedad; una respuesta parcial (RP) fue definida como una disminución igual o mayor al 30% en la suma de los diámetros más largos de las lesiones diana; la enfermedad estable (EE) fue considerada cuando la carga tumoral disminuyó menos del 30% o aumentó menos del 20%; y enfermedad progresiva (EP) fue señalada por un incremento mayor del 20% en la suma de los diámetros más largos de las lesiones diana o la aparición de una nueva lesión. Los pacientes fueron clasificados de acuerdo a la mejor respuesta a la quimioterapia, en 2 grupos: aquellos que lograron una respuesta objetiva (respondedores [R]: RC + RP) y aquellos que no lo hicieron (no respondedores [NR]: EE + EP). La supervivencia libre de progresión (SLP) fue definida como el tiempo transcurrido desde el inicio de la quimioterapia de primera línea hasta la primera evidencia de la progresión de la enfermedad. La supervivencia general (SG) fue calculada desde el inicio de la terapia para enfermedad avanzada hasta la fecha de la muerte por cualquier causa. El método de Kaplan-Meier del límite de producto, fue usado para estimar las variables tiempo dependientes (SLP y SG), y las diferencias observadas entre los subgrupos de pacientes fueron evaluadas por el test de log-rank. $P<0.05$ fue considerado significativo. Todos los análisis fueron desarrollados usando el paquete estadístico para Social Sciences software (SPSS 15.0 for Windows, SPSS Inc, Chicago, IL).

Microarrays

Los datos de imagen de microarray fueron analizados usando el GeneChip Operating Software (GCOS 1.4 Affymetrix). El partek genomics suite v7.3.1 (Partek Inc.; St. Louis, MO, USA) fue usado para el análisis estadístico. La calidad de los arrays fue evaluado usando los parámetros P llamado %, array outlier y el error estándar normalizado sin escala. Posteriormente, los datos fueron procesados a través del RMA (robusto promedio multichip), método para obtener los valores de intensidad individuales en cada array, después normalizados y filtrados para eliminar secuencias no informativas (incluyendo secuencias control, aquellas que presentan un señal de hibridación cerca del fondo y a aquellos sin cambios en la expresión en todas las muestras). Finalmente, 9619 secuencias fueron seleccionadas para generar la lista de trabajo. Un modelo de regresión lineal usando la tasa de falso descubrimiento (siglas en inglés FDR), análisis de componentes principales (ACP) y técnicas de agrupamiento fueron usadas para comparar el perfil de expresión génica entre pacientes R y NR después de la quimioterapia metastásica de primera línea, y considerando la SLP después.

Análisis de reacción en cadena de la polimerasa cuantitativa en tiempo real (RT-qPCR).

La expresión de los genes diana, fue normalizada en relación a la expresión de GAPDH. Los valores de ciclo umbral (siglas en inglés Ct) fueron calculados usando el software SDS v.2.3 (Applied Biosystems) usando condiciones automáticas basales y un umbral de 0.2. La expresión de cada gen diana fue calculada relativa a un control endógeno GAPDH. Los datos se presentan como diana de expresión génica = 2ΔCt, con ΔCt = (gen diana Ct-GAPDH Ct). Este método es una manera conveniente para analizar los cambios relativos en la expresión génica de los experimentos PCR cuantitativos en tiempo real. (Applied Biosystems user Bulletin no.2 (P/N 4303859)). La expresión génica fue calculada usando el software Real-Time Statminer ® v.4.2 (Integromics, Inc). Este software realiza un moderado t-test entre los grupos (R y NR) y los corrige usando el algoritmo Benjamini-Hochberg (Benjamini Y, et al 1995) con FDR establecido en el valor del 5%. Para el propósito de este estudio, la expresión génica significativa fue considerada cuando el gen había sido detectado al menos en el 50% de los pacientes en cada grupo comparado. Además, en situaciones en las que el gen es indetectable y los valores Ct están más allá del máximo Ct32, el software Statminer ® establece un valor igual al máximo.

RESULTADOS

La comparativa de los niveles de expresión génica relativa entre respondedores (23 pacientes; 62%) frente a no respondedores (14 pacientes; 38%) a la quimioterapia están representados en la figura 1.

Se encontraron diferencias de expresión ($p<0.05$) en 595 genes (6.2%) de las 9619 secuencias finales seleccionadas después del análisis. Usando el test FDR, el 5% de ellos

(480 genes) son considerados como hallazgos de falsos positivos. En un cluster supervisado, se observó la expresión génica desregulada y SLP como un marcador de respuesta, detectando perfiles de expresión asociados diferenciales (figura 2).

Basado en ambos análisis, seleccionados aquellos genes (n=161) con los valores p más significativos y su desregulación fue consistente en respuesta a la quimioterapia y en el análisis de supervivencia para ser validado usando qRT-PCR en una cohorte independiente de pacientes con CCR y muestras control no-tumorales.

Identificación del patrón de expresión génica pacientes con CCR de acuerdo a la respuesta a la quimioterapia.

Se confirmaron 24 de los 161 como genes diferencialmente expresados entre pacientes que lograron una respuesta objetivo a la quimioterapia (R: RC + RP) frente a aquellos que no lo hicieron (NR: EE + EP) ($p<0.05$) después qRT-PCR usando el software Statminer®: *AQP1, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1* y *WWC2*.

Tabla 4. Genes expresados diferencialmente en respuesta a la quimioterapia en pacientes con carcinoma colorrectal metastásico, según el análisis de PCR en tiempo real.

Gen	Gen ID	R vs NR (-ΔΔCt)	p-valor* ajustados
AQP1	358	1,200	**0,025**
CLEC3B	7123	1,614	**0,006**
DCK	1633	0,888	**0,044**
DEFA5	1670	1,599	**0,017**
DNAJC3	5611	1,421	**0,006**
FBLIM1	54751	0,947	**0,038**
GAS7	8522	1,000	**0,034**
IGFBP4	3487	0,803	**0,025**
KSR1	8844	0,997	**0,034**
LONP1	9361	0,800	**0,034**
MTHFD1L	25902	0,915	**0,044**
NAV1	89796	0,881	**0,038**

Gen	**Gen ID**	**R vs NR (-ΔΔCt)**	**p-valor* ajustados**
NIPBL	25836	1,049	**0,026**
PALM2	445815	1,203	**0,024**
PCDHGC3	5098	0,991	**0,038**
PROS1	5627	1,064	**0,026**
RARA	5914	0,960	**0,034**
RSF1	51773	0,796	**0,044**
TENC1	23371	0,942	**0,038**
TGFBR3	7049	1,150	**0,023**
TRAK2	66008	1,220	**0,017**
VSNL1	7447	0,966	**0,034**
WHSC1L1	54904	1,116	**0,026**
WWC2	80014	0,932	**0,044**

*Gen ID: número de acceso GenBank. * Los p-valores obtenidos se ajustaron para pruebas múltiples por el ajuste de Benjamini-Hochberg.*

Los pacientes se estratificaron en dos grupos, es decir, respondedores a quimioterapia (R), incluyendo pacientes con respuesta completa o respuesta parcial, y no respondedores (NR), incluyendo pacientes con enfermedad estable o progresión de la enfermedad sobre la base en el cambio en el tamaño de la lesión.

Para evaluar aún más las diferencias en la expresión génica potencialmente predictiva de la respuesta a la quimioterapia, se compararon los niveles de expresión génica entre muestras de pacientes R, NR y controles no-tumorales.

Los resultados se representan en la figura 3. Las diferencias significativas ($p<0.05$) fueron encontrados en 15/24 genes: *AQP, CLECL3B, DCK, PROS1, WHSC1L1, TGFBR3, FBLIM1, GAS7, IGFBP4, NAV1, PCDHGC3, RARA, RSF1, TENC1* y *TRAK2*. Y adicionalmente, el gen DNAJC3 mostró una significancia en el límite ($p=0,076$).

La identificación de patrones de expresión génica en pacientes con cáncer de colon, de acuerdo a la supervivencia libre de progresión (SLP).

El estimador Kaplan-Meier estima para la SLP de acuerdo a los niveles de expresión génica en pacientes agrupados como por arriba o por debajo de la media del tiempo (11,53 meses) mostró 4 genes con perfil de expresión diferencial ($p<0.05$); FAF1, KIAA1033, N4BP2L1 y SLC12A2. Otros 4 genes mostraron significancia límite, y fueron consideradas también por más análisis: DIDO1 ($p=0.076$), FBXO9 ($p=0.054$), RB1CC1 ($p=0.065$) y STARD13 ($p=0.051$)

Tabla 5. Genes expresados diferencialmente por supervivencia libre de progresión en pacientes con carcinoma colorrectal metastásico, según análisis de PCR en tiempo real.

Gen	**Gen ID**	**PFS_LM vs PFS_HM (-ΔΔCt)**	**p-valor* (95%CI)**
DIDO1	11083	-0.020	**0.076**
FAF1	11124	-0.021	**0.022**
FBXO9	26268	-0.116	**0.054**
KIAA1033	23325	-0.148	**0.026**
N4BP2L1	90634	-0.025	**0.001**
SLC12A2	6558	-0.047	**0.033**
STARD13	90627	-0.784	**0.051**
RB1CC1	9821	-0.052	**0.065**

*Los pacientes fueron estratificados en dos grupos. En pacientes con tiempo de supervivencia más baja que la progresión de la mediana (PFS_LM) o superior a la mediana (PFS_HM). * PFS se estimó mediante el método de Kaplan-Meier y los valores de p fueron evaluados mediante la prueba de log-rank. Gene ID: número de acceso GenBank, IC: intervalo de confianza.*

Luego, se compararon estos niveles de expresión génica entre pacientes agrupados por encima o por debajo de la media de tiempo de SLP y muestras control no-tumorales. Las diferencias significativas se mostraban en 5/8 genes: *N4BP2L1, STARD13, FAF1, FBXO9* y *SLC12A2*. (Figura 4).

REIVINDICACIONES

1. El uso simultáneo de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal.

2. Un método de obtención de datos útiles para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, que comprende:
    a. Obtener una muestra biológica aislada que comprende células del individuo, y
    b. Detectar la cantidad de producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* en la muestra aislada de (a).

3. El método según la reivindicación 2, que además comprende:
    c. Comparar los niveles de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* en la muestra obtenida en (a), con la cantidad de expresión detectada para dichos genes en una población de individuos de referencia de respuesta patológica conocida.

4. Un método para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, que comprende los pasos (a)-(c) según cualquiera de las reivindicaciones 2-3, y además comprende:
    d. incluir al individuo que presenta una cantidad de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9,*

KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1 significativamente superior a los niveles de expresión de los mismos genes en una población de referencia, en el grupo de individuos respondedores a la quimioterapia del cáncer colorrectal.

5. El método según cualquiera de las reivindicaciones 2-4, donde la muestra se obtiene de un tumor colorrectal.

6. El método según cualquiera de las reivindicaciones 2-5 en el que la cantidad de producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se obtiene mediante:
    a. Un procedimiento de perfilado génico, tal y como una micromatriz y/o
    b. Un procedimiento que comprende la PCR, tal como la PCR en tiempo real; y/o
    c. Transferencia Northern

7. El método según la reivindicación anterior, donde la cantidad de producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se obtiene mediante PCR cuantitativa a tiempo real.

8. El método según la reivindicación 7, donde la detección del producto de expresión se realiza mediante microarrays.

9. El método para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal según cualquiera de las reivindicaciones 2-8, donde el tratamiento quimioterápico comprende el uso de compuestos basados en platino, compuestos inhibidores de la topoisomerasa I, compuestos análogos de las pirimidinas, o cualquiera de sus combinaciones.

10. El método para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal según la reivindicación anterior, donde el compuesto basado en platino es el oxaliplatino, el inhibidor de la topoisomerasa I es el Irinotecan, y el análogo de pirimidina es el 5-fluorouracilo.

11. Un método de seguimiento de la evolución del cáncer colorrectal que comprende realizar al menos dos veces la secuencia de pasos (a) y (c) según cualquiera de las reivindicaciones 3-10, en muestras biológicas procedentes de un mismo individuo, y aisladas en momentos diferentes.

12. Un kit o dispositivo que comprende los cebadores y sondas diseñados a partir de las secuencias nucleotídicas de la Tabla 1.

13. Un microarray que comprende oligonucleótidos o microarreglos de canal único diseñados a partir de una secuencia conocida o de un ARNm de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*.

14. El microarray según la reivindicación anterior, donde la secuencia de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* es la secuencia nucleotídica SEQ ID recogida en la Tabla 1, respectivamente.

15. El uso del kit o dispositivo según la reivindicación 12, o del microarray según cualquiera de las reivindicaciones 13-14, para la obtención de datos útiles para predecir la respuesta al tratamiento en pacientes con cáncer de colorrectal.

FIG.1

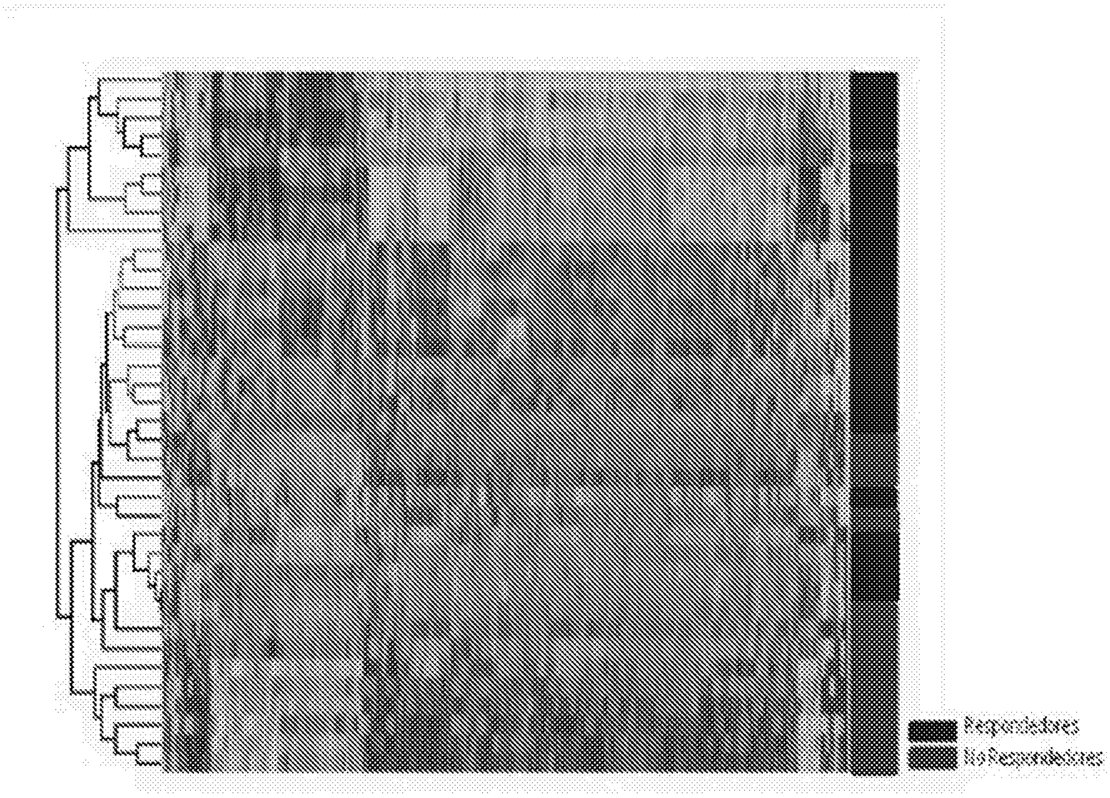
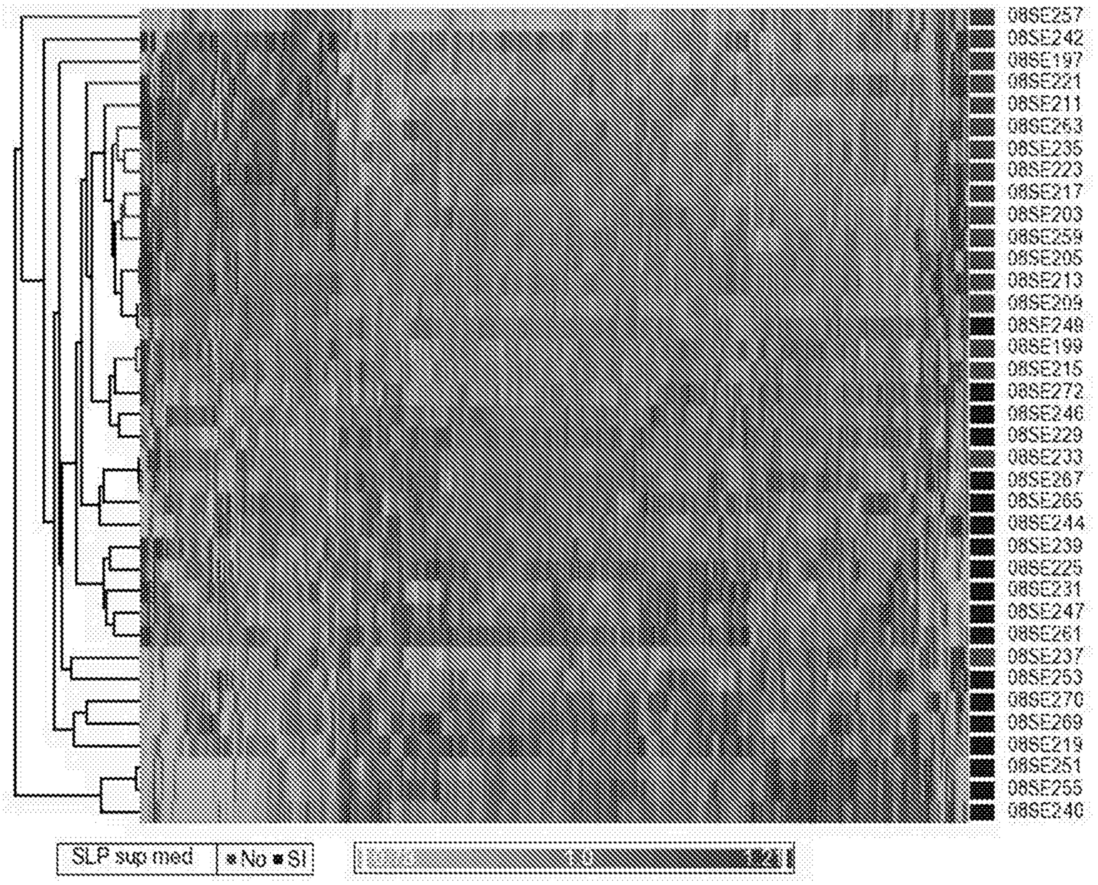


FIG.2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08SE231
08SE247
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SLP sup med
■ No ■ SI

FIG.3

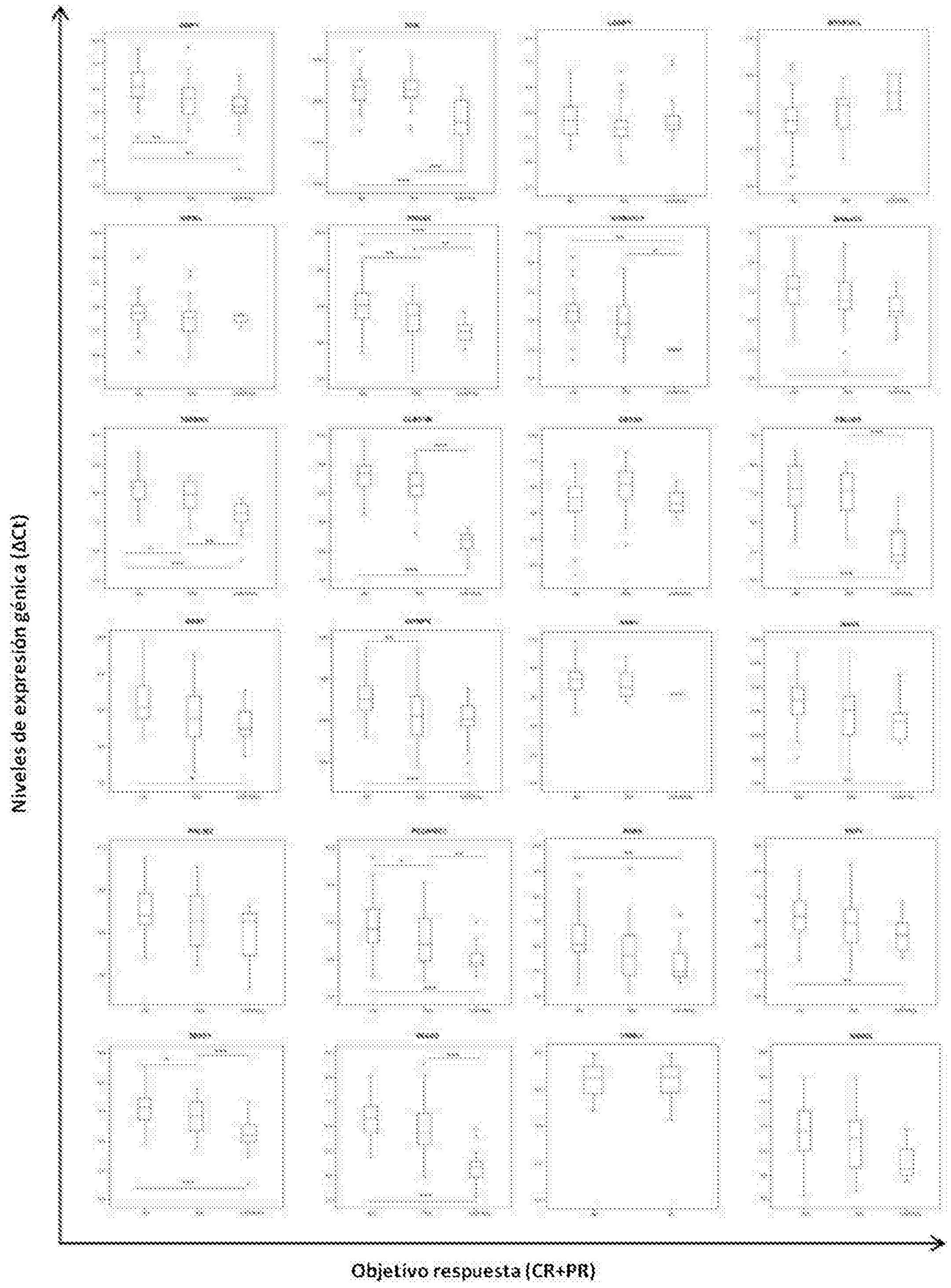
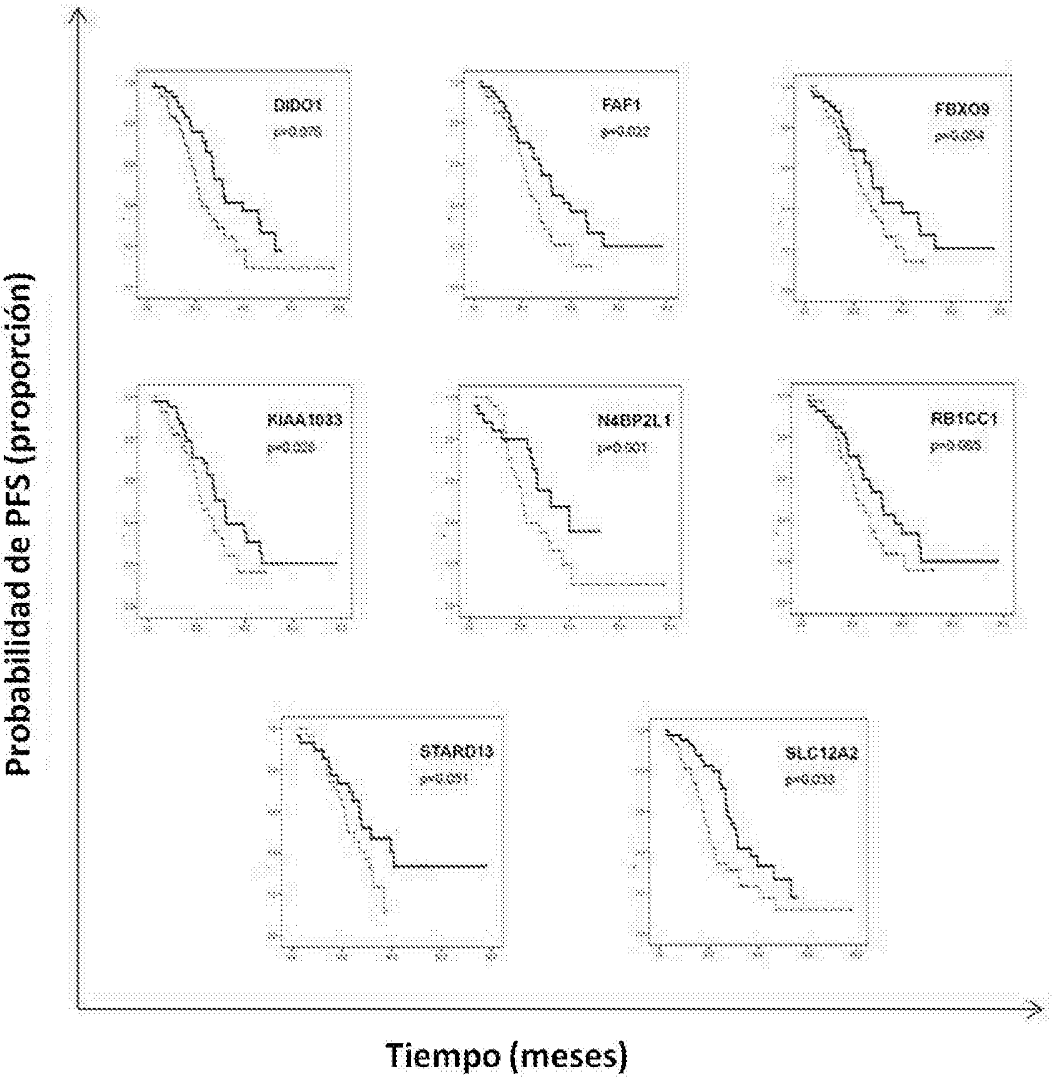


FIG.4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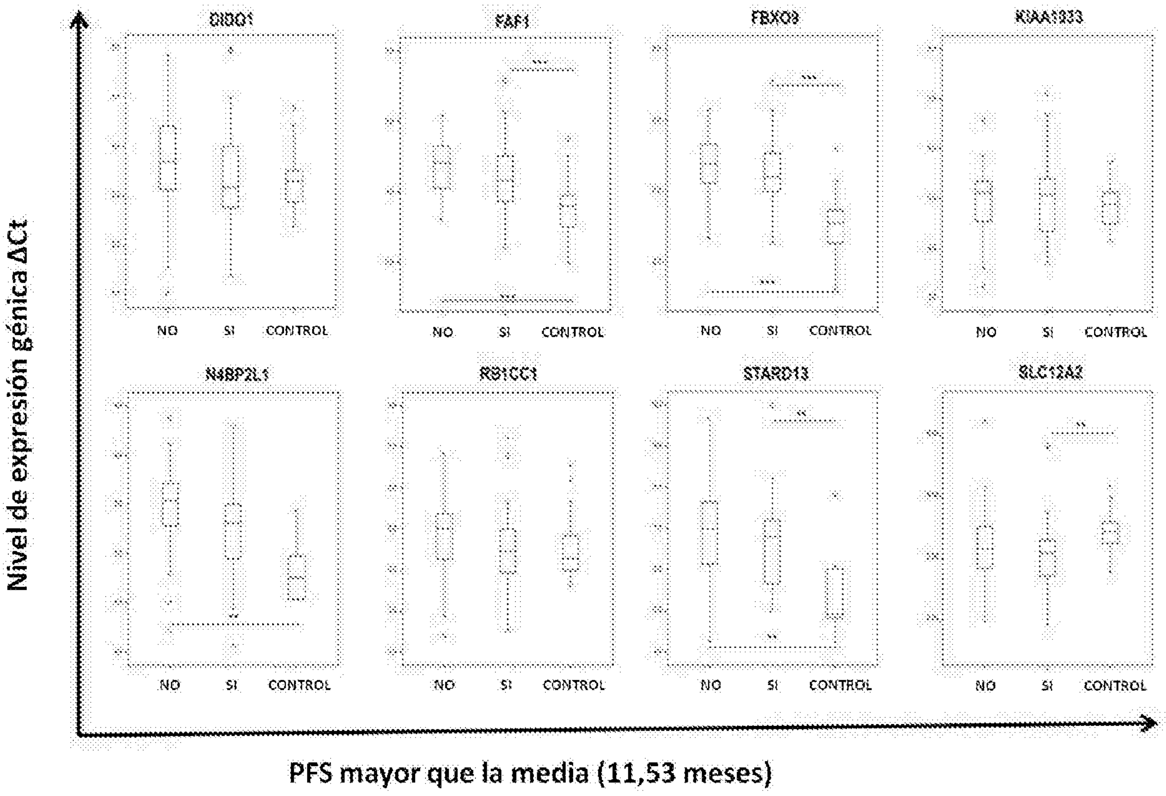
STARD13
SLC12A2
Probabilidad de PFS (proporción)
Tiempo (meses)

FIG.5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RB1CC1
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NO
SI
CONTROL
Nivel de expresión génica ΔCt
PFS mayor que la media (11,53 meses)

LISTADO DE SECUENCIAS

<110> SERVICIO ANDALUZ DE SALUD
CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS
FUNDACIÓN PÚBLICA ANDALUZA PARA LA GESTIÓN DE LA INVESTIGACIÓN EN SALUD EN SEVILLA
UNIVERSIDAD DE SEVILLA

<120> Método para predecir la respuesta al tratamiento con quimioterapia en pacientes de cáncer colorrectal.

<130> P-06647

<160> 164

<170> PatentIn version 3.5

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gcagatcgaa gagtgtgtac ctacagtgct gggacggata caaatccaat ttttcttttt 780

aacaaagaaa tgatcttatg tgatcgtcca cctgctattc ctaaaactac cttttcgaca 840

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<210> 83
<211> 269
<212> PRT
<213> Homo sapiens

<400> 83

Met Ala Ser Glu Phe Lys Lys Lys Leu Phe Trp Arg Ala Val Val Ala
1   5   10   15

Glu Phe Leu Ala Thr Thr Leu Phe Val Phe Ile Ser Ile Gly Ser Ala
            20   25   30

Leu Gly Phe Lys Tyr Pro Val Gly Asn Asn Gln Thr Ala Val Gln Asp
        35   40   45

Asn Val Lys Val Ser Leu Ala Phe Gly Leu Ser Ile Ala Thr Leu Ala
    50   55   60

Gln Ser Val Gly His Ile Ser Gly Ala His Leu Asn Pro Ala Val Thr
65   70   75   80

Leu Gly Leu Leu Leu Ser Cys Gln Ile Ser Ile Phe Arg Ala Leu Met
                85   90   95

Tyr Ile Ile Ala Gln Cys Val Gly Ala Ile Val Ala Thr Ala Ile Leu
            100   105   110

Ser Gly Ile Thr Ser Ser Leu Thr Gly Asn Ser Leu Gly Arg Asn Asp
        115   120   125

Leu Ala Asp Gly Val Asn Ser Gly Gln Gly Leu Gly Ile Glu Ile Ile
    130   135   140

```
Gly Thr Leu Gln Leu Val Leu Cys Val Leu Ala Thr Thr Asp Arg Arg
145                 150                 155                 160

Arg Arg Asp Leu Gly Gly Ser Ala Pro Leu Ala Ile Gly Leu Ser Val
                165                 170                 175

Ala Leu Gly His Leu Leu Ala Ile Asp Tyr Thr Gly Cys Gly Ile Asn
            180                 185                 190

Pro Ala Arg Ser Phe Gly Ser Ala Val Ile Thr His Asn Phe Ser Asn
        195                 200                 205

His Trp Ile Phe Trp Val Gly Pro Phe Ile Gly Gly Ala Leu Ala Val
    210                 215                 220

Leu Ile Tyr Asp Phe Ile Leu Ala Pro Arg Ser Ser Asp Leu Thr Asp
225                 230                 235                 240

Arg Val Lys Val Trp Thr Ser Gly Gln Val Glu Glu Tyr Asp Leu Asp
                245                 250                 255

Ala Asp Asp Ile Asn Ser Arg Val Glu Met Lys Pro Lys
            260                 265


<210>  84
<211>  186
<212>  PRT
<213>  Homo sapiens

<400>  84

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

Leu Ala Trp Met Gln Leu Asp Ala Lys Ala Pro Ala His Pro Arg Pro
            20                  25                  30

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

Gly Val Asn Ser Gly Gln Gly Leu Gly Ile Glu Ile Ile Gly Thr Leu
    50                  55                  60

Gln Leu Val Leu Cys Val Leu Ala Thr Thr Asp Arg Arg Arg Arg Asp
65                  70                  75                  80
```

```
Leu Gly Gly Ser Ala Pro Leu Ala Ile Gly Leu Ser Val Ala Leu Gly
                85                  90                  95


His Leu Leu Ala Ile Asp Tyr Thr Gly Cys Gly Ile Asn Pro Ala Arg
            100                 105                 110


Ser Phe Gly Ser Ala Val Ile Thr His Asn Phe Ser Asn His Trp Ile
        115                 120                 125


Phe Trp Val Gly Pro Phe Ile Gly Gly Ala Leu Ala Val Leu Ile Tyr
    130                 135                 140


Asp Phe Ile Leu Ala Pro Arg Ser Ser Asp Leu Thr Asp Arg Val Lys
145                 150                 155                 160


Val Trp Thr Ser Gly Gln Val Glu Glu Tyr Asp Leu Asp Ala Asp Asp
                165                 170                 175


Ile Asn Ser Arg Val Glu Met Lys Pro Lys
            180                 185


<210>  85
<211>  218
<212>  PRT
<213>  Homo sapiens

<400>  85

Met Phe Trp Thr Phe Gly Tyr Glu Ala Val Ser Pro Ala Gly Pro Ser
1               5                   10                  15


His Leu Phe Ala Ser Leu Leu Leu Gly Val Leu Leu Thr Ile Thr Phe
            20                  25                  30


Met Pro Gly Ala Arg Pro Leu Pro Leu Val Leu Val Pro Gln Asn Thr
        35                  40                  45


Leu Ala Trp Met Gln Leu Asp Ala Lys Ala Pro Ala His Pro Arg Pro
    50                  55                  60


Leu Gln Leu Leu Gly Arg Val Gly Pro Gly Ser Arg Gln Leu Ala Asp
65                  70                  75                  80


Gly Val Asn Ser Gly Gln Gly Leu Gly Ile Glu Ile Ile Gly Thr Leu
                85                  90                  95
```

```
Gln Leu Val Leu Cys Val Leu Ala Thr Thr Asp Arg Arg Arg Arg Asp
            100                 105                 110


Leu Gly Gly Ser Ala Pro Leu Ala Ile Gly Leu Ser Val Ala Leu Gly
        115                 120                 125


His Leu Leu Ala Ile Asp Tyr Thr Gly Cys Gly Ile Asn Pro Ala Arg
    130                 135                 140


Ser Phe Gly Ser Ala Val Ile Thr His Asn Phe Ser Asn His Trp Ile
145                 150                 155                 160


Phe Trp Val Gly Pro Phe Ile Gly Gly Ala Leu Ala Val Leu Ile Tyr
                165                 170                 175


Asp Phe Ile Leu Ala Pro Arg Ser Ser Asp Leu Thr Asp Arg Val Lys
            180                 185                 190


Val Trp Thr Ser Gly Gln Val Glu Glu Tyr Asp Leu Asp Ala Asp Asp
        195                 200                 205


Ile Asn Ser Arg Val Glu Met Lys Pro Lys
    210                 215


<210>  86
<211>  154
<212>  PRT
<213>  Homo sapiens

<400>  86

Met Gln Ser Gly Met Gly Trp Asn Val Leu Asp Phe Trp Leu Ala Asp
1               5                   10                  15


Gly Val Asn Ser Gly Gln Gly Leu Gly Ile Glu Ile Ile Gly Thr Leu
            20                  25                  30


Gln Leu Val Leu Cys Val Leu Ala Thr Thr Asp Arg Arg Arg Arg Asp
        35                  40                  45


Leu Gly Gly Ser Ala Pro Leu Ala Ile Gly Leu Ser Val Ala Leu Gly
    50                  55                  60


His Leu Leu Ala Ile Asp Tyr Thr Gly Cys Gly Ile Asn Pro Ala Arg
65                  70                  75                  80
```

Ser Phe Gly Ser Ala Val Ile Thr His Asn Phe Ser Asn His Trp Ile
85 90 95

Phe Trp Val Gly Pro Phe Ile Gly Gly Ala Leu Ala Val Leu Ile Tyr
100 105 110

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

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

Ile Asn Ser Arg Val Glu Met Lys Pro Lys
145 150

<210> 87
<211> 202
<212> PRT
<213> Homo sapiens

<400> 87

Met Glu Leu Trp Gly Ala Tyr Leu Leu Leu Cys Leu Phe Ser Leu Leu
1 5 10 15

Thr Gln Val Thr Thr Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val
20 25 30

Asn Ala Lys Lys Asp Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys
35 40 45

Ser Arg Leu Asp Thr Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln
50 55 60

Gln Ala Leu Gln Thr Val Cys Leu Lys Gly Thr Lys Val His Met Lys
65 70 75 80

Cys Phe Leu Ala Phe Thr Gln Thr Lys Thr Phe His Glu Ala Ser Glu
85 90 95

Asp Cys Ile Ser Arg Gly Gly Thr Leu Gly Thr Pro Gln Thr Gly Ser
100 105 110

Glu Asn Asp Ala Leu Tyr Glu Tyr Leu Arg Gln Ser Val Gly Asn Glu
115 120 125

```
Ala Glu Ile Trp Leu Gly Leu Asn Asp Met Ala Ala Glu Gly Thr Trp
    130                 135                 140


Val Asp Met Thr Gly Ala Arg Ile Ala Tyr Lys Asn Trp Glu Thr Glu
145                 150                 155                 160


Ile Thr Ala Gln Pro Asp Gly Gly Lys Thr Glu Asn Cys Ala Val Leu
                165                 170                 175


Ser Gly Ala Ala Asn Gly Lys Trp Phe Asp Lys Arg Cys Arg Asp Gln
            180                 185                 190


Leu Pro Tyr Ile Cys Gln Phe Gly Ile Val
        195                 200


<210>  88
<211>  514
<212>  PRT
<213>  Homo sapiens

<400>  88

Met Ala Asp Ala Glu Val Ile Ile Leu Pro Lys Lys His Lys Lys Lys
1               5                   10                  15


Lys Glu Arg Lys Ser Leu Pro Glu Glu Asp Val Ala Glu Ile Gln His
            20                  25                  30


Ala Glu Glu Phe Leu Ile Lys Pro Glu Ser Lys Val Ala Lys Leu Asp
        35                  40                  45


Thr Ser Gln Trp Pro Leu Leu Leu Lys Asn Phe Asp Lys Leu Asn Val
    50                  55                  60


Arg Thr Thr His Tyr Thr Pro Leu Ala Cys Gly Ser Asn Pro Leu Lys
65                  70                  75                  80


Arg Glu Ile Gly Asp Tyr Ile Arg Thr Gly Phe Ile Asn Leu Asp Lys
                85                  90                  95


Pro Ser Asn Pro Ser Ser His Glu Val Val Ala Trp Ile Arg Arg Ile
            100                 105                 110


Leu Arg Val Glu Lys Thr Gly His Ser Gly Thr Leu Asp Pro Lys Val
        115                 120                 125
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Thr Gly Cys Leu Ile Val Cys Ile Glu Arg Ala Thr Arg Leu Val Lys
    130                 135                 140


Ser Gln Gln Ser Ala Gly Lys Glu Tyr Val Gly Ile Val Arg Leu His
145                 150                 155                 160


Asn Ala Ile Glu Gly Gly Thr Gln Leu Ser Arg Ala Leu Glu Thr Leu
                165                 170                 175


Thr Gly Ala Leu Phe Gln Arg Pro Pro Leu Ile Ala Ala Val Lys Arg
            180                 185                 190


Gln Leu Arg Val Arg Thr Ile Tyr Glu Ser Lys Met Ile Glu Tyr Asp
        195                 200                 205


Pro Glu Arg Arg Leu Gly Ile Phe Trp Val Ser Cys Glu Ala Gly Thr
    210                 215                 220


Tyr Ile Arg Thr Leu Cys Val His Leu Gly Leu Leu Leu Gly Val Gly
225                 230                 235                 240


Gly Gln Met Gln Glu Leu Arg Arg Val Arg Ser Gly Val Met Ser Glu
                245                 250                 255


Lys Asp His Met Val Thr Met His Asp Val Leu Asp Ala Gln Trp Leu
            260                 265                 270


Tyr Asp Asn His Lys Asp Glu Ser Tyr Leu Arg Arg Val Val Tyr Pro
        275                 280                 285


Leu Glu Lys Leu Leu Thr Ser His Lys Arg Leu Val Met Lys Asp Ser
    290                 295                 300


Ala Val Asn Ala Ile Cys Tyr Gly Ala Lys Ile Met Leu Pro Gly Val
305                 310                 315                 320


Leu Arg Tyr Glu Asp Gly Ile Glu Val Asn Gln Glu Ile Val Val Ile
                325                 330                 335


Thr Thr Lys Gly Glu Ala Ile Cys Met Ala Ile Ala Leu Met Thr Thr
            340                 345                 350


Ala Val Ile Ser Thr Cys Asp His Gly Ile Val Ala Lys Ile Lys Arg
        355                 360                 365
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Val Ile Met Glu Arg Asp Thr Tyr Pro Arg Lys Trp Gly Leu Gly Pro
    370                 375                 380


Lys Ala Ser Gln Lys Lys Leu Met Ile Lys Gln Gly Leu Leu Asp Lys
385                 390                 395                 400


His Gly Lys Pro Thr Asp Ser Thr Pro Ala Thr Trp Lys Gln Glu Tyr
                405                 410                 415


Val Asp Tyr Ser Glu Ser Ala Lys Lys Glu Val Val Ala Glu Val Val
            420                 425                 430


Lys Ala Pro Gln Val Val Ala Glu Ala Ala Lys Thr Ala Lys Arg Lys
        435                 440                 445


Arg Glu Ser Glu Ser Glu Ser Asp Glu Thr Pro Pro Ala Ala Pro Gln
    450                 455                 460


Leu Ile Lys Lys Glu Lys Lys Lys Ser Lys Lys Asp Lys Lys Ala Lys
465                 470                 475                 480


Ala Gly Leu Glu Ser Gly Ala Glu Pro Gly Asp Gly Asp Ser Asp Thr
                485                 490                 495


Thr Lys Lys Lys Lys Lys Lys Lys Lys Ala Lys Glu Val Glu Leu Val
            500                 505                 510


Ser Glu



<210>  89
<211>  509
<212>  PRT
<213>  Homo sapiens

<400>  89

Met Ala Asp Ala Glu Val Ile Ile Leu Pro Lys Lys His Lys Lys Lys
1               5                   10                  15


Lys Glu Arg Lys Ser Leu Pro Glu Glu Asp Val Ala Glu Ile Gln His
            20                  25                  30


Ala Glu Glu Phe Leu Ile Lys Pro Glu Ser Lys Val Ala Lys Leu Asp
        35                  40                  45
```

```
Thr Ser Gln Trp Pro Leu Leu Leu Lys Asn Phe Asp Lys Leu Asn Val
    50                  55                  60

Arg Thr Thr His Tyr Thr Pro Leu Ala Cys Gly Ser Asn Pro Leu Lys
65                  70                  75                  80

Arg Glu Ile Gly Asp Tyr Ile Arg Thr Gly Phe Ile Asn Leu Asp Lys
                85                  90                  95

Pro Ser Asn Pro Ser Ser His Glu Val Val Ala Trp Ile Arg Arg Ile
            100                 105                 110

Leu Arg Val Glu Lys Thr Gly His Ser Gly Thr Leu Asp Pro Lys Val
        115                 120                 125

Thr Gly Cys Leu Ile Val Cys Ile Glu Arg Ala Thr Arg Leu Val Lys
    130                 135                 140

Ser Gln Gln Ser Ala Gly Lys Glu Tyr Val Gly Ile Val Arg Leu His
145                 150                 155                 160

Asn Ala Ile Glu Gly Gly Thr Gln Leu Ser Arg Ala Leu Glu Thr Leu
                165                 170                 175

Thr Gly Ala Leu Phe Gln Arg Pro Pro Leu Ile Ala Ala Val Lys Arg
            180                 185                 190

Gln Leu Arg Val Arg Thr Ile Tyr Glu Ser Lys Met Ile Glu Tyr Asp
        195                 200                 205

Pro Glu Arg Arg Leu Gly Ile Phe Trp Val Ser Cys Glu Ala Gly Thr
    210                 215                 220

Tyr Ile Arg Thr Leu Cys Val His Leu Gly Leu Leu Leu Gly Val Gly
225                 230                 235                 240

Gly Gln Met Gln Glu Leu Arg Arg Val Arg Ser Gly Val Met Ser Glu
                245                 250                 255

Lys Asp His Met Val Thr Met His Asp Val Leu Asp Ala Gln Trp Leu
            260                 265                 270
```

```
Tyr Asp Asn His Lys Asp Glu Ser Tyr Leu Arg Arg Val Val Tyr Pro
        275                 280                 285

Leu Glu Lys Leu Leu Thr Ser His Lys Arg Leu Val Met Lys Asp Ser
    290                 295                 300

Ala Val Asn Ala Ile Cys Tyr Gly Ala Lys Ile Met Leu Pro Gly Val
305                 310                 315                 320

Leu Arg Tyr Glu Asp Gly Ile Glu Val Asn Gln Glu Ile Val Val Ile
                325                 330                 335

Thr Thr Lys Gly Glu Ala Ile Cys Met Ala Ile Ala Leu Met Thr Thr
            340                 345                 350

Ala Val Ile Ser Thr Cys Asp His Gly Ile Val Ala Lys Ile Lys Arg
        355                 360                 365

Val Ile Met Glu Arg Asp Thr Tyr Pro Arg Lys Trp Gly Leu Gly Pro
    370                 375                 380

Lys Ala Ser Gln Lys Lys Leu Met Ile Lys Gln Gly Leu Leu Asp Lys
385                 390                 395                 400

His Gly Lys Pro Thr Asp Ser Thr Pro Ala Thr Trp Lys Gln Asp Glu
                405                 410                 415

Ser Ala Lys Lys Glu Val Val Ala Glu Val Val Lys Ala Pro Gln Val
            420                 425                 430

Val Ala Glu Ala Ala Lys Thr Ala Lys Arg Lys Arg Glu Ser Glu Ser
        435                 440                 445

Glu Ser Asp Glu Thr Pro Pro Ala Ala Pro Gln Leu Ile Lys Lys Glu
    450                 455                 460

Lys Lys Lys Ser Lys Lys Asp Lys Lys Ala Lys Ala Gly Leu Glu Ser
465                 470                 475                 480

Gly Ala Glu Pro Gly Asp Gly Asp Ser Asp Thr Thr Lys Lys Lys Lys
                485                 490                 495

Lys Lys Lys Lys Ala Lys Glu Val Glu Leu Val Ser Glu
            500                 505
```

```
<210>  90
<211>  676
<212>  PRT
<213>  Homo sapiens

<400>  90

Met Arg Val Leu Gly Gly Arg Cys Gly Ala Leu Leu Ala Cys Leu Leu
1               5                   10                  15


Leu Val Leu Pro Val Ser Glu Ala Asn Phe Leu Ser Lys Gln Gln Ala
            20                  25                  30


Ser Gln Val Leu Val Arg Lys Arg Arg Ala Asn Ser Leu Leu Glu Glu
        35                  40                  45


Thr Lys Gln Gly Asn Leu Glu Arg Glu Cys Ile Glu Glu Leu Cys Asn
    50                  55                  60


Lys Glu Glu Ala Arg Glu Val Phe Glu Asn Asp Pro Glu Thr Asp Tyr
65                  70                  75                  80


Phe Tyr Pro Lys Tyr Leu Val Cys Leu Arg Ser Phe Gln Thr Gly Leu
                85                  90                  95


Phe Thr Ala Ala Arg Gln Ser Thr Asn Ala Tyr Pro Asp Leu Arg Ser
            100                 105                 110


Cys Val Asn Ala Ile Pro Asp Gln Cys Ser Pro Leu Pro Cys Asn Glu
        115                 120                 125


Asp Gly Tyr Met Ser Cys Lys Asp Gly Lys Ala Ser Phe Thr Cys Thr
    130                 135                 140


Cys Lys Pro Gly Trp Gln Gly Glu Lys Cys Glu Phe Asp Ile Asn Glu
145                 150                 155                 160


Cys Lys Asp Pro Ser Asn Ile Asn Gly Gly Cys Ser Gln Ile Cys Asp
                165                 170                 175


Asn Thr Pro Gly Ser Tyr His Cys Ser Cys Lys Asn Gly Phe Val Met
            180                 185                 190


Leu Ser Asn Lys Lys Asp Cys Lys Asp Val Asp Glu Cys Ser Leu Lys
        195                 200                 205
```

```
Pro Ser Ile Cys Gly Thr Ala Val Cys Lys Asn Ile Pro Gly Asp Phe
    210                 215                 220

Glu Cys Glu Cys Pro Glu Gly Tyr Arg Tyr Asn Leu Lys Ser Lys Ser
225                 230                 235                 240

Cys Glu Asp Ile Asp Glu Cys Ser Glu Asn Met Cys Ala Gln Leu Cys
                245                 250                 255

Val Asn Tyr Pro Gly Gly Tyr Thr Cys Tyr Cys Asp Gly Lys Lys Gly
            260                 265                 270

Phe Lys Leu Ala Gln Asp Gln Lys Ser Cys Glu Val Val Ser Val Cys
        275                 280                 285

Leu Pro Leu Asn Leu Asp Thr Lys Tyr Glu Leu Leu Tyr Leu Ala Glu
    290                 295                 300

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

Ser Arg Phe Ser Ala Glu Phe Asp Phe Arg Thr Tyr Asp Ser Glu Gly
                325                 330                 335

Val Ile Leu Tyr Ala Glu Ser Ile Asp His Ser Ala Trp Leu Leu Ile
            340                 345                 350

Ala Leu Arg Gly Gly Lys Ile Glu Val Gln Leu Lys Asn Glu His Thr
        355                 360                 365

Ser Lys Ile Thr Thr Gly Gly Asp Val Ile Asn Asn Gly Leu Trp Asn
    370                 375                 380

Met Val Ser Val Glu Glu Leu Glu His Ser Ile Ser Ile Lys Ile Ala
385                 390                 395                 400

Lys Glu Ala Val Met Asp Ile Asn Lys Pro Gly Pro Leu Phe Lys Pro
                405                 410                 415

Glu Asn Gly Leu Leu Glu Thr Lys Val Tyr Phe Ala Gly Phe Pro Arg
            420                 425                 430

Lys Val Glu Ser Glu Leu Ile Lys Pro Ile Asn Pro Arg Leu Asp Gly
        435                 440                 445
```

```
Cys Ile Arg Ser Trp Asn Leu Met Lys Gln Gly Ala Ser Gly Ile Lys
    450                 455                 460


Glu Ile Ile Gln Glu Lys Gln Asn Lys His Cys Leu Val Thr Val Glu
465                 470                 475                 480


Lys Gly Ser Tyr Tyr Pro Gly Ser Gly Ile Ala Gln Phe His Ile Asp
                485                 490                 495


Tyr Asn Asn Val Ser Ser Ala Glu Gly Trp His Val Asn Val Thr Leu
            500                 505                 510


Asn Ile Arg Pro Ser Thr Gly Thr Gly Val Met Leu Ala Leu Val Ser
        515                 520                 525


Gly Asn Asn Thr Val Pro Phe Ala Val Ser Leu Val Asp Ser Thr Ser
    530                 535                 540


Glu Lys Ser Gln Asp Ile Leu Leu Ser Val Glu Asn Thr Val Ile Tyr
545                 550                 555                 560


Arg Ile Gln Ala Leu Ser Leu Cys Ser Asp Gln Gln Ser His Leu Glu
                565                 570                 575


Phe Arg Val Asn Arg Asn Asn Leu Glu Leu Ser Thr Pro Leu Lys Ile
            580                 585                 590


Glu Thr Ile Ser His Glu Asp Leu Gln Arg Gln Leu Ala Val Leu Asp
        595                 600                 605


Lys Ala Met Lys Ala Lys Val Ala Thr Tyr Leu Gly Gly Leu Pro Asp
    610                 615                 620


Val Pro Phe Ser Ala Thr Pro Val Asn Ala Phe Tyr Asn Gly Cys Met
625                 630                 635                 640


Glu Val Asn Ile Asn Gly Val Gln Leu Asp Leu Asp Glu Ala Ile Ser
                645                 650                 655


Lys His Asn Asp Ile Arg Ala His Ser Cys Pro Ser Val Trp Lys Lys
            660                 665                 670


Thr Lys Asn Ser
        675
```

```
<210>  91
<211>  1437
<212>  PRT
<213>  Homo sapiens

<400>  91

Met Asp Phe Ser Phe Ser Phe Met Gln Gly Ile Met Gly Asn Thr Ile
1               5                   10                  15


Gln Gln Pro Pro Gln Leu Ile Asp Ser Ala Asn Ile Arg Gln Glu Asp
            20                  25                  30


Ala Phe Asp Asn Asn Ser Asp Ile Ala Glu Asp Gly Gly Gln Thr Pro
        35                  40                  45


Tyr Glu Ala Thr Leu Gln Gln Gly Phe Gln Tyr Pro Ala Thr Thr Glu
    50                  55                  60


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


Glu Thr Gln Thr Lys Tyr Gln Ser Tyr Asn Gln Tyr Pro Asn Gly Ser
                85                  90                  95


Ala Asn Gly Phe Gly Ala Val Arg Asn Phe Ser Pro Thr Asp Tyr Tyr
            100                 105                 110


His Ser Glu Ile Pro Asn Thr Arg Pro His Glu Ile Leu Glu Lys Pro
        115                 120                 125


Ser Pro Pro Gln Pro Pro Pro Pro Pro Ser Val Pro Gln Thr Val Ile
    130                 135                 140


Pro Lys Lys Thr Gly Ser Pro Glu Ile Lys Leu Lys Ile Thr Lys Thr
145                 150                 155                 160


Ile Gln Asn Gly Arg Glu Leu Phe Glu Ser Ser Leu Cys Gly Asp Leu
                165                 170                 175


Leu Asn Glu Val Gln Ala Ser Glu His Thr Lys Ser Lys His Glu Ser
            180                 185                 190


Arg Lys Glu Lys Arg Lys Lys Ser Asn Lys His Asp Ser Ser Arg Ser
        195                 200                 205
```

```
Glu Glu Arg Lys Ser His Lys Ile Pro Lys Leu Glu Pro Glu Glu Gln
    210                 215                 220

Asn Arg Pro Asn Glu Arg Val Asp Thr Val Ser Glu Lys Pro Arg Glu
225                 230                 235                 240

Glu Pro Val Leu Lys Glu Glu Ala Pro Val Gln Pro Ile Leu Ser Ser
                245                 250                 255

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

Leu Val Trp Ser Lys Val Gly Thr Tyr Pro Trp Trp Pro Cys Met Val
        275                 280                 285

Ser Ser Asp Pro Gln Leu Glu Val His Thr Lys Ile Asn Thr Arg Gly
    290                 295                 300

Ala Arg Glu Tyr His Val Gln Phe Phe Ser Asn Gln Pro Glu Arg Ala
305                 310                 315                 320

Trp Val His Glu Lys Arg Val Arg Glu Tyr Lys Gly His Lys Gln Tyr
                325                 330                 335

Glu Glu Leu Leu Ala Glu Ala Thr Lys Gln Ala Ser Asn His Ser Glu
            340                 345                 350

Lys Gln Lys Ile Arg Lys Pro Arg Pro Gln Arg Glu Arg Ala Gln Trp
        355                 360                 365

Asp Ile Gly Ile Ala His Ala Glu Lys Ala Leu Lys Met Thr Arg Glu
    370                 375                 380

Glu Arg Ile Glu Gln Tyr Thr Phe Ile Tyr Ile Asp Lys Gln Pro Glu
385                 390                 395                 400

Glu Ala Leu Ser Gln Ala Lys Lys Ser Val Ala Ser Lys Thr Glu Val
                405                 410                 415

Lys Lys Thr Arg Arg Pro Arg Ser Val Leu Asn Thr Gln Pro Glu Gln
            420                 425                 430

Thr Asn Ala Gly Glu Val Ala Ser Ser Leu Ser Ser Thr Glu Ile Arg
        435                 440                 445
```

```
Arg His Ser Gln Arg Arg His Thr Ser Ala Glu Glu Glu Glu Pro Pro
    450                 455                 460


Pro Val Lys Ile Ala Trp Lys Thr Ala Ala Ala Arg Lys Ser Leu Pro
465                 470                 475                 480


Ala Ser Ile Thr Met His Lys Gly Ser Leu Asp Leu Gln Lys Cys Asn
                485                 490                 495


Met Ser Pro Val Val Lys Ile Glu Gln Val Phe Ala Leu Gln Asn Ala
            500                 505                 510


Thr Gly Asp Gly Lys Phe Ile Asp Gln Phe Val Tyr Ser Thr Lys Gly
        515                 520                 525


Ile Gly Asn Lys Thr Glu Ile Ser Val Arg Gly Gln Asp Arg Leu Ile
    530                 535                 540


Ile Ser Thr Pro Asn Gln Arg Asn Glu Lys Pro Thr Gln Ser Val Ser
545                 550                 555                 560


Ser Pro Glu Ala Thr Ser Gly Ser Thr Gly Ser Val Glu Lys Lys Gln
                565                 570                 575


Gln Arg Arg Ser Ile Arg Thr Arg Ser Glu Ser Glu Lys Ser Thr Glu
            580                 585                 590


Val Val Pro Lys Lys Lys Ile Lys Lys Glu Gln Val Glu Thr Val Pro
        595                 600                 605


Gln Ala Thr Val Lys Thr Gly Leu Gln Lys Gly Ala Ser Glu Ile Ser
    610                 615                 620


Asp Ser Cys Lys Pro Leu Lys Lys Arg Ser Arg Ala Ser Thr Asp Val
625                 630                 635                 640


Glu Met Thr Ser Ser Ala Tyr Arg Asp Thr Ser Asp Ser Asp Ser Arg
                645                 650                 655


Gly Leu Ser Asp Leu Gln Val Gly Phe Gly Lys Gln Val Asp Ser Pro
            660                 665                 670


Ser Ala Thr Ala Asp Ala Asp Val Ser Asp Val Gln Ser Met Asp Ser
        675                 680                 685
```

```
Ser Leu Ser Arg Arg Gly Thr Gly Met Ser Lys Lys Asp Thr Val Cys
    690                 695                 700

Gln Ile Cys Glu Ser Ser Gly Asp Ser Leu Ile Pro Cys Glu Gly Glu
705                 710                 715                 720

Cys Cys Lys His Phe His Leu Glu Cys Leu Gly Leu Ala Ser Leu Pro
                725                 730                 735

Asp Ser Lys Phe Ile Cys Met Glu Cys Lys Thr Gly Gln His Pro Cys
            740                 745                 750

Phe Ser Cys Lys Val Ser Gly Lys Asp Val Lys Arg Cys Ser Val Gly
        755                 760                 765

Ala Cys Gly Lys Phe Tyr His Glu Ala Cys Val Arg Lys Phe Pro Thr
    770                 775                 780

Ala Ile Phe Glu Ser Lys Gly Phe Arg Cys Pro Gln His Cys Cys Ser
785                 790                 795                 800

Ala Cys Ser Met Glu Lys Asp Ile His Lys Ala Ser Lys Gly Arg Met
                805                 810                 815

Met Arg Cys Leu Arg Cys Pro Val Ala Tyr His Ser Gly Asp Ala Cys
            820                 825                 830

Ile Ala Ala Gly Ser Met Leu Val Ser Ser Tyr Ile Leu Ile Cys Ser
        835                 840                 845

Asn His Ser Lys Arg Ser Ser Asn Ser Ser Ala Val Asn Val Gly Phe
    850                 855                 860

Cys Phe Val Cys Ala Arg Gly Leu Ile Val Gln Asp His Ser Asp Pro
865                 870                 875                 880

Met Phe Ser Ser Tyr Ala Tyr Lys Ser His Tyr Leu Leu Asn Glu Ser
                885                 890                 895

Asn Arg Ala Glu Leu Met Lys Leu Pro Met Ile Pro Ser Ser Ser Ala
            900                 905                 910

Ser Lys Lys Lys Cys Glu Lys Gly Gly Arg Leu Leu Cys Cys Glu Ser
        915                 920                 925
```

```
Cys Pro Ala Ser Phe His Pro Glu Cys Leu Ser Ile Glu Met Pro Glu
    930                 935                 940


Gly Cys Trp Asn Cys Asn Asp Cys Lys Ala Gly Lys Lys Leu His Tyr
945                 950                 955                 960


Lys Gln Ile Val Trp Val Lys Leu Gly Asn Tyr Arg Trp Trp Pro Ala
                965                 970                 975


Glu Ile Cys Asn Pro Arg Ser Val Pro Leu Asn Ile Gln Gly Leu Lys
            980                 985                 990


His Asp Leu Gly Asp Phe Pro Val  Phe Phe Phe Gly Ser  His Asp Tyr
        995                 1000                 1005


Tyr Trp  Val His Gln Gly Arg  Val Phe Pro Tyr Val  Glu Gly Asp
    1010                 1015                 1020


Lys Ser  Phe Ala Glu Gly Gln  Thr Ser Ile Asn Lys  Thr Phe Lys
    1025                 1030                 1035


Lys Ala  Leu Glu Glu Ala Ala  Lys Arg Phe Gln Glu  Leu Lys Ala
    1040                 1045                 1050


Gln Arg  Glu Ser Lys Glu Ala  Leu Glu Ile Glu Lys  Asn Ser Arg
    1055                 1060                 1065


Lys Pro  Pro Pro Tyr Lys His  Ile Lys Ala Asn Lys  Val Ile Gly
    1070                 1075                 1080


Lys Val  Gln Ile Gln Val Ala  Asp Leu Ser Glu Ile  Pro Arg Cys
    1085                 1090                 1095


Asn Cys  Lys Pro Ala Asp Glu  Asn Pro Cys Gly Leu  Glu Ser Glu
    1100                 1105                 1110


Cys Leu  Asn Arg Met Leu Gln  Tyr Glu Cys His Pro  Gln Val Cys
    1115                 1120                 1125


Pro Ala  Gly Asp Arg Cys Gln  Asn Gln Cys Phe Thr  Lys Arg Leu
    1130                 1135                 1140


Tyr Pro  Asp Ala Glu Ile Ile  Lys Thr Glu Arg Arg  Gly Trp Gly
    1145                 1150                 1155
```

```
Leu Arg  Thr Lys Arg Ser Ile  Lys Lys Gly Glu Phe  Val Asn Glu
    1160                 1165                 1170


Tyr Val  Gly Glu Leu Ile Asp  Glu Glu Glu Cys Arg  Leu Arg Ile
    1175                 1180                 1185


Lys Arg  Ala His Glu Asn Ser  Val Thr Asn Phe Tyr  Met Leu Thr
    1190                 1195                 1200


Val Thr  Lys Asp Arg Ile Ile  Asp Ala Gly Pro Lys  Gly Asn Tyr
    1205                 1210                 1215


Ser Arg  Phe Met Asn His Ser  Cys Asn Pro Asn Cys  Glu Thr Gln
    1220                 1225                 1230


Lys Trp  Thr Val Asn Gly Asp  Val Arg Val Gly Leu  Phe Ala Leu
    1235                 1240                 1245


Cys Asp  Ile Pro Ala Gly Met  Glu Leu Thr Phe Asn  Tyr Asn Leu
    1250                 1255                 1260


Asp Cys  Leu Gly Asn Gly Arg  Thr Glu Cys His Cys  Gly Ala Asp
    1265                 1270                 1275


Asn Cys  Ser Gly Phe Leu Gly  Val Arg Pro Lys Ser  Ala Cys Ala
    1280                 1285                 1290


Ser Thr  Asn Glu Glu Lys Ala  Lys Asn Ala Lys Leu  Lys Gln Lys
    1295                 1300                 1305


Arg Arg  Lys Ile Lys Thr Glu  Pro Lys Gln Met His  Glu Asp Tyr
    1310                 1315                 1320


Cys Phe  Gln Cys Gly Asp Gly  Gly Glu Leu Val Met  Cys Asp Lys
    1325                 1330                 1335


Lys Asp  Cys Pro Lys Ala Tyr  His Leu Leu Cys Leu  Asn Leu Thr
    1340                 1345                 1350


Gln Pro  Pro Tyr Gly Lys Trp  Glu Cys Pro Trp His  Gln Cys Asp
    1355                 1360                 1365


Glu Cys  Ser Ser Ala Ala Val  Ser Phe Cys Glu Phe  Cys Pro His
    1370                 1375                 1380
```

```
Ser Phe  Cys Lys Asp His Glu  Lys Gly Ala Leu Val  Pro Ser Ala
    1385                1390                1395


Leu Glu  Gly Arg Leu Cys Cys  Ser Glu His Asp Pro  Met Ala Pro
    1400                1405                1410


Val Ser  Pro Glu Tyr Trp Ser  Lys Ile Lys Cys Lys  Trp Glu Ser
    1415                1420                1425


Gln Asp  His Gly Glu Glu Val  Lys Glu
    1430                1435


<210>  92
<211>  850
<212>  PRT
<213>  Homo sapiens

<400>  92

Met Thr Ser His Tyr Val Ile Ala Ile Phe Ala Leu Met Ser Ser Cys
1               5                   10                  15


Leu Ala Thr Ala Gly Pro Glu Pro Gly Ala Leu Cys Glu Leu Ser Pro
            20                  25                  30


Val Ser Ala Ser His Pro Val Gln Ala Leu Met Glu Ser Phe Thr Val
        35                  40                  45


Leu Ser Gly Cys Ala Ser Arg Gly Thr Thr Gly Leu Pro Gln Glu Val
    50                  55                  60


His Val Leu Asn Leu Arg Thr Ala Gly Gln Gly Pro Gly Gln Leu Gln
65                  70                  75                  80


Arg Glu Val Thr Leu His Leu Asn Pro Ile Ser Ser Val His Ile His
                85                  90                  95


His Lys Ser Val Val Phe Leu Leu Asn Ser Pro His Pro Leu Val Trp
            100                 105                 110


His Leu Lys Thr Glu Arg Leu Ala Thr Gly Val Ser Arg Leu Phe Leu
        115                 120                 125


Val Ser Glu Gly Ser Val Val Gln Phe Ser Ser Ala Asn Phe Ser Leu
    130                 135                 140
```

```
Thr Ala Glu Thr Glu Glu Arg Asn Phe Pro His Gly Asn Glu His Leu
145                 150                 155                 160

Leu Asn Trp Ala Arg Lys Glu Tyr Gly Ala Val Thr Ser Phe Thr Glu
                165                 170                 175

Leu Lys Ile Ala Arg Asn Ile Tyr Ile Lys Val Gly Glu Asp Gln Val
            180                 185                 190

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

Leu Ala Glu Tyr Leu Gln Pro Lys Ala Ala Glu Gly Cys Val Met Ser
    210                 215                 220

Ser Gln Pro Gln Asn Glu Glu Val His Ile Ile Glu Leu Ile Thr Pro
225                 230                 235                 240

Asn Ser Asn Pro Tyr Ser Ala Phe Gln Val Asp Ile Thr Ile Asp Ile
                245                 250                 255

Arg Pro Ser Gln Glu Asp Leu Glu Val Val Lys Asn Leu Ile Leu Ile
            260                 265                 270

Leu Lys Cys Lys Lys Ser Val Asn Trp Val Ile Lys Ser Phe Asp Val
        275                 280                 285

Lys Gly Ser Leu Lys Ile Ile Ala Pro Asn Ser Ile Gly Phe Gly Lys
    290                 295                 300

Glu Ser Glu Arg Ser Met Thr Met Thr Lys Ser Ile Arg Asp Asp Ile
305                 310                 315                 320

Pro Ser Thr Gln Gly Asn Leu Val Lys Trp Ala Leu Asp Asn Gly Tyr
                325                 330                 335

Ser Pro Ile Thr Ser Tyr Thr Met Ala Pro Val Ala Asn Arg Phe His
            340                 345                 350

Leu Arg Leu Glu Asn Asn Glu Glu Met Gly Asp Glu Glu Val His Thr
        355                 360                 365

Ile Pro Pro Glu Leu Arg Ile Leu Leu Asp Pro Gly Ala Leu Pro Ala
    370                 375                 380
```

```
Leu Gln Asn Pro Pro Ile Arg Gly Gly Glu Gly Gln Asn Gly Gly Leu
385                 390                 395                 400

Pro Phe Pro Phe Pro Asp Ile Ser Arg Arg Val Trp Asn Glu Glu Gly
                405                 410                 415

Glu Asp Gly Leu Pro Arg Pro Lys Asp Pro Val Ile Pro Ser Ile Gln
            420                 425                 430

Leu Phe Pro Gly Leu Arg Glu Pro Glu Glu Val Gln Gly Ser Val Asp
        435                 440                 445

Ile Ala Leu Ser Val Lys Cys Asp Asn Glu Lys Met Ile Val Ala Val
    450                 455                 460

Glu Lys Asp Ser Phe Gln Ala Ser Gly Tyr Ser Gly Met Asp Val Thr
465                 470                 475                 480

Leu Leu Asp Pro Thr Cys Lys Ala Lys Met Asn Gly Thr His Phe Val
                485                 490                 495

Leu Glu Ser Pro Leu Asn Gly Cys Gly Thr Arg Pro Arg Trp Ser Ala
            500                 505                 510

Leu Asp Gly Val Val Tyr Tyr Asn Ser Ile Val Ile Gln Val Pro Ala
        515                 520                 525

Leu Gly Asp Ser Ser Gly Trp Pro Asp Gly Tyr Glu Asp Leu Glu Ser
    530                 535                 540

Gly Asp Asn Gly Phe Pro Gly Asp Met Asp Glu Gly Asp Ala Ser Leu
545                 550                 555                 560

Phe Thr Arg Pro Glu Ile Val Val Phe Asn Cys Ser Leu Gln Gln Val
                565                 570                 575

Arg Asn Pro Ser Ser Phe Gln Glu Gln Pro His Gly Asn Ile Thr Phe
            580                 585                 590

Asn Met Glu Leu Tyr Asn Thr Asp Leu Phe Leu Val Pro Ser Gln Gly
        595                 600                 605

Val Phe Ser Val Pro Glu Asn Gly His Val Tyr Val Glu Val Ser Val
    610                 615                 620
```

```
Thr Lys Ala Glu Gln Glu Leu Gly Phe Ala Ile Gln Thr Cys Phe Ile
625                 630                 635                 640

Ser Pro Tyr Ser Asn Pro Asp Arg Met Ser His Tyr Thr Ile Ile Glu
                645                 650                 655

Asn Ile Cys Pro Lys Asp Glu Ser Val Lys Phe Tyr Ser Pro Lys Arg
            660                 665                 670

Val His Phe Pro Ile Pro Gln Ala Asp Met Asp Lys Lys Arg Phe Ser
        675                 680                 685

Phe Val Phe Lys Pro Val Phe Asn Thr Ser Leu Leu Phe Leu Gln Cys
    690                 695                 700

Glu Leu Thr Leu Cys Thr Lys Met Glu Lys His Pro Gln Lys Leu Pro
705                 710                 715                 720

Lys Cys Val Pro Pro Asp Glu Ala Cys Thr Ser Leu Asp Ala Ser Ile
                725                 730                 735

Ile Trp Ala Met Met Gln Asn Lys Lys Thr Phe Thr Lys Pro Leu Ala
            740                 745                 750

Val Ile His His Glu Ala Glu Ser Lys Glu Lys Gly Pro Ser Met Lys
        755                 760                 765

Glu Pro Asn Pro Ile Ser Pro Pro Ile Phe His Gly Leu Asp Thr Leu
    770                 775                 780

Thr Val Met Gly Ile Ala Phe Ala Ala Phe Val Ile Gly Ala Leu Leu
785                 790                 795                 800

Thr Gly Ala Leu Trp Tyr Ile Tyr Ser His Thr Gly Glu Thr Ala Gly
                805                 810                 815

Arg Gln Gln Val Pro Thr Ser Pro Pro Ala Ser Glu Asn Ser Ser Ala
            820                 825                 830

Ala His Ser Ile Gly Ser Thr Gln Ser Thr Pro Cys Ser Ser Ser Ser
        835                 840                 845

Thr Ala
    850
```

```
<210>  93
<211>  850
<212>  PRT
<213>  Homo sapiens

<400>  93

Met Thr Ser His Tyr Val Ile Ala Ile Phe Ala Leu Met Ser Ser Cys
1               5                   10                  15


Leu Ala Thr Ala Gly Pro Glu Pro Gly Ala Leu Cys Glu Leu Ser Pro
            20                  25                  30


Val Ser Ala Ser His Pro Val Gln Ala Leu Met Glu Ser Phe Thr Val
        35                  40                  45


Leu Ser Gly Cys Ala Ser Arg Gly Thr Thr Gly Leu Pro Gln Glu Val
    50                  55                  60


His Val Leu Asn Leu Arg Thr Ala Gly Gln Gly Pro Gly Gln Leu Gln
65                  70                  75                  80


Arg Glu Val Thr Leu His Leu Asn Pro Ile Ser Ser Val His Ile His
                85                  90                  95


His Lys Ser Val Val Phe Leu Leu Asn Ser Pro His Pro Leu Val Trp
            100                 105                 110


His Leu Lys Thr Glu Arg Leu Ala Thr Gly Val Ser Arg Leu Phe Leu
        115                 120                 125


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


Thr Ala Glu Thr Glu Glu Arg Asn Phe Pro His Gly Asn Glu His Leu
145                 150                 155                 160


Leu Asn Trp Ala Arg Lys Glu Tyr Gly Ala Val Thr Ser Phe Thr Glu
                165                 170                 175


Leu Lys Ile Ala Arg Asn Ile Tyr Ile Lys Val Gly Glu Asp Gln Val
            180                 185                 190


Phe Pro Pro Lys Cys Asn Ile Gly Lys Asn Phe Leu Ser Leu Asn Tyr
        195                 200                 205
```

```
Leu Ala Glu Tyr Leu Gln Pro Lys Ala Ala Glu Gly Cys Val Met Ser
    210                 215                 220

Ser Gln Pro Gln Asn Glu Glu Val His Ile Ile Glu Leu Ile Thr Pro
225                 230                 235                 240

Asn Ser Asn Pro Tyr Ser Ala Phe Gln Val Asp Ile Thr Ile Asp Ile
                245                 250                 255

Arg Pro Ser Gln Glu Asp Leu Glu Val Val Lys Asn Leu Ile Leu Ile
            260                 265                 270

Leu Lys Cys Lys Lys Ser Val Asn Trp Val Ile Lys Ser Phe Asp Val
        275                 280                 285

Lys Gly Ser Leu Lys Ile Ile Ala Pro Asn Ser Ile Gly Phe Gly Lys
    290                 295                 300

Glu Ser Glu Arg Ser Met Thr Met Thr Lys Ser Ile Arg Asp Asp Ile
305                 310                 315                 320

Pro Ser Thr Gln Gly Asn Leu Val Lys Trp Ala Leu Asp Asn Gly Tyr
                325                 330                 335

Ser Pro Ile Thr Ser Tyr Thr Met Ala Pro Val Ala Asn Arg Phe His
            340                 345                 350

Leu Arg Leu Glu Asn Asn Glu Glu Met Gly Asp Glu Glu Val His Thr
        355                 360                 365

Ile Pro Pro Glu Leu Arg Ile Leu Leu Asp Pro Gly Ala Leu Pro Ala
    370                 375                 380

Leu Gln Asn Pro Pro Ile Arg Gly Gly Glu Gly Gln Asn Gly Gly Leu
385                 390                 395                 400

Pro Phe Pro Phe Pro Asp Ile Ser Arg Arg Val Trp Asn Glu Glu Gly
                405                 410                 415

Glu Asp Gly Leu Pro Arg Pro Lys Asp Pro Val Ile Pro Ser Ile Gln
            420                 425                 430

Leu Phe Pro Gly Leu Arg Glu Pro Glu Glu Val Gln Gly Ser Val Asp
        435                 440                 445
```

```
Ile Ala Leu Ser Val Lys Cys Asp Asn Glu Lys Met Ile Val Ala Val
    450                 455                 460

Glu Lys Asp Ser Phe Gln Ala Ser Gly Tyr Ser Gly Met Asp Val Thr
465                 470                 475                 480

Leu Leu Asp Pro Thr Cys Lys Ala Lys Met Asn Gly Thr His Phe Val
                485                 490                 495

Leu Glu Ser Pro Leu Asn Gly Cys Gly Thr Arg Pro Arg Trp Ser Ala
            500                 505                 510

Leu Asp Gly Val Val Tyr Tyr Asn Ser Ile Val Ile Gln Val Pro Ala
        515                 520                 525

Leu Gly Asp Ser Ser Gly Trp Pro Asp Gly Tyr Glu Asp Leu Glu Ser
    530                 535                 540

Gly Asp Asn Gly Phe Pro Gly Asp Met Asp Glu Gly Asp Ala Ser Leu
545                 550                 555                 560

Phe Thr Arg Pro Glu Ile Val Val Phe Asn Cys Ser Leu Gln Gln Val
                565                 570                 575

Arg Asn Pro Ser Ser Phe Gln Glu Gln Pro His Gly Asn Ile Thr Phe
            580                 585                 590

Asn Met Glu Leu Tyr Asn Thr Asp Leu Phe Leu Val Pro Ser Gln Gly
        595                 600                 605

Val Phe Ser Val Pro Glu Asn Gly His Val Tyr Val Glu Val Ser Val
    610                 615                 620

Thr Lys Ala Glu Gln Glu Leu Gly Phe Ala Ile Gln Thr Cys Phe Ile
625                 630                 635                 640

Ser Pro Tyr Ser Asn Pro Asp Arg Met Ser His Tyr Thr Ile Ile Glu
                645                 650                 655

Asn Ile Cys Pro Lys Asp Glu Ser Val Lys Phe Tyr Ser Pro Lys Arg
            660                 665                 670

Val His Phe Pro Ile Pro Gln Ala Asp Met Asp Lys Lys Arg Phe Ser
        675                 680                 685
```

```
Phe Val Phe Lys Pro Val Phe Asn Thr Ser Leu Leu Phe Leu Gln Cys
    690                 695                 700


Glu Leu Thr Leu Cys Thr Lys Met Glu Lys His Pro Gln Lys Leu Pro
705                 710                 715                 720


Lys Cys Val Pro Pro Asp Glu Ala Cys Thr Ser Leu Asp Ala Ser Ile
                725                 730                 735


Ile Trp Ala Met Met Gln Asn Lys Lys Thr Phe Thr Lys Pro Leu Ala
            740                 745                 750


Val Ile His His Glu Ala Glu Ser Lys Glu Lys Gly Pro Ser Met Lys
        755                 760                 765


Glu Pro Asn Pro Ile Ser Pro Pro Ile Phe His Gly Leu Asp Thr Leu
    770                 775                 780


Thr Val Met Gly Ile Ala Phe Ala Ala Phe Val Ile Gly Ala Leu Leu
785                 790                 795                 800


Thr Gly Ala Leu Trp Tyr Ile Tyr Ser His Thr Gly Glu Thr Ala Gly
                805                 810                 815


Arg Gln Gln Val Pro Thr Ser Pro Pro Ala Ser Glu Asn Ser Ser Ala
            820                 825                 830


Ala His Ser Ile Gly Ser Thr Gln Ser Thr Pro Cys Ser Ser Ser Ser
        835                 840                 845


Thr Ala
    850


<210>  94
<211>  851
<212>  PRT
<213>  Homo sapiens

<400>  94

Met Thr Ser His Tyr Val Ile Ala Ile Phe Ala Leu Met Ser Ser Cys
1               5                   10                  15


Leu Ala Thr Ala Gly Pro Glu Pro Gly Ala Leu Cys Glu Leu Ser Pro
            20                  25                  30
```

```
Val Ser Ala Ser His Pro Val Gln Ala Leu Met Glu Ser Phe Thr Val
        35                  40                  45

Leu Ser Gly Cys Ala Ser Arg Gly Thr Thr Gly Leu Pro Gln Glu Val
    50                  55                  60

His Val Leu Asn Leu Arg Thr Ala Gly Gln Gly Pro Gly Gln Leu Gln
65                  70                  75                  80

Arg Glu Val Thr Leu His Leu Asn Pro Ile Ser Ser Val His Ile His
                85                  90                  95

His Lys Ser Val Val Phe Leu Leu Asn Ser Pro His Pro Leu Val Trp
            100                 105                 110

His Leu Lys Thr Glu Arg Leu Ala Thr Gly Val Ser Arg Leu Phe Leu
        115                 120                 125

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

Thr Ala Glu Thr Glu Glu Arg Asn Phe Pro His Gly Asn Glu His Leu
145                 150                 155                 160

Leu Asn Trp Ala Arg Lys Glu Tyr Gly Ala Val Thr Ser Phe Thr Glu
                165                 170                 175

Leu Lys Ile Ala Arg Asn Ile Tyr Ile Lys Val Gly Glu Asp Gln Val
            180                 185                 190

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

Leu Ala Glu Tyr Leu Gln Pro Lys Ala Ala Glu Gly Cys Val Met Ser
    210                 215                 220

Ser Gln Pro Gln Asn Glu Glu Val His Ile Ile Glu Leu Ile Thr Pro
225                 230                 235                 240

Asn Ser Asn Pro Tyr Ser Ala Phe Gln Val Asp Ile Thr Ile Asp Ile
                245                 250                 255

Arg Pro Ser Gln Glu Asp Leu Glu Val Val Lys Asn Leu Ile Leu Ile
            260                 265                 270
```

Leu Lys Cys Lys Lys Ser Val Asn Trp Val Ile Lys Ser Phe Asp Val
275 280 285

Lys Gly Ser Leu Lys Ile Ile Ala Pro Asn Ser Ile Gly Phe Gly Lys
290 295 300

Glu Ser Glu Arg Ser Met Thr Met Thr Lys Ser Ile Arg Asp Asp Ile
305 310 315 320

Pro Ser Thr Gln Gly Asn Leu Val Lys Trp Ala Leu Asp Asn Gly Tyr
325 330 335

Ser Pro Ile Thr Ser Tyr Thr Met Ala Pro Val Ala Asn Arg Phe His
340 345 350

Leu Arg Leu Glu Asn Asn Ala Glu Glu Met Gly Asp Glu Glu Val His
355 360 365

Thr Ile Pro Pro Glu Leu Arg Ile Leu Leu Asp Pro Gly Ala Leu Pro
370 375 380

Ala Leu Gln Asn Pro Pro Ile Arg Gly Gly Glu Gly Gln Asn Gly Gly
385 390 395 400

Leu Pro Phe Pro Phe Pro Asp Ile Ser Arg Arg Val Trp Asn Glu Glu
405 410 415

Gly Glu Asp Gly Leu Pro Arg Pro Lys Asp Pro Val Ile Pro Ser Ile
420 425 430

Gln Leu Phe Pro Gly Leu Arg Glu Pro Glu Glu Val Gln Gly Ser Val
435 440 445

Asp Ile Ala Leu Ser Val Lys Cys Asp Asn Glu Lys Met Ile Val Ala
450 455 460

Val Glu Lys Asp Ser Phe Gln Ala Ser Gly Tyr Ser Gly Met Asp Val
465 470 475 480

Thr Leu Leu Asp Pro Thr Cys Lys Ala Lys Met Asn Gly Thr His Phe
485 490 495

Val Leu Glu Ser Pro Leu Asn Gly Cys Gly Thr Arg Pro Arg Trp Ser
500 505 510

```
Ala Leu Asp Gly Val Val Tyr Tyr Asn Ser Ile Val Ile Gln Val Pro
        515                 520                 525


Ala Leu Gly Asp Ser Ser Gly Trp Pro Asp Gly Tyr Glu Asp Leu Glu
    530                 535                 540


Ser Gly Asp Asn Gly Phe Pro Gly Asp Met Asp Glu Gly Asp Ala Ser
545                 550                 555                 560


Leu Phe Thr Arg Pro Glu Ile Val Val Phe Asn Cys Ser Leu Gln Gln
                565                 570                 575


Val Arg Asn Pro Ser Ser Phe Gln Glu Gln Pro His Gly Asn Ile Thr
            580                 585                 590


Phe Asn Met Glu Leu Tyr Asn Thr Asp Leu Phe Leu Val Pro Ser Gln
        595                 600                 605


Gly Val Phe Ser Val Pro Glu Asn Gly His Val Tyr Val Glu Val Ser
    610                 615                 620


Val Thr Lys Ala Glu Gln Glu Leu Gly Phe Ala Ile Gln Thr Cys Phe
625                 630                 635                 640


Ile Ser Pro Tyr Ser Asn Pro Asp Arg Met Ser His Tyr Thr Ile Ile
                645                 650                 655


Glu Asn Ile Cys Pro Lys Asp Glu Ser Val Lys Phe Tyr Ser Pro Lys
            660                 665                 670


Arg Val His Phe Pro Ile Pro Gln Ala Asp Met Asp Lys Lys Arg Phe
        675                 680                 685


Ser Phe Val Phe Lys Pro Val Phe Asn Thr Ser Leu Leu Phe Leu Gln
    690                 695                 700


Cys Glu Leu Thr Leu Cys Thr Lys Met Glu Lys His Pro Gln Lys Leu
705                 710                 715                 720


Pro Lys Cys Val Pro Pro Asp Glu Ala Cys Thr Ser Leu Asp Ala Ser
                725                 730                 735


Ile Ile Trp Ala Met Met Gln Asn Lys Lys Thr Phe Thr Lys Pro Leu
            740                 745                 750
```

```
Ala Val Ile His His Glu Ala Glu Ser Lys Glu Lys Gly Pro Ser Met
        755                 760                 765


Lys Glu Pro Asn Pro Ile Ser Pro Pro Ile Phe His Gly Leu Asp Thr
    770                 775                 780


Leu Thr Val Met Gly Ile Ala Phe Ala Ala Phe Val Ile Gly Ala Leu
785                 790                 795                 800


Leu Thr Gly Ala Leu Trp Tyr Ile Tyr Ser His Thr Gly Glu Thr Ala
                805                 810                 815


Gly Arg Gln Gln Val Pro Thr Ser Pro Pro Ala Ser Glu Asn Ser Ser
            820                 825                 830


Ala Ala His Ser Ile Gly Ser Thr Gln Ser Thr Pro Cys Ser Ser Ser
        835                 840                 845


Ser Thr Ala
    850


<210>  95
<211>  373
<212>  PRT
<213>  Homo sapiens

<400>  95

Met Ala Ser Lys Pro Glu Lys Arg Val Ala Ser Ser Val Phe Ile Thr
1               5                   10                  15


Leu Ala Pro Pro Arg Arg Asp Val Ala Val Ala Glu Glu Val Arg Gln
            20                  25                  30


Ala Val Cys Glu Ala Arg Arg Gly Arg Pro Trp Glu Ala Pro Ala Pro
        35                  40                  45


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


Thr Pro Gly Arg Ala Ala Ala Thr Val Pro Ala Ala Pro Met Gln Leu
65                  70                  75                  80


Phe Asn Gly Gly Cys Pro Pro Pro Pro Pro Val Leu Asp Gly Glu Asp
                85                  90                  95
```

```
Val Leu Pro Asp Leu Asp Leu Leu Pro Pro Pro Pro Pro Pro Pro Pro
            100                 105                 110

Val Leu Leu Pro Ser Glu Glu Glu Ala Pro Ala Pro Met Gly Ala Ser
        115                 120                 125

Leu Ile Ala Asp Leu Glu Gln Leu His Leu Ser Pro Pro Pro Pro Pro
    130                 135                 140

Pro Gln Ala Pro Ala Glu Gly Pro Ser Val Gln Pro Gly Pro Leu Arg
145                 150                 155                 160

Pro Met Glu Glu Glu Leu Pro Pro Pro Pro Ala Glu Pro Val Glu Lys
                165                 170                 175

Gly Ala Ser Thr Asp Ile Cys Ala Phe Cys His Lys Thr Val Ser Pro
            180                 185                 190

Arg Glu Leu Ala Val Glu Ala Met Lys Arg Gln Tyr His Ala Gln Cys
        195                 200                 205

Phe Thr Cys Arg Thr Cys Arg Arg Gln Leu Ala Gly Gln Ser Phe Tyr
    210                 215                 220

Gln Lys Asp Gly Arg Pro Leu Cys Glu Pro Cys Tyr Gln Asp Thr Leu
225                 230                 235                 240

Glu Arg Cys Gly Lys Cys Gly Glu Val Val Arg Asp His Ile Ile Arg
                245                 250                 255

Ala Leu Gly Gln Ala Phe His Pro Ser Cys Phe Thr Cys Val Thr Cys
            260                 265                 270

Ala Arg Cys Ile Gly Asp Glu Ser Phe Ala Leu Gly Ser Gln Asn Glu
        275                 280                 285

Val Tyr Cys Leu Asp Asp Phe Tyr Arg Lys Phe Ala Pro Val Cys Ser
    290                 295                 300

Ile Cys Glu Asn Pro Ile Ile Pro Arg Asp Gly Lys Asp Ala Phe Lys
305                 310                 315                 320

Ile Glu Cys Met Gly Arg Asn Phe His Glu Asn Cys Tyr Arg Cys Glu
                325                 330                 335
```

```
Asp Cys Arg Ile Leu Leu Ser Val Glu Pro Thr Asp Gln Gly Cys Tyr
            340                 345                 350


Pro Leu Asn Asn His Leu Phe Cys Lys Pro Cys His Val Lys Arg Ser
        355                 360                 365


Ala Ala Gly Cys Cys
    370


<210>  96
<211>  374
<212>  PRT
<213>  Homo sapiens

<400>  96

Met Ala Ser Lys Pro Glu Lys Arg Val Ala Ser Ser Val Phe Ile Thr
1               5                   10                  15


Leu Ala Pro Pro Arg Arg Asp Val Ala Val Ala Glu Glu Val Arg Gln
            20                  25                  30


Ala Val Cys Glu Ala Arg Arg Gly Arg Pro Trp Glu Ala Pro Ala Pro
        35                  40                  45


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


Thr Pro Gly Arg Ala Ala Ala Thr Val Pro Ala Ala Pro Met Gln Leu
65                  70                  75                  80


Phe Asn Gly Gly Cys Pro Pro Pro Pro Pro Val Leu Asp Gly Glu Asp
                85                  90                  95


Val Leu Pro Asp Leu Asp Leu Leu Pro Pro Pro Pro Pro Pro Pro Pro
            100                 105                 110


Val Leu Leu Pro Ser Glu Glu Glu Ala Pro Ala Pro Met Gly Ala Ser
        115                 120                 125


Leu Ile Ala Asp Leu Glu Gln Leu His Leu Ser Pro Pro Pro Pro Pro
    130                 135                 140


Pro Gln Ala Pro Ala Glu Gly Pro Ser Val Gln Pro Gly Pro Leu Arg
145                 150                 155                 160
```

```
Pro Met Glu Glu Glu Leu Pro Pro Pro Pro Ala Glu Pro Val Glu Lys
                165                 170                 175

Gly Ala Ser Thr Asp Ile Cys Ala Phe Cys His Lys Thr Val Ser Pro
            180                 185                 190

Arg Glu Leu Ala Val Glu Ala Met Lys Arg Gln Tyr His Ala Gln Cys
        195                 200                 205

Phe Thr Cys Arg Thr Cys Arg Arg Gln Leu Ala Gly Gln Ser Phe Tyr
    210                 215                 220

Gln Lys Asp Gly Arg Pro Leu Cys Glu Pro Cys Tyr Gln Asp Thr Leu
225                 230                 235                 240

Glu Arg Cys Gly Lys Cys Gly Glu Val Val Arg Asp His Ile Ile Arg
                245                 250                 255

Ala Leu Gly Gln Ala Phe His Pro Ser Cys Phe Thr Cys Val Thr Cys
            260                 265                 270

Ala Arg Cys Ile Gly Asp Glu Ser Phe Ala Leu Gly Ser Gln Asn Glu
        275                 280                 285

Val Tyr Cys Leu Asp Asp Phe Tyr Arg Tyr Glu Lys Gly Leu Cys Thr
    290                 295                 300

Gly Trp Gly Ala Gly Thr Gly Arg Asp Pro Ser Arg Val Lys Glu Leu
305                 310                 315                 320

Ser Leu Ser Pro Gly Cys Trp Ala Arg Val Ser Cys Leu Leu Val Tyr
                325                 330                 335

Tyr Lys Glu Tyr Tyr Arg Ala Gly Leu Gly Ala Val Ala His Ala Cys
            340                 345                 350

Asn Pro Ser Thr Leu Gly Gly Arg Gly Gly Trp Ile Thr Arg Ser Gly
        355                 360                 365

Asp Arg Asp His Pro Gly
    370


<210>  97
<211>  276
```

```
<212>  PRT
<213>  Homo sapiens

<400>  97

Met Ala Ser Lys Pro Glu Lys Arg Val Ala Ser Ser Val Phe Ile Thr
1               5                   10                  15


Leu Ala Pro Pro Arg Arg Asp Val Ala Val Ala Glu Glu Val Arg Gln
            20                  25                  30


Ala Val Cys Glu Ala Arg Arg Gly Arg Pro Trp Glu Ala Pro Ala Pro
        35                  40                  45


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


Thr Pro Gly Arg Ala Ala Ala Thr Val Pro Ala Ala Pro Met Gln Leu
65                  70                  75                  80


Phe Asn Gly Asp Ile Cys Ala Phe Cys His Lys Thr Val Ser Pro Arg
                85                  90                  95


Glu Leu Ala Val Glu Ala Met Lys Arg Gln Tyr His Ala Gln Cys Phe
            100                 105                 110


Thr Cys Arg Thr Cys Arg Arg Gln Leu Ala Gly Gln Ser Phe Tyr Gln
        115                 120                 125


Lys Asp Gly Arg Pro Leu Cys Glu Pro Cys Tyr Gln Asp Thr Leu Glu
    130                 135                 140


Arg Cys Gly Lys Cys Gly Glu Val Val Arg Asp His Ile Ile Arg Ala
145                 150                 155                 160


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


Arg Cys Ile Gly Asp Glu Ser Phe Ala Leu Gly Ser Gln Asn Glu Val
            180                 185                 190


Tyr Cys Leu Asp Asp Phe Tyr Arg Lys Phe Ala Pro Val Cys Ser Ile
        195                 200                 205
```

```
Cys Glu Asn Pro Ile Ile Pro Arg Asp Gly Lys Asp Ala Phe Lys Ile
    210                 215                 220


Glu Cys Met Gly Arg Asn Phe His Glu Asn Cys Tyr Arg Cys Glu Asp
225                 230                 235                 240


Cys Arg Ile Leu Leu Ser Val Glu Pro Thr Asp Gln Gly Cys Tyr Pro
                245                 250                 255


Leu Asn Asn His Leu Phe Cys Lys Pro Cys His Val Lys Arg Ser Ala
            260                 265                 270


Ala Gly Cys Cys
        275


<210>  98
<211>  476
<212>  PRT
<213>  Homo sapiens

<400>  98

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


His Gly Gln Gly Leu Arg Phe Ala Ala Gly Glu Leu Ile Thr Leu Leu
            20                  25                  30


Gln Val Pro Asp Gly Gly Trp Trp Glu Gly Glu Lys Glu Asp Gly Leu
        35                  40                  45


Arg Gly Trp Phe Pro Ala Ser Tyr Val Gln Leu Leu Glu Lys Pro Gly
    50                  55                  60


Met Val Pro Pro Pro Pro Gly Glu Glu Ser Gln Thr Val Ile Leu Pro
65                  70                  75                  80


Pro Gly Trp Gln Ser Tyr Leu Ser Pro Gln Gly Arg Arg Tyr Tyr Val
                85                  90                  95


Asn Thr Thr Thr Asn Glu Thr Thr Trp Glu Arg Pro Ser Ser Ser Pro
            100                 105                 110


Gly Ile Pro Ala Ser Pro Gly Ser His Arg Ser Ser Leu Pro Pro Thr
        115                 120                 125
```

```
Val Asn Gly Tyr His Ala Ser Gly Thr Pro Ala His Pro Pro Glu Thr
    130                 135                 140

Ala His Met Ser Val Arg Lys Ser Thr Gly Asp Ser Gln Asn Leu Gly
145                 150                 155                 160

Ser Ser Ser Pro Ser Lys Lys Gln Ser Lys Glu Asn Thr Ile Thr Ile
                165                 170                 175

Asn Cys Val Thr Phe Pro His Pro Asp Thr Met Pro Glu Gln Gln Leu
            180                 185                 190

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

Lys Asp Pro Gln Gly Asn Gly Thr Val Ala Gly Phe Glu Leu Leu Leu
    210                 215                 220

Gln Lys Gln Leu Lys Gly Lys Gln Met Gln Lys Glu Met Ser Glu Phe
225                 230                 235                 240

Ile Arg Glu Arg Ile Lys Ile Glu Glu Asp Tyr Ala Lys Asn Leu Ala
                245                 250                 255

Lys Leu Ser Gln Asn Ser Leu Ala Ser Gln Glu Glu Gly Ser Leu Gly
            260                 265                 270

Glu Ala Trp Ala Gln Val Lys Lys Ser Leu Ala Asp Glu Ala Glu Val
        275                 280                 285

His Leu Lys Phe Ser Ala Lys Leu His Ser Glu Val Glu Lys Pro Leu
    290                 295                 300

Met Asn Phe Arg Glu Asn Phe Lys Lys Asp Met Lys Lys Cys Asp His
305                 310                 315                 320

His Ile Ala Asp Leu Arg Lys Gln Leu Ala Ser Arg Tyr Ala Ser Val
                325                 330                 335

Glu Lys Ala Arg Lys Ala Leu Thr Glu Arg Gln Arg Asp Leu Glu Met
            340                 345                 350

Lys Thr Gln Gln Leu Glu Ile Lys Leu Ser Asn Lys Thr Glu Glu Asp
        355                 360                 365
```

```
Ile Lys Lys Ala Arg Arg Lys Ser Thr Gln Ala Gly Asp Asp Leu Met
    370                 375                 380


Arg Cys Val Asp Leu Tyr Asn Gln Ala Gln Ser Lys Trp Phe Glu Glu
385                 390                 395                 400


Met Val Thr Thr Thr Leu Glu Leu Glu Arg Leu Glu Val Glu Arg Val
                405                 410                 415


Glu Met Ile Arg Gln His Leu Cys Gln Tyr Thr Gln Leu Arg His Glu
            420                 425                 430


Thr Asp Met Phe Asn Gln Ser Thr Val Glu Pro Val Asp Gln Leu Leu
        435                 440                 445


Arg Lys Val Asp Pro Ala Lys Asp Arg Glu Leu Trp Val Arg Glu His
    450                 455                 460


Lys Thr Gly Asn Ile Arg Pro Val Asp Met Glu Ile
465                 470                 475


<210>  99
<211>  416
<212>  PRT
<213>  Homo sapiens

<400>  99

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


Val Ile Leu Pro Pro Gly Trp Gln Ser Tyr Leu Ser Pro Gln Gly Arg
            20                  25                  30


Arg Tyr Tyr Val Asn Thr Thr Thr Asn Glu Thr Thr Trp Glu Arg Pro
        35                  40                  45


Ser Ser Ser Pro Gly Ile Pro Ala Ser Pro Gly Ser His Arg Ser Ser
    50                  55                  60


Leu Pro Pro Thr Val Asn Gly Tyr His Ala Ser Gly Thr Pro Ala His
65                  70                  75                  80


Pro Pro Glu Thr Ala His Met Ser Val Arg Lys Ser Thr Gly Asp Ser
                85                  90                  95
```

```
Gln Asn Leu Gly Ser Ser Ser Pro Ser Lys Lys Gln Ser Lys Glu Asn
            100                 105                 110

Thr Ile Thr Ile Asn Cys Val Thr Phe Pro His Pro Asp Thr Met Pro
        115                 120                 125

Glu Gln Gln Leu Leu Lys Pro Thr Glu Trp Ser Tyr Cys Asp Tyr Phe
    130                 135                 140

Trp Ala Asp Lys Lys Asp Pro Gln Gly Asn Gly Thr Val Ala Gly Phe
145                 150                 155                 160

Glu Leu Leu Leu Gln Lys Gln Leu Lys Gly Lys Gln Met Gln Lys Glu
                165                 170                 175

Met Ser Glu Phe Ile Arg Glu Arg Ile Lys Ile Glu Glu Asp Tyr Ala
            180                 185                 190

Lys Asn Leu Ala Lys Leu Ser Gln Asn Ser Leu Ala Ser Gln Glu Glu
        195                 200                 205

Gly Ser Leu Gly Glu Ala Trp Ala Gln Val Lys Lys Ser Leu Ala Asp
    210                 215                 220

Glu Ala Glu Val His Leu Lys Phe Ser Ala Lys Leu His Ser Glu Val
225                 230                 235                 240

Glu Lys Pro Leu Met Asn Phe Arg Glu Asn Phe Lys Lys Asp Met Lys
                245                 250                 255

Lys Cys Asp His His Ile Ala Asp Leu Arg Lys Gln Leu Ala Ser Arg
            260                 265                 270

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

Asp Leu Glu Met Lys Thr Gln Gln Leu Glu Ile Lys Leu Ser Asn Lys
    290                 295                 300

Thr Glu Glu Asp Ile Lys Lys Ala Arg Arg Lys Ser Thr Gln Ala Gly
305                 310                 315                 320

Asp Asp Leu Met Arg Cys Val Asp Leu Tyr Asn Gln Ala Gln Ser Lys
                325                 330                 335
```

Trp Phe Glu Glu Met Val Thr Thr Thr Leu Glu Leu Glu Arg Leu Glu
340 345 350

Val Glu Arg Val Glu Met Ile Arg Gln His Leu Cys Gln Tyr Thr Gln
355 360 365

Leu Arg His Glu Thr Asp Met Phe Asn Gln Ser Thr Val Glu Pro Val
370 375 380

Asp Gln Leu Leu Arg Lys Val Asp Pro Ala Lys Asp Arg Glu Leu Trp
385 390 395 400

Val Arg Glu His Lys Thr Gly Asn Ile Arg Pro Val Asp Met Glu Ile
405 410 415

<210> 100
<211> 412
<212> PRT
<213> Homo sapiens

<400> 100

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

Pro Gly Trp Gln Ser Tyr Leu Ser Pro Gln Gly Arg Arg Tyr Tyr Val
20 25 30

Asn Thr Thr Thr Asn Glu Thr Thr Trp Glu Arg Pro Ser Ser Ser Pro
35 40 45

Gly Ile Pro Ala Ser Pro Gly Ser His Arg Ser Ser Leu Pro Pro Thr
50 55 60

Val Asn Gly Tyr His Ala Ser Gly Thr Pro Ala His Pro Pro Glu Thr
65 70 75 80

Ala His Met Ser Val Arg Lys Ser Thr Gly Asp Ser Gln Asn Leu Gly
85 90 95

Ser Ser Ser Pro Ser Lys Lys Gln Ser Lys Glu Asn Thr Ile Thr Ile
100 105 110

Asn Cys Val Thr Phe Pro His Pro Asp Thr Met Pro Glu Gln Gln Leu
115 120 125

```
Leu Lys Pro Thr Glu Trp Ser Tyr Cys Asp Tyr Phe Trp Ala Asp Lys
    130                 135                 140


Lys Asp Pro Gln Gly Asn Gly Thr Val Ala Gly Phe Glu Leu Leu Leu
145                 150                 155                 160


Gln Lys Gln Leu Lys Gly Lys Gln Met Gln Lys Glu Met Ser Glu Phe
                165                 170                 175


Ile Arg Glu Arg Ile Lys Ile Glu Glu Asp Tyr Ala Lys Asn Leu Ala
            180                 185                 190


Lys Leu Ser Gln Asn Ser Leu Ala Ser Gln Glu Glu Gly Ser Leu Gly
        195                 200                 205


Glu Ala Trp Ala Gln Val Lys Lys Ser Leu Ala Asp Glu Ala Glu Val
    210                 215                 220


His Leu Lys Phe Ser Ala Lys Leu His Ser Glu Val Glu Lys Pro Leu
225                 230                 235                 240


Met Asn Phe Arg Glu Asn Phe Lys Lys Asp Met Lys Lys Cys Asp His
                245                 250                 255


His Ile Ala Asp Leu Arg Lys Gln Leu Ala Ser Arg Tyr Ala Ser Val
            260                 265                 270


Glu Lys Ala Arg Lys Ala Leu Thr Glu Arg Gln Arg Asp Leu Glu Met
        275                 280                 285


Lys Thr Gln Gln Leu Glu Ile Lys Leu Ser Asn Lys Thr Glu Glu Asp
    290                 295                 300


Ile Lys Lys Ala Arg Arg Lys Ser Thr Gln Ala Gly Asp Asp Leu Met
305                 310                 315                 320


Arg Cys Val Asp Leu Tyr Asn Gln Ala Gln Ser Lys Trp Phe Glu Glu
                325                 330                 335


Met Val Thr Thr Thr Leu Glu Leu Glu Arg Leu Glu Val Glu Arg Val
            340                 345                 350


Glu Met Ile Arg Gln His Leu Cys Gln Tyr Thr Gln Leu Arg His Glu
        355                 360                 365
```

```
Thr Asp Met Phe Asn Gln Ser Thr Val Glu Pro Val Asp Gln Leu Leu
    370                 375                 380


Arg Lys Val Asp Pro Ala Lys Asp Arg Glu Leu Trp Val Arg Glu His
385                 390                 395                 400


Lys Thr Gly Asn Ile Arg Pro Val Asp Met Glu Ile
                405                 410


<210>  101
<211>  336
<212>  PRT
<213>  Homo sapiens

<400>  101

Met Ser Asn Met Glu Asn Ser Phe Asp Asp Val Ser Cys Leu Ser Pro
1               5                   10                  15


Gln Asn Leu Gly Ser Ser Ser Pro Ser Lys Lys Gln Ser Lys Glu Asn
            20                  25                  30


Thr Ile Thr Ile Asn Cys Val Thr Phe Pro His Pro Asp Thr Met Pro
        35                  40                  45


Glu Gln Gln Leu Leu Lys Pro Thr Glu Trp Ser Tyr Cys Asp Tyr Phe
    50                  55                  60


Trp Ala Asp Lys Lys Asp Pro Gln Gly Asn Gly Thr Val Ala Gly Phe
65                  70                  75                  80


Glu Leu Leu Leu Gln Lys Gln Leu Lys Gly Lys Gln Met Gln Lys Glu
                85                  90                  95


Met Ser Glu Phe Ile Arg Glu Arg Ile Lys Ile Glu Glu Asp Tyr Ala
            100                 105                 110


Lys Asn Leu Ala Lys Leu Ser Gln Asn Ser Leu Ala Ser Gln Glu Glu
        115                 120                 125


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


Glu Ala Glu Val His Leu Lys Phe Ser Ala Lys Leu His Ser Glu Val
145                 150                 155                 160
```

```
Glu Lys Pro Leu Met Asn Phe Arg Glu Asn Phe Lys Lys Asp Met Lys
                165                 170                 175


Lys Cys Asp His His Ile Ala Asp Leu Arg Lys Gln Leu Ala Ser Arg
            180                 185                 190


Tyr Ala Ser Val Glu Lys Ala Arg Lys Ala Leu Thr Glu Arg Gln Arg
        195                 200                 205


Asp Leu Glu Met Lys Thr Gln Gln Leu Glu Ile Lys Leu Ser Asn Lys
    210                 215                 220


Thr Glu Glu Asp Ile Lys Lys Ala Arg Arg Lys Ser Thr Gln Ala Gly
225                 230                 235                 240


Asp Asp Leu Met Arg Cys Val Asp Leu Tyr Asn Gln Ala Gln Ser Lys
                245                 250                 255


Trp Phe Glu Glu Met Val Thr Thr Thr Leu Glu Leu Glu Arg Leu Glu
            260                 265                 270


Val Glu Arg Val Glu Met Ile Arg Gln His Leu Cys Gln Tyr Thr Gln
        275                 280                 285


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


Asp Gln Leu Leu Arg Lys Val Asp Pro Ala Lys Asp Arg Glu Leu Trp
305                 310                 315                 320


Val Arg Glu His Lys Thr Gly Asn Ile Arg Pro Val Asp Met Glu Ile
                325                 330                 335


<210>  102
<211>  258
<212>  PRT
<213>  Homo sapiens

<400>  102

Met Leu Pro Leu Cys Leu Val Ala Ala Leu Leu Leu Ala Ala Gly Pro
1               5                   10                  15


Gly Pro Ser Leu Gly Asp Glu Ala Ile His Cys Pro Pro Cys Ser Glu
            20                  25                  30
```

```
Glu Lys Leu Ala Arg Cys Arg Pro Pro Val Gly Cys Glu Glu Leu Val
        35                  40                  45


Arg Glu Pro Gly Cys Gly Cys Cys Ala Thr Cys Ala Leu Gly Leu Gly
    50                  55                  60


Met Pro Cys Gly Val Tyr Thr Pro Arg Cys Gly Ser Gly Leu Arg Cys
65                  70                  75                  80


Tyr Pro Pro Arg Gly Val Glu Lys Pro Leu His Thr Leu Met His Gly
                85                  90                  95


Gln Gly Val Cys Met Glu Leu Ala Glu Ile Glu Ala Ile Gln Glu Ser
            100                 105                 110


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


Ser Pro Cys Ser Ala His Asp Arg Arg Cys Leu Gln Lys His Phe Ala
    130                 135                 140


Lys Ile Arg Asp Arg Ser Thr Ser Gly Gly Lys Met Lys Val Asn Gly
145                 150                 155                 160


Ala Pro Arg Glu Asp Ala Arg Pro Val Pro Gln Gly Ser Cys Gln Ser
                165                 170                 175


Glu Leu His Arg Ala Leu Glu Arg Leu Ala Ala Ser Gln Ser Arg Thr
            180                 185                 190


His Glu Asp Leu Tyr Ile Ile Pro Ile Pro Asn Cys Asp Arg Asn Gly
        195                 200                 205


Asn Phe His Pro Lys Gln Cys His Pro Ala Leu Asp Gly Gln Arg Gly
    210                 215                 220


Lys Cys Trp Cys Val Asp Arg Lys Thr Gly Val Lys Leu Pro Gly Gly
225                 230                 235                 240


Leu Glu Pro Lys Gly Glu Leu Asp Cys His Gln Leu Ala Asp Ser Phe
                245                 250                 255


Arg Glu
```

```
<210>  103
<211>  1877
<212>  PRT
<213>  Homo sapiens

<400>  103

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


Ser Gly Gly Gly Asp Glu Gly Ala Asp Glu Pro Arg Gly Ala Gly Arg
            20                  25                  30


Lys Ala Ala Ala Ala Asp Gly Arg Gly Met Leu Pro Lys Arg Ala Lys
        35                  40                  45


Ala Pro Gly Gly Gly Gly Gly Met Ala Lys Ala Ser Ala Ala Glu Leu
    50                  55                  60


Lys Val Phe Lys Ser Gly Ser Val Asp Ser Arg Val Pro Gly Gly Pro
65                  70                  75                  80


Pro Ala Ser Asn Leu Arg Lys Gln Lys Ser Leu Thr Asn Leu Ser Phe
                85                  90                  95


Leu Thr Asp Ser Glu Lys Lys Leu Gln Leu Tyr Glu Pro Glu Trp Ser
            100                 105                 110


Asp Asp Met Ala Lys Ala Pro Lys Gly Leu Gly Lys Val Gly Ser Lys
        115                 120                 125


Gly Arg Glu Ala Pro Leu Met Ser Lys Thr Leu Ser Lys Ser Glu His
    130                 135                 140


Ser Leu Phe Gln Ala Lys Gly Ser Pro Ala Gly Gly Ala Lys Thr Pro
145                 150                 155                 160


Leu Ala Pro Leu Ala Pro Asn Leu Gly Lys Pro Ser Arg Ile Pro Arg
                165                 170                 175


Gly Pro Tyr Ala Glu Val Lys Pro Leu Ser Lys Ala Pro Glu Ala Ala
            180                 185                 190


Val Ser Glu Asp Gly Lys Ser Asp Asp Glu Leu Leu Ser Ser Lys Ala
        195                 200                 205
```

```
Lys Ala Gln Lys Ser Ser Gly Pro Val Pro Ser Ala Lys Gly Gln Glu
    210                 215                 220

Glu Arg Ala Phe Leu Lys Val Asp Pro Glu Leu Val Val Thr Val Leu
225                 230                 235                 240

Gly Asp Leu Glu Gln Leu Leu Phe Ser Gln Met Leu Asp Pro Glu Ser
                245                 250                 255

Gln Arg Lys Arg Thr Val Gln Asn Val Leu Asp Leu Arg Gln Asn Leu
            260                 265                 270

Glu Glu Thr Met Ser Ser Leu Arg Gly Ser Gln Val Thr His Ser Ser
        275                 280                 285

Leu Glu Met Thr Cys Tyr Asp Ser Asp Asp Ala Asn Pro Arg Ser Val
    290                 295                 300

Ser Ser Leu Ser Asn Arg Ser Ser Pro Leu Ser Trp Arg Tyr Gly Gln
305                 310                 315                 320

Ser Ser Pro Arg Leu Gln Ala Gly Asp Ala Pro Ser Val Gly Gly Ser
                325                 330                 335

Cys Arg Ser Glu Gly Thr Pro Ala Trp Tyr Met His Gly Glu Arg Ala
            340                 345                 350

His Tyr Ser His Thr Met Pro Met Arg Ser Pro Ser Lys Leu Ser His
        355                 360                 365

Ile Ser Arg Leu Glu Leu Val Glu Ser Leu Asp Ser Asp Glu Val Asp
    370                 375                 380

Leu Lys Ser Gly Tyr Met Ser Asp Ser Asp Leu Met Gly Lys Thr Met
385                 390                 395                 400

Thr Glu Asp Asp Asp Ile Thr Thr Gly Trp Asp Glu Ser Ser Ser Ile
                405                 410                 415

Ser Ser Gly Leu Ser Asp Ala Ser Asp Asn Leu Ser Ser Glu Glu Phe
            420                 425                 430

Asn Ala Ser Ser Ser Leu Asn Ser Leu Pro Ser Thr Pro Thr Ala Ser
        435                 440                 445
```

```
Arg Arg Asn Ser Thr Ile Val Leu Arg Thr Asp Ser Glu Lys Arg Ser
    450                 455                 460

Leu Ala Glu Ser Gly Leu Ser Trp Phe Ser Glu Ser Glu Glu Lys Ala
465                 470                 475                 480

Pro Lys Lys Leu Glu Tyr Asp Ser Gly Ser Leu Lys Met Glu Pro Gly
                485                 490                 495

Thr Ser Lys Trp Arg Arg Glu Arg Pro Glu Ser Cys Asp Asp Ser Ser
            500                 505                 510

Lys Gly Gly Glu Leu Lys Lys Pro Ile Ser Leu Gly His Pro Gly Ser
        515                 520                 525

Leu Lys Lys Gly Lys Thr Pro Pro Val Ala Val Thr Ser Pro Ile Thr
    530                 535                 540

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

Ala Thr Asp Lys Gly Lys Leu Ala Val Lys Asn Thr Gly Leu Gln Arg
                565                 570                 575

Ser Ser Ser Asp Ala Gly Arg Asp Arg Leu Ser Asp Ala Lys Lys Pro
            580                 585                 590

Pro Ser Gly Ile Ala Arg Pro Ser Thr Ser Gly Ser Phe Gly Tyr Lys
        595                 600                 605

Lys Pro Pro Pro Ala Thr Gly Thr Ala Thr Val Met Gln Thr Gly Gly
    610                 615                 620

Ser Ala Thr Leu Ser Lys Ile Gln Lys Ser Ser Gly Ile Pro Val Lys
625                 630                 635                 640

Pro Val Asn Gly Arg Lys Thr Ser Leu Asp Val Ser Asn Ser Ala Glu
                645                 650                 655

Pro Gly Phe Leu Ala Pro Gly Ala Arg Ser Asn Ile Gln Tyr Arg Ser
            660                 665                 670

Leu Pro Arg Pro Ala Lys Ser Ser Ser Met Ser Val Thr Gly Gly Arg
        675                 680                 685
```

```
Gly Gly Pro Arg Pro Val Ser Ser Ser Ile Asp Pro Ser Leu Leu Ser
    690                 695                 700


Thr Lys Gln Gly Gly Leu Thr Pro Ser Arg Leu Lys Glu Pro Thr Lys
705                 710                 715                 720


Val Ala Ser Gly Arg Thr Thr Pro Ala Pro Val Asn Gln Thr Asp Arg
                725                 730                 735


Glu Lys Glu Lys Ala Lys Ala Lys Ala Val Ala Leu Asp Ser Asp Asn
            740                 745                 750


Ile Ser Leu Lys Ser Ile Gly Ser Pro Glu Ser Thr Pro Lys Asn Gln
        755                 760                 765


Ala Ser His Pro Thr Ala Thr Lys Leu Ala Glu Leu Pro Pro Thr Pro
    770                 775                 780


Leu Arg Ala Thr Ala Lys Ser Phe Val Lys Pro Pro Ser Leu Ala Asn
785                 790                 795                 800


Leu Asp Lys Val Asn Ser Asn Ser Leu Asp Leu Pro Ser Ser Ser Asp
                805                 810                 815


Thr Thr His Ala Ser Lys Val Pro Asp Leu His Ala Thr Ser Ser Ala
            820                 825                 830


Ser Gly Gly Pro Leu Pro Ser Cys Phe Thr Pro Ser Pro Ala Pro Ile
        835                 840                 845


Leu Asn Ile Asn Ser Ala Ser Phe Ser Gln Gly Leu Glu Leu Met Ser
    850                 855                 860


Gly Phe Ser Val Pro Lys Glu Thr Arg Met Tyr Pro Lys Leu Ser Gly
865                 870                 875                 880


Leu His Arg Ser Met Glu Ser Leu Gln Met Pro Met Ser Leu Pro Ser
                885                 890                 895


Ala Phe Pro Ser Ser Thr Pro Val Pro Thr Pro Pro Ala Pro Pro Ala
            900                 905                 910


Ala Pro Thr Glu Glu Glu Thr Glu Glu Leu Thr Trp Ser Gly Ser Pro
        915                 920                 925
```

```
Arg Ala Gly Gln Leu Asp Ser Asn Gln Arg Asp Arg Asn Thr Leu Pro
    930                 935                 940


Lys Lys Gly Leu Arg Tyr Gln Leu Gln Ser Gln Glu Glu Thr Lys Glu
945                 950                 955                 960


Arg Arg His Ser His Thr Ile Gly Gly Leu Pro Glu Ser Asp Asp Gln
                965                 970                 975


Ser Glu Leu Pro Ser Pro Pro Ala Leu Pro Met Ser Leu Ser Ala Lys
            980                 985                 990


Gly Gln Leu Thr Asn Ile Val Ser  Pro Thr Ala Ala Thr  Thr Pro Arg
        995                 1000                 1005


Ile Thr  Arg Ser Asn Ser Ile  Pro Thr His Glu Ala  Ala Phe Glu
    1010                 1015                 1020


Leu Tyr  Ser Gly Ser Gln Met  Gly Ser Thr Leu Ser  Leu Ala Glu
    1025                 1030                 1035


Arg Pro  Lys Gly Met Ile Arg  Ser Gly Ser Phe Arg  Asp Pro Thr
    1040                 1045                 1050


Asp Asp  Val His Gly Ser Val  Leu Ser Leu Ala Ser  Ser Ala Ser
    1055                 1060                 1065


Ser Thr  Tyr Ser Ser Ala Glu  Glu Arg Met Gln Ser  Glu Gln Ile
    1070                 1075                 1080


Arg Lys  Leu Arg Arg Glu Leu  Glu Ser Ser Gln Glu  Lys Val Ala
    1085                 1090                 1095


Thr Leu  Thr Ser Gln Leu Ser  Ala Asn Ala Asn Leu  Val Ala Ala
    1100                 1105                 1110


Phe Glu  Gln Ser Leu Val Asn  Met Thr Ser Arg Leu  Arg His Leu
    1115                 1120                 1125


Ala Glu  Thr Ala Glu Glu Lys  Asp Thr Glu Leu Leu  Asp Leu Arg
    1130                 1135                 1140


Glu Thr  Ile Asp Phe Leu Lys  Lys Lys Asn Ser Glu  Ala Gln Ala
    1145                 1150                 1155
```

```
Val Ile  Gln Gly Ala Leu Asn  Ala Ser Glu Thr Thr  Pro Lys Glu
    1160                1165                1170


Leu Arg  Ile Lys Arg Gln Asn  Ser Ser Asp Ser Ile  Ser Ser Leu
    1175                1180                1185


Asn Ser  Ile Thr Ser His Ser  Ser Ile Gly Ser Ser  Lys Asp Ala
    1190                1195                1200


Asp Ala  Lys Lys Lys Lys Lys  Lys Ser Trp Val Tyr  Glu Leu Arg
    1205                1210                1215


Ser Ser  Phe Asn Lys Ala Phe  Ser Ile Lys Lys Gly  Pro Lys Ser
    1220                1225                1230


Ala Ser  Ser Tyr Ser Asp Ile  Glu Glu Ile Ala Thr  Pro Asp Ser
    1235                1240                1245


Ser Ala  Pro Ser Ser Pro Lys  Leu Gln His Gly Ser  Thr Glu Thr
    1250                1255                1260


Ala Ser  Pro Ser Ile Lys Ser  Ser Thr Ser Ser Ser  Val Gly Thr
    1265                1270                1275


Asp Val  Thr Glu Gly Pro Ala  His Pro Ala Pro His  Thr Arg Leu
    1280                1285                1290


Phe His  Ala Asn Glu Glu Glu  Glu Pro Glu Lys Lys  Glu Val Ser
    1295                1300                1305


Glu Leu  Arg Ser Glu Leu Trp  Glu Lys Glu Met Lys  Leu Thr Asp
    1310                1315                1320


Ile Arg  Leu Glu Ala Leu Asn  Ser Ala His Gln Leu  Asp Gln Leu
    1325                1330                1335


Arg Glu  Thr Met His Asn Met  Gln Leu Glu Val Asp  Leu Leu Lys
    1340                1345                1350


Ala Glu  Asn Asp Arg Leu Lys  Val Ala Pro Gly Pro  Ser Ser Gly
    1355                1360                1365


Ser Thr  Pro Gly Gln Val Pro  Gly Ser Ser Ala Leu  Ser Ser Pro
    1370                1375                1380
```

```
Arg Arg  Ser Leu Gly Leu Ala  Leu Thr His Ser Phe  Gly Pro Ser
    1385                 1390                 1395


Leu Ala  Asp Thr Asp Leu Ser  Pro Met Asp Gly Ile  Ser Thr Cys
    1400                 1405                 1410


Gly Pro  Lys Glu Glu Val Thr  Leu Arg Val Val Val  Arg Met Pro
    1415                 1420                 1425


Pro Gln  His Ile Ile Lys Gly  Asp Leu Lys Gln Gln  Glu Phe Phe
    1430                 1435                 1440


Leu Gly  Cys Ser Lys Val Ser  Gly Lys Val Asp Trp  Lys Met Leu
    1445                 1450                 1455


Asp Glu  Ala Val Phe Gln Val  Phe Lys Asp Tyr Ile  Ser Lys Met
    1460                 1465                 1470


Asp Pro  Ala Ser Thr Leu Gly  Leu Ser Thr Glu Ser  Ile His Gly
    1475                 1480                 1485


Tyr Ser  Ile Ser His Val Lys  Arg Val Leu Asp Ala  Glu Pro Pro
    1490                 1495                 1500


Glu Met  Pro Pro Cys Arg Arg  Gly Val Asn Asn Ile  Ser Val Ser
    1505                 1510                 1515


Leu Lys  Gly Leu Lys Glu Lys  Cys Val Asp Ser Leu  Val Phe Glu
    1520                 1525                 1530


Thr Leu  Ile Pro Lys Pro Met  Met Gln His Tyr Ile  Ser Leu Leu
    1535                 1540                 1545


Leu Lys  His Arg Arg Leu Val  Leu Ser Gly Pro Ser  Gly Thr Gly
    1550                 1555                 1560


Lys Thr  Tyr Leu Thr Asn Arg  Leu Ala Glu Tyr Leu  Val Glu Arg
    1565                 1570                 1575


Ser Gly  Arg Glu Val Thr Glu  Gly Ile Val Ser Thr  Phe Asn Met
    1580                 1585                 1590


His Gln  Gln Ser Cys Lys Asp  Leu Gln Leu Tyr Leu  Ser Asn Leu
    1595                 1600                 1605
```

```
Ala Asn  Gln Ile Asp Arg Glu  Thr Gly Ile Gly Asp  Val Pro Leu
    1610                 1615                 1620

Val Ile  Leu Leu Asp Asp Leu  Ser Glu Ala Gly Ser  Ile Ser Glu
    1625                 1630                 1635

Leu Val  Asn Gly Ala Leu Thr  Cys Lys Tyr His Lys  Cys Pro Tyr
    1640                 1645                 1650

Ile Ile  Gly Thr Thr Asn Gln  Pro Val Lys Met Thr  Pro Asn His
    1655                 1660                 1665

Gly Leu  His Leu Ser Phe Arg  Met Leu Thr Phe Ser  Asn Asn Val
    1670                 1675                 1680

Glu Pro  Ala Asn Gly Phe Leu  Val Arg Tyr Leu Arg  Arg Lys Leu
    1685                 1690                 1695

Val Glu  Ser Asp Ser Asp Ile  Asn Ala Asn Lys Glu  Glu Leu Leu
    1700                 1705                 1710

Arg Val  Leu Asp Trp Val Pro  Lys Leu Trp Tyr His  Leu His Thr
    1715                 1720                 1725

Phe Leu  Glu Lys His Ser Thr  Ser Asp Phe Leu Ile  Gly Pro Cys
    1730                 1735                 1740

Phe Phe  Leu Ser Cys Pro Ile  Gly Ile Glu Asp Phe  Arg Thr Trp
    1745                 1750                 1755

Phe Ile  Asp Leu Trp Asn Asn  Ser Ile Ile Pro Tyr  Leu Gln Glu
    1760                 1765                 1770

Gly Ala  Lys Asp Gly Ile Lys  Val His Gly Gln Lys  Ala Ala Trp
    1775                 1780                 1785

Glu Asp  Pro Val Glu Trp Val  Arg Asp Thr Leu Pro  Trp Pro Ser
    1790                 1795                 1800

Ala Gln  Gln Asp Gln Ser Lys  Leu Tyr His Leu Pro  Pro Pro Thr
    1805                 1810                 1815

Val Gly  Pro His Ser Ile Ala  Ser Pro Pro Glu Asp  Arg Thr Val
    1820                 1825                 1830
```

```
Lys Asp  Ser Thr Pro Ser Ser  Leu Asp Ser Asp Pro  Leu Met Ala
    1835                 1840                 1845


Met Leu  Leu Lys Leu Gln Glu  Ala Ala Asn Tyr Ile  Glu Ser Pro
    1850                 1855                 1860


Asp Arg  Glu Thr Ile Leu Asp  Pro Asn Leu Gln Ala  Thr Leu
    1865                 1870                 1875


<210>  104
<211>  1483
<212>  PRT
<213>  Homo sapiens

<400>  104

Met Leu His Leu Pro Leu Pro Arg Ser Gly Arg Thr Val Asn Phe Pro
1               5                   10                  15


Arg Ser Trp Asp Glu Ser Ser Ser Ile Ser Ser Gly Leu Ser Asp Ala
            20                  25                  30


Ser Asp Asn Leu Ser Ser Glu Glu Phe Asn Ala Ser Ser Ser Leu Asn
        35                  40                  45


Ser Leu Pro Ser Thr Pro Thr Ala Ser Arg Arg Asn Ser Thr Ile Val
    50                  55                  60


Leu Arg Thr Asp Ser Glu Lys Arg Ser Leu Ala Glu Ser Gly Leu Ser
65                  70                  75                  80


Trp Phe Ser Glu Ser Glu Glu Lys Ala Pro Lys Lys Leu Glu Tyr Asp
                85                  90                  95


Ser Gly Ser Leu Lys Met Glu Pro Gly Thr Ser Lys Trp Arg Arg Glu
            100                 105                 110


Arg Pro Glu Ser Cys Asp Asp Ser Ser Lys Gly Gly Glu Leu Lys Lys
        115                 120                 125


Pro Ile Ser Leu Gly His Pro Gly Ser Leu Lys Lys Gly Lys Thr Pro
    130                 135                 140


Pro Val Ala Val Thr Ser Pro Ile Thr His Thr Ala Gln Ser Ala Leu
145                 150                 155                 160
```

```
Lys Val Ala Gly Lys Pro Glu Gly Lys Ala Thr Asp Lys Gly Lys Leu
                165                 170                 175

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

Asp Arg Leu Ser Asp Ala Lys Lys Pro Pro Ser Gly Ile Ala Arg Pro
        195                 200                 205

Ser Thr Ser Gly Ser Phe Gly Tyr Lys Lys Pro Pro Pro Ala Thr Gly
    210                 215                 220

Thr Ala Thr Val Met Gln Thr Gly Gly Ser Ala Thr Leu Ser Lys Ile
225                 230                 235                 240

Gln Lys Ser Ser Gly Ile Pro Val Lys Pro Val Asn Gly Arg Lys Thr
                245                 250                 255

Ser Leu Asp Val Ser Asn Ser Ala Glu Pro Gly Phe Leu Ala Pro Gly
            260                 265                 270

Ala Arg Ser Asn Ile Gln Tyr Arg Ser Leu Pro Arg Pro Ala Lys Ser
        275                 280                 285

Ser Ser Met Ser Val Thr Gly Gly Arg Gly Gly Pro Arg Pro Val Ser
    290                 295                 300

Ser Ser Ile Asp Pro Ser Leu Leu Ser Thr Lys Gln Gly Gly Leu Thr
305                 310                 315                 320

Pro Ser Arg Leu Lys Glu Pro Thr Lys Val Ala Ser Gly Arg Thr Thr
                325                 330                 335

Pro Ala Pro Val Asn Gln Thr Asp Arg Glu Lys Glu Lys Ala Lys Ala
            340                 345                 350

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

Ser Pro Glu Ser Thr Pro Lys Asn Gln Ala Ser His Pro Thr Ala Thr
    370                 375                 380

Lys Leu Ala Glu Leu Pro Pro Thr Pro Leu Arg Ala Thr Ala Lys Ser
385                 390                 395                 400
```

```
Phe Val Lys Pro Pro Ser Leu Ala Asn Leu Asp Lys Val Asn Ser Asn
                405                 410                 415

Ser Leu Asp Leu Pro Ser Ser Ser Asp Thr Thr His Ala Ser Lys Val
            420                 425                 430

Pro Asp Leu His Ala Thr Ser Ser Ala Ser Gly Gly Pro Leu Pro Ser
        435                 440                 445

Cys Phe Thr Pro Ser Pro Ala Pro Ile Leu Asn Ile Asn Ser Ala Ser
    450                 455                 460

Phe Ser Gln Gly Leu Glu Leu Met Ser Gly Phe Ser Val Pro Lys Glu
465                 470                 475                 480

Thr Arg Met Tyr Pro Lys Leu Ser Gly Leu His Arg Ser Met Glu Ser
                485                 490                 495

Leu Gln Met Pro Met Ser Leu Pro Ser Ala Phe Pro Ser Ser Thr Pro
            500                 505                 510

Val Pro Thr Pro Pro Ala Pro Pro Ala Ala Pro Thr Glu Glu Glu Thr
        515                 520                 525

Glu Glu Leu Thr Trp Ser Gly Ser Pro Arg Ala Gly Gln Leu Asp Ser
    530                 535                 540

Asn Gln Arg Asp Arg Asn Thr Leu Pro Lys Lys Gly Leu Arg Tyr Gln
545                 550                 555                 560

Leu Gln Ser Gln Glu Glu Thr Lys Glu Arg Arg His Ser His Thr Ile
                565                 570                 575

Gly Gly Leu Pro Glu Ser Asp Asp Gln Ser Glu Leu Pro Ser Pro Pro
            580                 585                 590

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

Ser Pro Thr Ala Ala Thr Thr Pro Arg Ile Thr Arg Ser Asn Ser Ile
    610                 615                 620

Pro Thr His Glu Ala Ala Phe Glu Leu Tyr Ser Gly Ser Gln Met Gly
625                 630                 635                 640
```

```
Ser Thr Leu Ser Leu Ala Glu Arg Pro Lys Gly Met Ile Arg Ser Gly
                645                 650                 655

Ser Phe Arg Asp Pro Thr Asp Asp Val His Gly Ser Val Leu Ser Leu
            660                 665                 670

Ala Ser Ser Ala Ser Ser Thr Tyr Ser Ser Ala Glu Glu Arg Met Gln
        675                 680                 685

Ser Glu Gln Ile Arg Lys Leu Arg Arg Glu Leu Glu Ser Ser Gln Glu
    690                 695                 700

Lys Val Ala Thr Leu Thr Ser Gln Leu Ser Ala Asn Ala Asn Leu Val
705                 710                 715                 720

Ala Ala Phe Glu Gln Ser Leu Val Asn Met Thr Ser Arg Leu Arg His
                725                 730                 735

Leu Ala Glu Thr Ala Glu Glu Lys Asp Thr Glu Leu Leu Asp Leu Arg
            740                 745                 750

Glu Thr Ile Asp Phe Leu Lys Lys Lys Asn Ser Glu Ala Gln Ala Val
        755                 760                 765

Ile Gln Gly Ala Leu Asn Ala Ser Glu Thr Thr Pro Lys Glu Leu Arg
    770                 775                 780

Ile Lys Arg Gln Asn Ser Ser Asp Ser Ile Ser Ser Leu Asn Ser Ile
785                 790                 795                 800

Thr Ser His Ser Ser Ile Gly Ser Ser Lys Asp Ala Asp Ala Lys Lys
                805                 810                 815

Lys Lys Lys Lys Ser Trp Leu Arg Ser Ser Phe Asn Lys Ala Phe Ser
            820                 825                 830

Ile Lys Lys Gly Pro Lys Ser Ala Ser Ser Tyr Ser Asp Ile Glu Glu
        835                 840                 845

Ile Ala Thr Pro Asp Ser Ser Ala Pro Ser Ser Pro Lys Leu Gln His
    850                 855                 860

Gly Ser Thr Glu Thr Ala Ser Pro Ser Ile Lys Ser Ser Thr Ser Ser
865                 870                 875                 880
```

Ser Val Gly Thr Asp Val Thr Glu Gly Pro Ala His Pro Ala Pro His
885 890 895

Thr Arg Leu Phe His Ala Asn Glu Glu Glu Glu Pro Glu Lys Lys Glu
900 905 910

Val Ser Glu Leu Arg Ser Glu Leu Trp Glu Lys Glu Met Lys Leu Thr
915 920 925

Asp Ile Arg Leu Glu Ala Leu Asn Ser Ala His Gln Leu Asp Gln Leu
930 935 940

Arg Glu Thr Met His Asn Met Gln Leu Glu Val Asp Leu Leu Lys Ala
945 950 955 960

Glu Asn Asp Arg Leu Lys Val Ala Pro Gly Pro Ser Ser Gly Ser Thr
965 970 975

Pro Gly Gln Val Pro Gly Ser Ser Ala Leu Ser Ser Pro Arg Arg Ser
980 985 990

Leu Gly Leu Ala Leu Thr His Ser Phe Gly Pro Ser Leu Ala Asp Thr
995 1000 1005

Asp Leu Ser Pro Met Asp Gly Ile Ser Thr Cys Gly Pro Lys Glu
1010 1015 1020

Glu Val Thr Leu Arg Val Val Val Arg Met Pro Pro Gln His Ile
1025 1030 1035

Ile Lys Gly Asp Leu Lys Gln Gln Glu Phe Phe Leu Gly Cys Ser
1040 1045 1050

Lys Val Ser Gly Lys Val Asp Trp Lys Met Leu Asp Glu Ala Val
1055 1060 1065

Phe Gln Val Phe Lys Asp Tyr Ile Ser Lys Met Asp Pro Ala Ser
1070 1075 1080

Thr Leu Gly Leu Ser Thr Glu Ser Ile His Gly Tyr Ser Ile Ser
1085 1090 1095

His Val Lys Arg Val Leu Asp Ala Glu Pro Pro Glu Met Pro Pro
1100 1105 1110

```
Cys Arg  Arg Gly Val Asn Asn  Ile Ser Val Ser Leu  Lys Gly Leu
    1115                 1120                 1125

Lys Glu  Lys Cys Val Asp Ser  Leu Val Phe Glu Thr  Leu Ile Pro
    1130                 1135                 1140

Lys Pro  Met Met Gln His Tyr  Ile Ser Leu Leu Leu  Lys His Arg
    1145                 1150                 1155

Arg Leu  Val Leu Ser Gly Pro  Ser Gly Thr Gly Lys  Thr Tyr Leu
    1160                 1165                 1170

Thr Asn  Arg Leu Ala Glu Tyr  Leu Val Glu Arg Ser  Gly Arg Glu
    1175                 1180                 1185

Val Thr  Glu Gly Ile Val Ser  Thr Phe Asn Met His  Gln Gln Ser
    1190                 1195                 1200

Cys Lys  Asp Leu Gln Leu Tyr  Leu Ser Asn Leu Ala  Asn Gln Ile
    1205                 1210                 1215

Asp Arg  Glu Thr Gly Ile Gly  Asp Val Pro Leu Val  Ile Leu Leu
    1220                 1225                 1230

Asp Asp  Leu Ser Glu Ala Gly  Ser Ile Ser Glu Leu  Val Asn Gly
    1235                 1240                 1245

Ala Leu  Thr Cys Lys Tyr His  Lys Cys Pro Tyr Ile  Ile Gly Thr
    1250                 1255                 1260

Thr Asn  Gln Pro Val Lys Met  Thr Pro Asn His Gly  Leu His Leu
    1265                 1270                 1275

Ser Phe  Arg Met Leu Thr Phe  Ser Asn Asn Val Glu  Pro Ala Asn
    1280                 1285                 1290

Gly Phe  Leu Val Arg Tyr Leu  Arg Arg Lys Leu Val  Glu Ser Asp
    1295                 1300                 1305

Ser Asp  Ile Asn Ala Asn Lys  Glu Glu Leu Leu Arg  Val Leu Asp
    1310                 1315                 1320

Trp Val  Pro Lys Leu Trp Tyr  His Leu His Thr Phe  Leu Glu Lys
    1325                 1330                 1335
```

```
His Ser  Thr Ser Asp Phe Leu  Ile Gly Pro Cys Phe  Phe Leu Ser
    1340                 1345                 1350


Cys Pro  Ile Gly Ile Glu Asp  Phe Arg Thr Trp Phe  Ile Asp Leu
    1355                 1360                 1365


Trp Asn  Asn Ser Ile Ile Pro  Tyr Leu Gln Glu Gly  Ala Lys Asp
    1370                 1375                 1380


Gly Ile  Lys Val His Gly Gln  Lys Ala Ala Trp Glu  Asp Pro Val
    1385                 1390                 1395


Glu Trp  Val Arg Asp Thr Leu  Pro Trp Pro Ser Ala  Gln Gln Asp
    1400                 1405                 1410


Gln Ser  Lys Leu Tyr His Leu  Pro Pro Pro Thr Val  Gly Pro His
    1415                 1420                 1425


Ser Ile  Ala Ser Pro Pro Glu  Asp Arg Thr Val Lys  Asp Ser Thr
    1430                 1435                 1440


Pro Ser  Ser Leu Asp Ser Asp  Pro Leu Met Ala Met  Leu Leu Lys
    1445                 1450                 1455


Leu Gln  Glu Ala Ala Asn Tyr  Ile Glu Ser Pro Asp  Arg Glu Thr
    1460                 1465                 1470


Ile Leu  Asp Pro Asn Leu Gln  Ala Thr Leu
    1475                 1480


<210>  105
<211>  931
<212>  PRT
<213>  Homo sapiens

<400>  105

Met Lys Ile Gln Lys Lys Leu Thr Gly Cys Ser Arg Leu Met Leu Leu
1               5                   10                  15


Cys Leu Ser Leu Glu Leu Leu Leu Glu Ala Gly Ala Gly Asn Ile His
            20                  25                  30


Tyr Ser Val Pro Glu Glu Thr Asp Lys Gly Ser Phe Val Gly Asn Ile
        35                  40                  45
```

```
Ala Lys Asp Leu Gly Leu Gln Pro Gln Glu Leu Ala Asp Gly Gly Val
    50                  55                  60


Arg Ile Val Ser Arg Gly Arg Met Pro Leu Phe Ala Leu Asn Pro Arg
65                  70                  75                  80


Ser Gly Ser Leu Ile Thr Ala Arg Arg Ile Asp Arg Glu Glu Leu Cys
                85                  90                  95


Ala Gln Ser Met Pro Cys Leu Val Ser Phe Asn Ile Leu Val Glu Asp
            100                 105                 110


Lys Met Lys Leu Phe Pro Val Glu Val Glu Ile Ile Asp Ile Asn Asp
        115                 120                 125


Asn Thr Pro Gln Phe Gln Leu Glu Glu Leu Glu Phe Lys Met Asn Glu
    130                 135                 140


Ile Thr Thr Pro Gly Thr Arg Val Ser Leu Pro Phe Gly Gln Asp Leu
145                 150                 155                 160


Asp Val Gly Met Asn Ser Leu Gln Ser Tyr Gln Leu Ser Ser Asn Pro
                165                 170                 175


His Phe Ser Leu Asp Val Gln Gln Gly Ala Asp Gly Pro Gln His Pro
            180                 185                 190


Glu Met Val Leu Gln Ser Pro Leu Asp Arg Glu Glu Glu Ala Val His
        195                 200                 205


His Leu Ile Leu Thr Ala Ser Asp Gly Gly Glu Pro Val Arg Ser Gly
    210                 215                 220


Thr Leu Arg Ile Tyr Ile Gln Val Val Asp Ala Asn Asp Asn Pro Pro
225                 230                 235                 240


Ala Phe Thr Gln Ala Gln Tyr His Ile Asn Val Pro Glu Asn Val Pro
                245                 250                 255


Leu Gly Thr Gln Leu Leu Met Val Asn Ala Thr Asp Pro Asp Glu Gly
            260                 265                 270


Ala Asn Gly Glu Val Thr Tyr Ser Phe His Asn Val Asp His Arg Val
        275                 280                 285
```

```
Ala Gln Ile Phe Arg Leu Asp Ser Tyr Thr Gly Glu Ile Ser Asn Lys
    290                 295                 300


Glu Pro Leu Asp Phe Glu Glu Tyr Lys Met Tyr Ser Met Glu Val Gln
305                 310                 315                 320


Ala Gln Asp Gly Ala Gly Leu Met Ala Lys Val Lys Val Leu Ile Lys
                325                 330                 335


Val Leu Asp Val Asn Asp Asn Ala Pro Glu Val Thr Ile Thr Ser Val
            340                 345                 350


Thr Thr Ala Val Pro Glu Asn Phe Pro Pro Gly Thr Ile Ile Ala Leu
        355                 360                 365


Ile Ser Val His Asp Gln Asp Ser Gly Asp Asn Gly Tyr Thr Thr Cys
    370                 375                 380


Phe Ile Pro Gly Asn Leu Pro Phe Lys Leu Glu Lys Leu Val Asp Asn
385                 390                 395                 400


Tyr Tyr Arg Leu Val Thr Glu Arg Thr Leu Asp Arg Glu Leu Ile Ser
                405                 410                 415


Gly Tyr Asn Ile Thr Ile Thr Ala Ile Asp Gln Gly Thr Pro Ala Leu
            420                 425                 430


Ser Thr Glu Thr His Ile Ser Leu Leu Val Thr Asp Ile Asn Asp Asn
        435                 440                 445


Ser Pro Val Phe His Gln Asp Ser Tyr Ser Ala Tyr Ile Pro Glu Asn
    450                 455                 460


Asn Pro Arg Gly Ala Ser Ile Phe Ser Val Arg Ala His Asp Leu Asp
465                 470                 475                 480


Ser Asn Glu Asn Ala Gln Ile Thr Tyr Ser Leu Ile Glu Asp Thr Ile
                485                 490                 495


Gln Gly Ala Pro Leu Ser Ala Tyr Leu Ser Ile Asn Ser Asp Thr Gly
            500                 505                 510


Val Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln Phe Arg Asp Met
        515                 520                 525
```

```
Gln Leu Lys Val Met Ala Arg Asp Ser Gly Asp Pro Pro Leu Ser Ser
    530                 535                 540

Asn Val Ser Leu Ser Leu Phe Leu Leu Asp Gln Asn Asp Asn Ala Pro
545                 550                 555                 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu
                565                 570                 575

Leu Ala Pro Leu Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu
        595                 600                 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly
    610                 615                 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln
625                 630                 635                 640

Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Arg Ile Ser Asp Ile Leu
            660                 665                 670

Ala Asp Leu Gly Ser Leu Glu Pro Ser Ala Lys Pro Asn Asp Ser Asp
        675                 680                 685

Leu Thr Leu Tyr Leu Val Val Ala Ala Ala Ala Val Ser Cys Val Phe
    690                 695                 700

Leu Ala Phe Val Ile Val Leu Leu Ala His Arg Leu Arg Arg Trp His
705                 710                 715                 720

Lys Ser Arg Leu Leu Gln Ala Ser Gly Gly Gly Leu Ala Ser Met Pro
                725                 730                 735

Gly Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr
            740                 745                 750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu
        755                 760                 765
```

```
Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile Ser Gln Glu Ser
    770                 775                 780


Cys Glu Lys Lys Gly Phe Leu Ser Ala Pro Gln Ser Leu Leu Glu Asp
785                 790                 795                 800


Lys Lys Glu Pro Phe Ser Gln Gln Ala Pro Pro Asn Thr Asp Trp Arg
                805                 810                 815


Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp
            820                 825                 830


Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln
        835                 840                 845


Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr
    850                 855                 860


Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro
865                 870                 875                 880


Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile
                885                 890                 895


Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly
            900                 905                 910


Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys
        915                 920                 925


Glu Lys Lys
    930


<210>  106
<211>  932
<212>  PRT
<213>  Homo sapiens

<400>  106

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


Cys Phe Leu Leu Ala Thr Leu Trp Glu Ala Arg Ala Gly Gln Ile Arg
            20                  25                  30
```

```
Tyr Ser Val Arg Glu Glu Ile Asp Arg Gly Ser Phe Val Gly Asn Ile
        35                  40                  45

Ala Lys Asp Leu Gly Leu Glu Pro Leu Ala Leu Ala Glu Gln Gly Val
    50                  55                  60

Arg Ile Val Ser Arg Gly Arg Ser Gln Leu Phe Ala Leu Asn Pro Arg
65                  70                  75                  80

Ser Gly Ser Leu Val Thr Ala Asn Arg Ile Asp Arg Glu Glu Leu Cys
                85                  90                  95

Ala Gln Ser Ala Pro Cys Leu Leu Asn Phe Asn Ile Leu Leu Glu Asp
            100                 105                 110

Lys Leu Thr Ile Tyr Ser Val Glu Val Glu Ile Thr Asp Ile Asn Asp
        115                 120                 125

Asn Ala Pro Arg Phe Gly Val Glu Glu Leu Glu Leu Lys Ile Ser Glu
    130                 135                 140

Thr Thr Thr Pro Gly Phe Arg Ile Pro Leu Lys Asn Ala His Asp Ala
145                 150                 155                 160

Asp Val Gly Glu Asn Ala Leu Gln Lys Tyr Ala Leu Asn Pro Asn Asp
                165                 170                 175

His Phe Ser Leu Asp Val Arg Arg Gly Ala Asp Gly Asn Lys Tyr Pro
            180                 185                 190

Glu Leu Val Leu Glu Arg Ser Leu Asp Arg Glu Glu Glu Ala Val His
        195                 200                 205

His Leu Val Leu Val Ala Ser Asp Gly Gly Asp Pro Val Leu Ser Gly
    210                 215                 220

Thr Ser Arg Ile Cys Val Lys Val Leu Asp Ala Asn Asp Asn Ala Pro
225                 230                 235                 240

Val Phe Thr Gln Pro Glu Tyr Arg Ile Ser Ile Pro Glu Asn Thr Leu
                245                 250                 255

Val Gly Thr Arg Ile Leu Thr Val Thr Ala Thr Asp Ala Asp Glu Gly
            260                 265                 270
```

```
Tyr Tyr Ala Gln Val Val Tyr Phe Leu Glu Lys Ser Pro Gly Glu Thr
        275                 280                 285

Ser Glu Val Phe Glu Leu Lys Ser Thr Ser Gly Glu Leu Thr Ile Ile
    290                 295                 300

Lys Asp Leu Asp Tyr Glu Asp Ala Thr Phe His Glu Ile Asp Ile Glu
305                 310                 315                 320

Ala Gln Asp Gly Pro Gly Leu Leu Thr Arg Ala Lys Val Ile Val Thr
                325                 330                 335

Val Leu Asp Val Asn Asp Asn Ala Pro Glu Phe Tyr Met Thr Ser Ala
            340                 345                 350

Thr Ser Ser Val Ser Glu Asp Ser Leu Pro Gly Thr Ile Ile Gly Leu
        355                 360                 365

Phe Asn Val His Asp Arg Asp Ser Gly Gln Asn Ala Phe Thr Thr Cys
    370                 375                 380

Ser Leu Pro Glu Asp Leu Pro Phe Lys Leu Glu Lys Ser Val Asp Asn
385                 390                 395                 400

Tyr Tyr Arg Leu Val Thr Thr Arg Ala Leu Asp Arg Glu Gln Phe Ser
                405                 410                 415

Phe Tyr Asn Ile Thr Leu Thr Ala Lys Asp Gly Gly Asn Pro Ser Leu
            420                 425                 430

Ser Thr Asp Ala His Ile Leu Leu Gln Val Ala Asp Ile Asn Asp Asn
        435                 440                 445

Ala Pro Ala Phe Ser Arg Thr Ser Tyr Ser Thr Tyr Ile Pro Glu Asn
    450                 455                 460

Asn Pro Arg Gly Ala Ser Val Phe Ser Val Thr Ala His Asp Pro Asp
465                 470                 475                 480

Ser Asn Asp Asn Ala His Val Thr Tyr Ser Phe Ala Glu Asp Thr Val
                485                 490                 495

Gln Gly Ala Pro Leu Ser Ser Tyr Ile Ser Ile Asn Ser Asp Thr Gly
            500                 505                 510
```

```
Val Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln Leu Arg Asp Leu
        515                 520                 525

Gln Val Trp Val Ile Ala Arg Asp Ser Gly Asn Pro Pro Leu Ser Ser
    530                 535                 540

Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala Pro
545                 550                 555                 560

Glu Ile Leu Tyr Pro Ala Phe Pro Thr Asp Gly Ser Thr Gly Val Glu
                565                 570                 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr His Leu
        595                 600                 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly
    610                 615                 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln
625                 630                 635                 640

Ser Leu Val Val Ala Ile Gln Asp His Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Arg Ile Pro Asp Ile Leu
            660                 665                 670

Ala Asp Leu Gly Ser Leu Glu Pro Ser Ala Ile Pro Asn Asp Ser Asp
        675                 680                 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val Ser Cys Val Phe
    690                 695                 700

Leu Ala Phe Val Ile Val Leu Leu Ala His Arg Leu Arg Arg Trp His
705                 710                 715                 720

Lys Ser Arg Leu Leu Gln Ala Ser Gly Gly Ser Leu Thr Gly Met Gln
                725                 730                 735

Ser Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr
            740                 745                 750
```

```
Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu
        755                 760                 765


Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile Ser Gln Glu Ser
    770                 775                 780


Cys Glu Lys Lys Asp Phe Leu Ser Ala Pro Gln Ser Leu Leu Glu Glu
785                 790                 795                 800


Glu Arg Glu Glu Thr Phe Ser Gln Gln Ala Pro Pro Asn Thr Asp Trp
                805                 810                 815


Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly
            820                 825                 830


Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu
        835                 840                 845


Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser
    850                 855                 860


Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly
865                 870                 875                 880


Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr
                885                 890                 895


Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp
            900                 905                 910


Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys
        915                 920                 925


Lys Glu Lys Lys
    930


<210>  107
<211>  927
<212>  PRT
<213>  Homo sapiens

<400>  107

Met Gln Arg Ala Arg Glu Ala Glu Met Met Lys Ser Gln Val Leu Phe
1               5                   10                  15
```

```
Pro Phe Leu Leu Ser Leu Phe Cys Gly Ala Ile Ser Gln Gln Ile Arg
            20                  25                  30

Tyr Thr Ile Pro Glu Glu Leu Ala Asn Gly Ser Arg Val Gly Lys Leu
        35                  40                  45

Ala Lys Asp Leu Gly Leu Ser Val Arg Glu Leu Pro Thr Arg Lys Leu
    50                  55                  60

Arg Val Ser Ala Glu Asp Tyr Phe Asn Val Ser Leu Glu Ser Gly Asp
65                  70                  75                  80

Leu Leu Val Asn Gly Arg Ile Asp Arg Glu Lys Ile Cys Gly Arg Lys
                85                  90                  95

Leu Glu Cys Ala Leu Glu Phe Glu Thr Val Ala Glu Asn Pro Met Asn
            100                 105                 110

Val Phe His Val Val Val Val Ile Gln Asp Ile Asn Asp Asn Ala Pro
        115                 120                 125

Arg Phe Val Ala Lys Gly Ile Asp Leu Glu Ile Cys Glu Ser Ala Leu
    130                 135                 140

Pro Gly Val Lys Phe Ser Leu Asp Ser Ala Gln Asp Ala Asp Val Glu
145                 150                 155                 160

Gly Asn Ser Leu Lys Leu Tyr Thr Ile Asn Pro Asn Gln Tyr Phe Ser
                165                 170                 175

Leu Ser Thr Lys Glu Ser Pro Asp Gly Ser Lys Tyr Pro Val Leu Leu
            180                 185                 190

Leu Glu Lys Pro Leu Asp Arg Glu His Gln Ser Ser His Arg Leu Ile
        195                 200                 205

Leu Thr Ala Met Asp Gly Gly Asp Pro Pro Leu Ser Gly Thr Thr His
    210                 215                 220

Ile Trp Ile Arg Val Thr Asp Ala Asn Asp Asn Ala Pro Val Phe Ser
225                 230                 235                 240

Gln Glu Val Tyr Arg Val Ser Leu Gln Glu Asn Val Pro Trp Gly Thr
                245                 250                 255
```

```
Ser Val Leu Arg Val Met Ala Thr Asp Gln Asp Glu Gly Ile Asn Ala
            260                 265                 270

Glu Ile Thr Tyr Ala Phe Leu Asn Ser Pro Ile Ser Thr Ser Leu Phe
        275                 280                 285

Asn Leu Asn Pro Asn Thr Gly Asp Ile Thr Thr Asn Gly Thr Leu Asp
    290                 295                 300

Phe Glu Glu Thr Ser Arg Tyr Val Leu Ser Val Glu Ala Lys Asp Gly
305                 310                 315                 320

Gly Val His Thr Ala His Cys Asn Val Gln Ile Glu Ile Val Asp Glu
                325                 330                 335

Asn Asp Asn Ala Pro Glu Val Thr Phe Met Ser Phe Ser Asn Gln Ile
            340                 345                 350

Pro Glu Asp Ser Asp Leu Gly Thr Val Ile Ala Leu Ile Lys Val Arg
        355                 360                 365

Asp Lys Asp Ser Gly Gln Asn Gly Met Val Thr Cys Tyr Thr Gln Glu
    370                 375                 380

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

Val Ile Ala Gly Ala Leu Asn Arg Glu Gln Thr Ala Asp Tyr Asn Val
                405                 410                 415

Thr Ile Ile Ala Thr Asp Lys Gly Lys Pro Ala Leu Ser Ser Arg Thr
            420                 425                 430

Ser Ile Thr Leu His Ile Ser Asp Ile Asn Asp Asn Ala Pro Val Phe
        435                 440                 445

His Gln Ala Ser Tyr Val Val His Val Ser Glu Asn Asn Pro Pro Gly
    450                 455                 460

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

Gly Arg Val Ser Tyr Ser Ile Leu Ala Ser Asp Leu Glu Pro Arg Glu
                485                 490                 495
```

```
Leu Leu Ser Tyr Val Ser Val Ser Pro Gln Ser Gly Val Val Phe Ala
            500                 505                 510

Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe Glu Leu Thr Leu
        515                 520                 525

Gln Ala Arg Asp Gln Gly Ser Pro Ala Leu Ser Ala Asn Val Ser Leu
    530                 535                 540

Arg Val Leu Val Gly Asp Leu Asn Asp Asn Ala Pro Arg Val Leu Tyr
545                 550                 555                 560

Pro Ala Leu Gly Pro Asp Gly Ser Ala Leu Phe Asp Met Val Pro Arg
                565                 570                 575

Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val Ala Val Asp Ala
            580                 585                 590

Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val Leu Gln Ala Ser
        595                 600                 605

Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly Glu Val Arg Thr
    610                 615                 620

Ala Arg Ala Leu Gly Asp Arg Asp Ala Ala Arg Gln Arg Leu Leu Val
625                 630                 635                 640

Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala Thr Ala Thr Leu
                645                 650                 655

His Leu Ile Phe Ala Asp Ser Leu Gln Glu Val Leu Pro Asp Leu Ser
            660                 665                 670

Asp Arg Pro Glu Pro Ser Asp Pro Gln Thr Glu Leu Gln Phe Tyr Leu
        675                 680                 685

Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu Leu Ala Val Ile
    690                 695                 700

Leu Ala Ile Ala Leu Arg Leu Arg Arg Ser Ser Ser Leu Asp Thr Glu
705                 710                 715                 720

Gly Cys Phe Gln Thr Gly Leu Cys Ser Lys Ser Gly Pro Gly Val Pro
                725                 730                 735
```

```
Pro Asn His Ser Glu Gly Thr Leu Pro Tyr Ser Tyr Asn Leu Cys Ile
            740                 745                 750


Ala Ser His Ser Ala Lys Thr Glu Phe Asn Ser Leu Asn Leu Thr Pro
        755                 760                 765


Glu Met Ala Pro Pro Gln Asp Leu Leu Cys Asp Asp Pro Ser Met Val
    770                 775                 780


Val Cys Ala Ser Asn Glu Asp His Lys Ile Ala Tyr Asp Pro Ser Leu
785                 790                 795                 800


Ser Ser His Gln Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser Gln Ala
                805                 810                 815


Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr Gly Thr
            820                 825                 830


Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln Ala Met Ile Leu
        835                 840                 845


Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly Gly Gly
    850                 855                 860


Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe Thr Leu
865                 870                 875                 880


Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly Ser Asn
                885                 890                 895


Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala Pro Ala
            900                 905                 910


Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys Lys
        915                 920                 925


<210>  108
<211>  931
<212>  PRT
<213>  Homo sapiens

<400>  108

Met Ala Ala Pro Pro Ala Arg Pro Asp His Thr Arg Leu Leu Gln Ile
1               5                   10                  15
```

```
Cys Leu Leu Leu Gly Val Leu Val Glu Ile Arg Ala Glu Gln Ile Leu
            20                  25                  30

Tyr Ser Val Phe Glu Glu Gln Glu Glu Gly Ser Val Val Gly Asn Ile
        35                  40                  45

Ala Lys Asp Leu Gly Leu Ala Pro Arg Glu Leu Ala Glu Arg Gly Val
    50                  55                  60

Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ala Leu Asn Pro Arg
65                  70                  75                  80

Ser Gly Thr Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys
                85                  90                  95

Asp Arg Ser Pro Asn Cys Val Thr Asn Leu Glu Ile Leu Leu Glu Asp
            100                 105                 110

Thr Val Lys Ile Leu Arg Val Glu Val Glu Ile Ile Asp Val Asn Asp
        115                 120                 125

Asn Pro Pro Ser Phe Gly Thr Glu Gln Arg Glu Ile Lys Val Ala Glu
    130                 135                 140

Asn Glu Asn Pro Gly Ala Arg Phe Pro Leu Pro Glu Ala Phe Asp Pro
145                 150                 155                 160

Asp Val Gly Val Asn Ser Leu Gln Gly Tyr Gln Leu Asn Ser Asn Gly
                165                 170                 175

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

Glu Leu Val Leu Glu Arg Ala Leu Asp Arg Glu Glu Glu Ala Val His
        195                 200                 205

His Leu Val Leu Thr Ala Phe Asp Gly Gly Asp Pro Val Arg Ser Gly
    210                 215                 220

Thr Ala Arg Ile Leu Ile Ile Leu Val Asp Thr Asn Asp Asn Ala Pro
225                 230                 235                 240

Val Phe Thr Gln Pro Glu Tyr His Val Ser Val Arg Glu Asn Val Pro
                245                 250                 255
```

```
Val Gly Thr Arg Leu Leu Thr Val Lys Ala Thr Asp Pro Asp Glu Gly
            260                 265                 270

Ala Asn Gly Asp Val Thr Tyr Ser Phe Arg Lys Val Arg Asp Lys Ile
        275                 280                 285

Ser Gln Leu Phe Gln Leu Asn Ser Leu Ser Gly Asp Ile Thr Ile Leu
    290                 295                 300

Gly Gly Leu Asp Tyr Glu Asp Ser Gly Phe Tyr Asp Ile Asp Val Glu
305                 310                 315                 320

Ala His Asp Gly Pro Gly Leu Arg Ala Arg Ser Lys Val Leu Val Thr
                325                 330                 335

Val Leu Asp Glu Asn Asp Asn Ala Pro Glu Val Thr Val Thr Ser Leu
            340                 345                 350

Thr Ser Ser Val Gln Glu Ser Ser Ser Pro Gly Thr Val Ile Ala Leu
        355                 360                 365

Phe Asn Val His Asp Ser Asp Ser Gly Gly Asn Gly Leu Val Thr Cys
    370                 375                 380

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

Tyr Tyr Arg Leu Leu Thr His Arg Thr Leu Asp Arg Glu Glu Val Ser
                405                 410                 415

Glu Tyr Asn Ile Thr Val Thr Ala Thr Asp Gln Gly Thr Pro Pro Leu
            420                 425                 430

Ser Thr Glu Thr His Ile Ser Leu Gln Val Met Asp Ile Asn Asp Asn
        435                 440                 445

Pro Pro Thr Phe Pro His Ala Ser Tyr Ser Ala Tyr Ile Pro Glu Asn
    450                 455                 460

Asn Pro Arg Gly Ala Ser Ile Leu Ser Met Thr Ala Gln Asp Pro Asp
465                 470                 475                 480

Ser Gly Asp Asn Ala Arg Ile Thr Tyr Ser Leu Ala Glu Asp Thr Phe
                485                 490                 495
```

```
Gln Gly Ala Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asn Thr Gly
            500                 505                 510

Ile Leu Tyr Ala Leu Cys Ser Phe Asp Tyr Glu Gln Phe Arg Asp Leu
        515                 520                 525

Gln Leu Leu Met Thr Ala Ser Asp Ser Gly Asp Pro Pro Leu Ser Ser
    530                 535                 540

Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Val Pro
545                 550                 555                 560

Glu Ile Leu Tyr Pro Thr Phe Pro Thr Asp Gly Ser Thr Gly Val Glu
                565                 570                 575

Leu Ala Pro Arg Ser Ala Asp Ser Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Ser Leu
        595                 600                 605

Leu Lys Ser Ser Glu Pro Gly Leu Phe Ala Val Gly Leu His Thr Gly
    610                 615                 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln
625                 630                 635                 640

Arg Leu Val Val Val Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile Pro Asp Val Leu
            660                 665                 670

Ala Asp Leu Gly Ser Leu Lys Pro Ser Ala Asp Pro Asp Asp Ser Gly
        675                 680                 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val Ser Cys Val Phe
    690                 695                 700

Leu Ala Phe Val Thr Val Leu Leu Ala Leu Lys Leu Arg Arg Trp His
705                 710                 715                 720

Lys Ser Arg Leu Leu His Ala Glu Gly Ser Arg Leu Ala Gly Val Pro
                725                 730                 735
```

```
Ala Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr
            740                 745                 750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu
        755                 760                 765

Ile Phe Ser Gln Pro Ser Tyr Ala Asp Thr Leu Ile Ser Arg Glu Ser
    770                 775                 780

Cys Glu Lys Ser Glu Pro Leu Leu Ile Thr Gln Asp Leu Leu Glu Thr
785                 790                 795                 800

Lys Gly Asp Pro Asn Leu Gln Gln Ala Pro Pro Asn Thr Asp Trp Arg
                805                 810                 815

Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp
            820                 825                 830

Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln
        835                 840                 845

Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr
    850                 855                 860

Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro
865                 870                 875                 880

Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile
                885                 890                 895

Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly
            900                 905                 910

Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys
        915                 920                 925

Glu Lys Lys
    930


<210>  109
<211>  931
<212>  PRT
<213>  Homo sapiens

<400>  109
```

```
Met Lys Ala Ser Ser Gly Arg Cys Gly Leu Val Arg Trp Leu Gln Val
1               5                   10                  15

Leu Leu Pro Phe Leu Leu Ser Leu Phe Pro Gly Ala Leu Pro Val Gln
            20                  25                  30

Ile Arg Tyr Ser Ile Pro Glu Glu Leu Ala Lys Asn Ser Val Val Gly
        35                  40                  45

Asn Leu Ala Lys Asp Leu Gly Leu Ser Val Arg Asp Leu Pro Ala Arg
    50                  55                  60

Lys Leu Arg Val Ser Ala Glu Lys Glu Tyr Phe Thr Val Asn Pro Glu
65                  70                  75                  80

Ser Gly Asp Leu Leu Val Ser Asp Arg Ile Asp Arg Glu Gln Ile Cys
                85                  90                  95

Gly Lys Gln Pro Leu Cys Val Leu Asp Phe Asp Thr Val Ala Glu Asn
            100                 105                 110

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

Asn Thr Pro Leu Phe Lys Gln Thr Lys Ile Asn Leu Lys Ile Gly Glu
    130                 135                 140

Ser Thr Lys Pro Gly Thr Thr Phe Pro Leu Asp Pro Ala Leu Asp Ser
145                 150                 155                 160

Asp Val Gly Pro Asn Ser Leu Gln Arg Tyr His Leu Asn Asp Asn Glu
                165                 170                 175

Tyr Phe Asp Leu Ala Glu Lys Gln Thr Pro Asp Gly Arg Lys Tyr Pro
            180                 185                 190

Glu Leu Ile Leu Lys His Ser Leu Asp Arg Glu Glu His Ser Leu His
        195                 200                 205

Gln Leu Val Leu Thr Ala Val Asp Gly Gly Asp Pro Pro Gln Ser Gly
    210                 215                 220

Thr Thr Gln Ile Arg Ile Lys Val Thr Asp Ala Asn Asp Asn Pro Pro
225                 230                 235                 240
```

```
Val Phe Ser Gln Asp Val Tyr Arg Val Thr Leu Arg Glu Asp Val Pro
                245                 250                 255

Pro Gly Phe Phe Val Leu Gln Val Thr Ala Thr Asp Arg Asp Glu Gly
            260                 265                 270

Ile Asn Ala Glu Ile Thr Tyr Ser Phe His Asn Val Asp Glu Gln Val
        275                 280                 285

Lys His Phe Phe Asn Leu Asn Glu Lys Thr Gly Glu Ile Thr Thr Lys
    290                 295                 300

Asp Asp Leu Asp Phe Glu Ile Ala Ser Ser Tyr Thr Leu Ser Ile Glu
305                 310                 315                 320

Ala Lys Asp Pro Gly Asp Leu Ala Ala His Cys Ser Ile Gln Val Glu
                325                 330                 335

Ile Leu Asp Asp Asn Asp Cys Ala Pro Glu Val Ile Val Thr Ser Val
            340                 345                 350

Ser Thr Pro Leu Pro Glu Asp Ser Pro Pro Gly Thr Val Ile Ala Leu
        355                 360                 365

Ile Lys Thr Arg Asp Arg Asp Ser Gly Glu Asn Gly Glu Val Tyr Cys
    370                 375                 380

Gln Val Leu Gly Asn Ala Lys Phe Ile Leu Lys Ser Ser Ser Lys Asn
385                 390                 395                 400

Tyr Tyr Lys Leu Val Thr Asp Gly Ala Leu Asp Arg Glu Glu Ile Pro
                405                 410                 415

Glu Tyr Asn Leu Thr Ile Thr Ala Thr Asp Gly Gly Lys Pro Pro Leu
            420                 425                 430

Ser Ser Ser Ile Ile Val Thr Leu His Ile Ser Asp Val Asn Asp Asn
        435                 440                 445

Ala Pro Val Phe Gln Gln Thr Ser Tyr Met Val His Val Ala Glu Asn
    450                 455                 460

Asn Pro Pro Gly Ala Ser Ile Ala Gln Ile Ser Ala Ser Asp Pro Asp
465                 470                 475                 480
```

```
Leu Gly Pro Ser Gly Gln Val Ser Tyr Ser Ile Val Ala Ser Asp Leu
                485                 490                 495

Lys Pro Arg Glu Ile Leu Ser Tyr Val Ser Val Ser Ala Gln Ser Gly
            500                 505                 510

Val Val Phe Ala Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe
        515                 520                 525

Glu Leu Thr Leu Gln Ala Arg Asp Gln Gly Ser Pro Ala Leu Ser Ala
    530                 535                 540

Asn Val Ser Leu Arg Val Leu Val Gly Asp Leu Asn Asp Asn Ala Pro
545                 550                 555                 560

Arg Val Leu Tyr Pro Ala Leu Gly Pro Asp Gly Ser Ala Leu Phe Asp
                565                 570                 575

Met Val Pro Arg Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Ala Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val
        595                 600                 605

Leu Gln Ala Ser Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly
    610                 615                 620

Glu Val Arg Thr Ala Arg Ala Leu Gly Asp Arg Asp Ala Ala Arg Gln
625                 630                 635                 640

Arg Leu Leu Val Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655

Thr Ala Thr Leu His Leu Ile Phe Ala Asp Ser Leu Gln Glu Val Leu
            660                 665                 670

Pro Asp Leu Ser Asp Arg Arg Glu Pro Ser Asp Pro Gln Ala Lys Leu
        675                 680                 685

Gln Phe Tyr Leu Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Phe
    690                 695                 700

Leu Ala Val Ile Leu Ala Ile Ser Leu Arg Leu Arg Leu Ser Ser Arg
705                 710                 715                 720
```

```
Ser Asp Ala Trp Asp Cys Phe Gln Pro Gly Leu Ser Ser Lys Pro Gly
                725                 730                 735

Pro Gly Val Leu Pro Asn Tyr Ser Glu Gly Thr Leu Pro Tyr Ser Tyr
            740                 745                 750

Asn Leu Cys Val Ala Ser Gln Ser Ala Lys Thr Glu Phe Asn Phe Leu
        755                 760                 765

Asn Ile Thr Pro Glu Leu Val Pro Ala Gln Asp Leu Val Cys Asp Asn
    770                 775                 780

Ala Ser Trp Glu Gln Asn Thr Asn His Gly Ala Ala Gly Val Pro Phe
785                 790                 795                 800

Ala Ser Asp Thr Ile Leu Lys Gln Ala Pro Pro Asn Thr Asp Trp Arg
                805                 810                 815

Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp
            820                 825                 830

Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln
        835                 840                 845

Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr
    850                 855                 860

Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro
865                 870                 875                 880

Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile
                885                 890                 895

Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly
            900                 905                 910

Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys
        915                 920                 925

Glu Lys Lys
    930


<210>  110
<211>  931
```

```
<212>  PRT
<213>  Homo sapiens

<400>  110

Met Ala Ser Pro Pro Arg Gly Trp Gly Cys Gly Glu Leu Leu Leu Pro
1               5                   10                  15


Phe Met Leu Leu Gly Thr Leu Cys Glu Pro Gly Ser Gly Gln Ile Arg
            20                  25                  30


Tyr Ser Met Pro Glu Glu Leu Asp Lys Gly Ser Phe Val Gly Asn Ile
        35                  40                  45


Ala Lys Asp Leu Gly Leu Glu Pro Gln Glu Leu Ala Glu Arg Gly Val
    50                  55                  60


Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ala Leu Asn Pro Arg
65                  70                  75                  80


Ser Gly Ser Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys
                85                  90                  95


Ala Gln Ser Pro Leu Cys Val Val Asn Phe Asn Ile Leu Val Glu Asn
            100                 105                 110


Lys Met Lys Ile Tyr Gly Val Glu Val Glu Ile Ile Asp Ile Asn Asp
        115                 120                 125


Asn Phe Pro Arg Phe Arg Asp Glu Glu Leu Lys Val Lys Val Asn Glu
    130                 135                 140


Asn Ala Ala Ala Gly Thr Arg Leu Val Leu Pro Phe Ala Arg Asp Ala
145                 150                 155                 160


Asp Val Gly Val Asn Ser Leu Arg Ser Tyr Gln Leu Ser Ser Asn Leu
                165                 170                 175


His Phe Ser Leu Asp Val Val Ser Gly Thr Asp Gly Gln Lys Tyr Pro
            180                 185                 190


Glu Leu Val Leu Glu Gln Pro Leu Asp Arg Glu Lys Glu Thr Val His
        195                 200                 205
```

```
Asp Leu Leu Leu Thr Ala Leu Asp Gly Gly Asp Pro Val Leu Ser Gly
    210                 215                 220

Thr Thr His Ile Arg Val Thr Val Leu Asp Ala Asn Asp Asn Ala Pro
225                 230                 235                 240

Leu Phe Thr Pro Ser Glu Tyr Ser Val Ser Val Pro Glu Asn Ile Pro
                245                 250                 255

Val Gly Thr Arg Leu Leu Met Leu Thr Ala Thr Asp Pro Asp Glu Gly
            260                 265                 270

Ile Asn Gly Lys Leu Thr Tyr Ser Phe Arg Asn Glu Glu Glu Lys Ile
        275                 280                 285

Ser Glu Thr Phe Gln Leu Asp Ser Asn Leu Gly Glu Ile Ser Thr Leu
    290                 295                 300

Gln Ser Leu Asp Tyr Glu Glu Ser Arg Phe Tyr Leu Met Glu Val Val
305                 310                 315                 320

Ala Gln Asp Gly Gly Ala Leu Val Ala Ser Ala Lys Val Val Val Thr
                325                 330                 335

Val Gln Asp Val Asn Asp Asn Ala Pro Glu Val Ile Leu Thr Ser Leu
            340                 345                 350

Thr Ser Ser Ile Ser Glu Asp Cys Leu Pro Gly Thr Val Ile Ala Leu
        355                 360                 365

Phe Ser Val His Asp Gly Asp Ser Gly Glu Asn Gly Glu Ile Ala Cys
    370                 375                 380

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

Tyr Tyr His Leu Leu Thr Thr Arg Asp Leu Asp Arg Glu Glu Thr Ser
                405                 410                 415

Asp Tyr Asn Ile Thr Leu Thr Val Met Asp His Gly Thr Pro Pro Leu
            420                 425                 430

Ser Thr Glu Ser His Ile Pro Leu Lys Val Ala Asp Val Asn Asp Asn
        435                 440                 445
```

```
Pro Pro Asn Phe Pro Gln Ala Ser Tyr Ser Thr Ser Val Thr Glu Asn
    450                 455                 460

Asn Pro Arg Gly Val Ser Ile Phe Ser Val Thr Ala His Asp Pro Asp
465                 470                 475                 480

Ser Gly Asp Asn Ala Arg Val Thr Tyr Ser Leu Ala Glu Asp Thr Phe
                485                 490                 495

Gln Gly Ala Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asp Thr Gly
            500                 505                 510

Val Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln Leu Arg Asp Leu
        515                 520                 525

Gln Leu Trp Val Thr Ala Ser Asp Ser Gly Asn Pro Pro Leu Ser Ser
    530                 535                 540

Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Thr Pro
545                 550                 555                 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu
                565                 570                 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Lys Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu
        595                 600                 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly Leu His Thr Gly
    610                 615                 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln
625                 630                 635                 640

Ser Leu Val Val Ala Val Glu Asp His Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655

Thr Phe Thr Val Thr Val Ala Val Ala Asp Arg Ile Pro Asp Ile Leu
            660                 665                 670

Ala Asp Leu Gly Ser Ile Lys Thr Pro Ile Asp Pro Glu Asp Leu Asp
        675                 680                 685
```

```
Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val Ser Cys Val Phe
    690                 695                 700

Leu Ala Phe Val Ile Val Leu Leu Val Leu Arg Leu Arg Arg Trp His
705                 710                 715                 720

Lys Ser Arg Leu Leu Gln Ala Glu Gly Ser Arg Leu Ala Gly Val Pro
                725                 730                 735

Ala Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr
            740                 745                 750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu
        755                 760                 765

Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Leu Ser Glu Glu Ser
    770                 775                 780

Cys Glu Lys Ser Glu Pro Leu Leu Met Ser Asp Lys Val Asp Ala Asn
785                 790                 795                 800

Lys Glu Glu Arg Arg Val Gln Gln Ala Pro Pro Asn Thr Asp Trp Arg
                805                 810                 815

Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp
            820                 825                 830

Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln
        835                 840                 845

Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr
    850                 855                 860

Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro
865                 870                 875                 880

Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile
                885                 890                 895

Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly
            900                 905                 910

Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys
        915                 920                 925
```

Glu Lys Lys
    930

<210> 111
<211> 929
<212> PRT
<213> Homo sapiens

<400> 111

Met Gly Asn Ser Ser Gly Trp Arg Gly Pro Ala Gly Gln Arg Arg Met
1   5   10   15

Leu Phe Leu Phe Leu Leu Ser Leu Leu Asp Gln Val Leu Ser Glu Pro
            20   25   30

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

Asn Leu Ala Lys Asp Leu Gly Phe Gly Val Gly Asp Leu Pro Thr Arg
    50   55   60

Asn Leu Arg Val Ile Ala Glu Lys Lys Phe Phe Thr Val Ser Pro Glu
65   70   75   80

Asn Gly Asn Leu Leu Val Ser Asp Arg Ile Asp Arg Glu Glu Ile Cys
                85   90   95

Gly Lys Lys Ser Thr Cys Val Leu Glu Phe Glu Met Val Ala Glu Lys
            100   105   110

Pro Leu Asn Phe Phe His Val Thr Val Leu Ile Gln Asp Ile Asn Asp
        115   120   125

Asn Pro Pro Thr Phe Ser Gln Asn Ile Thr Glu Leu Glu Ile Ser Glu
    130   135   140

Leu Ala Leu Thr Gly Ala Thr Phe Ala Leu Glu Ser Ala Gln Asp Pro
145   150   155   160

Asp Val Gly Val Asn Ser Leu Gln Gln Tyr Tyr Leu Ser Pro Asp Pro
                165   170   175

His Phe Ser Leu Ile Gln Lys Glu Asn Leu Asp Gly Ser Arg Tyr Pro
            180   185   190

```
Glu Leu Val Leu Lys Ala Pro Leu Asp Arg Glu Glu Gln Pro His His
        195                 200                 205

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

Thr Thr Gln Ile Arg Val Ile Val Ala Asp Ala Asn Asp Asn Pro Pro
225                 230                 235                 240

Val Phe Thr Gln Asp Met Tyr Arg Val Asn Val Ala Glu Asn Leu Pro
                245                 250                 255

Ala Gly Ser Ser Val Leu Lys Val Met Ala Ile Asp Met Asp Glu Gly
            260                 265                 270

Ile Asn Ala Glu Ile Ile Tyr Ala Phe Ile Asn Ile Gly Lys Glu Val
        275                 280                 285

Arg Gln Leu Phe Lys Leu Asp Ser Lys Thr Gly Glu Leu Thr Thr Ile
    290                 295                 300

Gly Glu Leu Asp Phe Glu Glu Arg Asp Ser Tyr Thr Ile Gly Val Glu
305                 310                 315                 320

Ala Lys Asp Gly Gly His His Thr Ala Tyr Cys Lys Val Gln Ile Asp
                325                 330                 335

Ile Ser Asp Glu Asn Asp Asn Ala Pro Glu Ile Thr Leu Ala Ser Glu
            340                 345                 350

Ser Gln His Ile Gln Glu Asp Ala Glu Leu Gly Thr Ala Val Ala Leu
        355                 360                 365

Ile Lys Thr His Asp Leu Asp Ser Gly Phe Asn Gly Glu Ile Leu Cys
    370                 375                 380

Gln Leu Lys Gly Asn Phe Pro Phe Lys Ile Val Gln Asp Thr Lys Asn
385                 390                 395                 400

Thr Tyr Arg Leu Val Thr Asp Gly Ala Leu Asp Arg Glu Gln Ile Pro
                405                 410                 415

Glu Tyr Asn Val Thr Ile Thr Ala Thr Asp Lys Gly Asn Pro Pro Leu
            420                 425                 430
```

```
Ser Ser Ser Lys Thr Ile Thr Leu His Ile Leu Asp Val Asn Asp Asn
        435                 440                 445

Val Pro Val Phe His Gln Ala Ser Tyr Thr Val His Val Ala Glu Asn
    450                 455                 460

Asn Pro Pro Gly Ala Ser Ile Ala His Val Arg Ala Ser Asp Pro Asp
465                 470                 475                 480

Leu Gly Pro Asn Gly Leu Val Ser Tyr Tyr Ile Val Ala Ser Asp Leu
                485                 490                 495

Glu Pro Arg Glu Leu Ser Ser Tyr Val Ser Val Ser Ala Arg Ser Gly
            500                 505                 510

Val Val Phe Ala Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe
        515                 520                 525

Glu Leu Thr Leu Gln Ala Arg Asp Gln Gly Ser Pro Thr Leu Ser Ala
    530                 535                 540

Asn Val Ser Leu Arg Val Leu Val Asp Asp Arg Asn Asp Asn Ala Pro
545                 550                 555                 560

Leu Val Leu Tyr Pro Ala Leu Gly Pro Glu Gly Ser Ala Leu Phe Asp
                565                 570                 575

Met Val Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Ala Asp Ser Gly Tyr Asn Ala Trp Leu Ser Tyr His Ile
        595                 600                 605

Val Gln Ala Ser Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly
    610                 615                 620

Glu Val Arg Thr Ala Arg Thr Leu Gly Asp Arg Glu Ala Ala Arg Gln
625                 630                 635                 640

Arg Leu Leu Val Thr Val Arg Asp Gly Gly Gln Gln Pro Leu Ser Ala
                645                 650                 655

Thr Val Met Leu His Leu Ile Phe Ala Asp Ser Leu Gln Glu Ile Gln
            660                 665                 670
```

```
Pro Asp Leu Ser Asp Arg Pro Thr Pro Ser Asp Pro Gln Ala Glu Leu
        675                 680                 685

Gln Phe His Leu Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu
    690                 695                 700

Leu Ala Val Ile Leu Ala Ile Ser Leu Arg Leu Arg Cys Ser Ser Arg
705                 710                 715                 720

Pro Ala Thr Glu Gly Tyr Phe Gln Pro Gly Val Cys Phe Lys Thr Val
                725                 730                 735

Pro Gly Val Leu Pro Thr Tyr Ser Glu Arg Thr Leu Pro Tyr Ser Tyr
            740                 745                 750

Asn Pro Cys Ala Ala Ser His Ser Ser Asn Thr Glu Phe Lys Phe Leu
        755                 760                 765

Asn Ile Lys Ala Glu Asn Ala Ala Pro Gln Asp Leu Leu Cys Asp Glu
    770                 775                 780

Ala Ser Trp Phe Glu Ser Asn Asp Asn Pro Glu Met Pro Ser Asn Ser
785                 790                 795                 800

Gly Asn Leu Gln Lys Gln Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser
                805                 810                 815

Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr
            820                 825                 830

Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln Ala Met
        835                 840                 845

Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly
    850                 855                 860

Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe
865                 870                 875                 880

Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly
                885                 890                 895

Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala
            900                 905                 910
```

```
Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys
        915                 920                 925


Lys



<210>  112
<211>  932
<212>  PRT
<213>  Homo sapiens

<400>  112

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


Leu Thr Leu Leu Gly Thr Leu Trp Gly Ala Ala Ala Ala Gln Ile Arg
            20                  25                  30


Tyr Ser Ile Pro Glu Glu Leu Glu Lys Gly Ser Phe Val Gly Asn Ile
        35                  40                  45


Val Lys Asp Leu Gly Leu Glu Pro Gln Glu Leu Ala Glu His Gly Val
    50                  55                  60


Arg Ile Val Ser Arg Gly Arg Met Gln Leu Phe Ser Leu Asn Pro Arg
65                  70                  75                  80


Asn Gly Ser Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys
                85                  90                  95


Ala Gln Ser Pro Arg Cys Leu Val Ser Phe Asn Ile Leu Val Glu Asp
            100                 105                 110


Lys Leu Asn Leu Tyr Pro Val Glu Val Glu Ile Val Asp Ile Asn Asp
        115                 120                 125


Asn Thr Pro Arg Phe Leu Lys Glu Glu Leu Glu Val Lys Ile Leu Glu
    130                 135                 140


Asn Ala Ala Pro Ser Ser Arg Phe Pro Leu Met Glu Val Tyr Asp Pro
145                 150                 155                 160


Asp Val Gly Met Asn Ser Leu Gln Gly Phe Lys Leu Ser Gly Asn Ser
                165                 170                 175
```

```
His Phe Ser Val Asp Val Gln Ser Glu Ala His Gly Pro Lys Tyr Pro
            180                 185                 190


Glu Leu Val Leu Glu Gly Thr Leu Asp Arg Glu Gly Glu Ala Val Tyr
        195                 200                 205


Arg Leu Val Leu Thr Ala Met Asp Gly Gly Asp Pro Val Arg Ser Ser
    210                 215                 220


Val Ala Gln Ile Leu Val Thr Val Leu Asp Val Asn Asp Asn Thr Pro
225                 230                 235                 240


Met Phe Thr Gln Pro Val Tyr Arg Val Ser Val Pro Glu Asn Leu Pro
                245                 250                 255


Val Gly Thr Pro Val Leu Ala Val Thr Ala Thr Asp Gln Asp Glu Gly
            260                 265                 270


Val His Gly Glu Val Thr Tyr Ser Phe Val Lys Ile Thr Glu Lys Ile
        275                 280                 285


Ser Gln Ile Phe Cys Leu Asn Val Leu Thr Gly Glu Ile Ser Thr Ser
    290                 295                 300


Ala Asn Leu Asp Tyr Glu Asp Ser Ser Phe Tyr Glu Leu Gly Val Glu
305                 310                 315                 320


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


Ile Leu Asp Val Asn Asp Asn Val Pro Glu Val Val Val Thr Ser Gly
            340                 345                 350


Ser Arg Thr Ile Ala Glu Ser Ala Pro Pro Gly Thr Val Ile Ala Leu
        355                 360                 365


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


Ser Ile Pro Arg Ser Leu Pro Phe Glu Leu Glu Lys Ser Val Gly Asn
385                 390                 395                 400


Tyr Tyr Arg Leu Val Thr Asn Ala Ala Leu Asp Arg Glu Glu Val Phe
                405                 410                 415
```

```
Leu Tyr Asn Ile Thr Val Thr Ala Thr Asp Lys Gly Thr Pro Pro Leu
            420                 425                 430

Ser Thr Glu Thr Ile Ile Ser Leu Asn Val Ala Asp Thr Asn Asp Asn
        435                 440                 445

Pro Pro Thr Phe Pro His Ser Ser Tyr Ser Val Tyr Val Leu Glu Asn
    450                 455                 460

Asn Pro Arg Gly Ala Ser Ile Phe Ser Val Asn Ala Leu Asp Pro Asp
465                 470                 475                 480

Val Asp Gln Asn Ala Gln Val Ser Tyr Ser Leu Ala Glu Asp Thr Leu
                485                 490                 495

Gln Gly Ala Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asp Thr Gly
            500                 505                 510

Ile Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln Leu Arg Asp Leu
        515                 520                 525

Gln Leu Trp Val Thr Ala Ser Asp Ser Gly Asp Pro Pro Leu Ser Ser
    530                 535                 540

Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala Pro
545                 550                 555                 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu
                565                 570                 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu
        595                 600                 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly
    610                 615                 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln
625                 630                 635                 640

Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655
```

```
Thr Val Thr Leu Thr Val Ala Val Ala Asp Arg Ile Pro Asp Ile Leu
            660                 665                 670

Ala Asp Leu Gly Ser Leu Glu Pro Ser Ala Lys Pro Asn Asp Ser Asp
        675                 680                 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val Ser Cys Val Phe
    690                 695                 700

Leu Ala Phe Val Ile Val Leu Leu Ala Leu Arg Leu Gln Arg Trp His
705                 710                 715                 720

Lys Ser Arg Leu Leu Gln Ala Ser Gly Gly Gly Leu Ala Ser Met Pro
                725                 730                 735

Gly Ser His Phe Val Gly Val Glu Gly Val Arg Ala Phe Leu Gln Thr
            740                 745                 750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu
        755                 760                 765

Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile Asn Gln Glu Ser
    770                 775                 780

Tyr Glu Lys Ser Glu Pro Leu Leu Ile Thr Gln Asp Leu Leu Glu Thr
785                 790                 795                 800

Lys Gly Glu Pro Arg Gln Leu Gln Gln Ala Pro Pro Asn Thr Asp Trp
                805                 810                 815

Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly
            820                 825                 830

Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu
        835                 840                 845

Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser
    850                 855                 860

Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly
865                 870                 875                 880

Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr
                885                 890                 895
```

```
Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp
            900                 905                 910


Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys
        915                 920                 925


Lys Glu Lys Lys
    930


<210>  113
<211>  932
<212>  PRT
<213>  Homo sapiens

<400>  113

Met Ala Ala Gln Pro Arg Gly Gly Asp Tyr Arg Gly Phe Phe Leu Leu
1               5                   10                  15


Ser Ile Leu Leu Gly Thr Pro Trp Glu Ala Trp Ala Gly Arg Ile Leu
            20                  25                  30


Tyr Ser Val Ser Glu Glu Thr Asp Lys Gly Ser Phe Val Gly Asp Ile
        35                  40                  45


Ala Lys Asp Leu Gly Leu Glu Pro Arg Glu Leu Ala Glu Arg Gly Val
    50                  55                  60


Arg Ile Ile Ser Arg Gly Arg Thr Gln Leu Phe Ala Leu Asn Gln Arg
65                  70                  75                  80


Ser Gly Ser Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Ile Cys
                85                  90                  95


Ala Gln Ser Ala Arg Cys Leu Val Asn Phe Asn Ile Leu Met Glu Asp
            100                 105                 110


Lys Met Asn Leu Tyr Pro Ile Asp Val Glu Ile Ile Asp Ile Asn Asp
        115                 120                 125


Asn Val Pro Arg Phe Leu Thr Glu Glu Ile Asn Val Lys Ile Met Glu
    130                 135                 140


Asn Thr Ala Pro Gly Val Arg Phe Pro Leu Ser Glu Ala Gly Asp Pro
145                 150                 155                 160
```

```
Asp Val Gly Thr Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn Arg
                165                 170                 175

His Phe Ser Leu Ala Val Gln Ser Gly Asp Asp Glu Thr Lys Tyr Pro
            180                 185                 190

Glu Leu Val Leu Glu Arg Val Leu Asp Arg Glu Glu Glu Arg Val His
        195                 200                 205

His Leu Val Leu Thr Ala Ser Asp Gly Gly Asp Pro Pro Arg Ser Ser
    210                 215                 220

Thr Ala His Ile Gln Val Thr Val Val Asp Val Asn Asp His Thr Pro
225                 230                 235                 240

Val Phe Ser Leu Pro Gln Tyr Gln Val Thr Val Pro Glu Asn Val Pro
                245                 250                 255

Val Gly Thr Arg Leu Leu Thr Val His Ala Ile Asp Leu Asp Glu Gly
            260                 265                 270

Val Asn Gly Glu Val Thr Tyr Ser Phe Arg Lys Ile Thr Pro Lys Leu
        275                 280                 285

Pro Lys Met Phe His Leu Asn Ser Leu Thr Gly Glu Ile Ser Thr Leu
    290                 295                 300

Glu Gly Leu Asp Tyr Glu Glu Thr Ala Phe Tyr Glu Met Glu Val Gln
305                 310                 315                 320

Ala Gln Asp Gly Pro Gly Ser Leu Thr Lys Ala Lys Val Leu Ile Thr
                325                 330                 335

Val Leu Asp Val Asn Asp Asn Ala Pro Glu Val Thr Met Thr Ser Leu
            340                 345                 350

Ser Ser Ser Ile Pro Glu Asp Thr Pro Leu Gly Thr Val Ile Ala Leu
        355                 360                 365

Phe Tyr Leu Gln Asp Arg Asp Ser Gly Lys Asn Gly Glu Val Thr Cys
    370                 375                 380

Thr Ile Pro Glu Asn Leu Pro Phe Lys Leu Glu Lys Ser Ile Asp Asn
385                 390                 395                 400
```

```
Tyr Tyr Arg Leu Val Thr Thr Lys Asn Leu Asp Arg Glu Thr Leu Ser
                405                 410                 415

Leu Tyr Asn Ile Thr Leu Lys Ala Thr Asp Gly Gly Thr Pro Pro Leu
            420                 425                 430

Ser Arg Glu Thr His Ile Phe Met Gln Val Ala Asp Thr Asn Asp Asn
        435                 440                 445

Pro Pro Thr Phe Pro His Ser Ser Tyr Ser Val Tyr Ile Ala Glu Asn
    450                 455                 460

Asn Pro Arg Gly Ala Ser Ile Phe Leu Val Thr Ala Gln Asp His Asp
465                 470                 475                 480

Ser Glu Asp Asn Ala Gln Ile Thr Tyr Ser Leu Ala Glu Asp Thr Ile
                485                 490                 495

Gln Gly Ala Pro Val Ser Ser Tyr Val Ser Ile Asn Ser Asp Thr Gly
            500                 505                 510

Val Leu Tyr Ala Leu Gln Ser Phe Asp Tyr Glu Gln Leu Arg Glu Leu
        515                 520                 525

Gln Leu Arg Val Thr Ala His Asp Ser Gly Asp Pro Pro Leu Ser Ser
    530                 535                 540

Asn Met Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Pro Pro
545                 550                 555                 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Met Glu
                565                 570                 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Lys Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Leu Leu
        595                 600                 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly Leu Tyr Thr Gly
    610                 615                 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln
625                 630                 635                 640
```

```
Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile Pro Glu Val Leu
            660                 665                 670

Ala Asp Leu Gly Ser Leu Glu Pro Ser Asp Gly Pro Tyr Asn Tyr Asp
        675                 680                 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Thr Val Ser Cys Val Phe
    690                 695                 700

Leu Ala Phe Val Leu Val Leu Leu Ala Leu Arg Leu Arg Arg Trp His
705                 710                 715                 720

Lys Ser Arg Leu Leu Gln Ala Ser Glu Gly Gly Leu Ala Asn Val Pro
                725                 730                 735

Thr Ser His Phe Val Gly Met Asp Gly Val Gln Ala Phe Leu Gln Thr
            740                 745                 750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu
        755                 760                 765

Ile Phe Pro Gln Pro Asn Tyr Val Asp Met Leu Ile Ser Gln Glu Ser
    770                 775                 780

Cys Glu Lys Asn Asp Ser Leu Leu Thr Ser Val Asp Phe Gln Glu Cys
785                 790                 795                 800

Lys Glu Asn Leu Pro Ser Ile Gln Gln Ala Pro Pro Asn Thr Asp Trp
                805                 810                 815

Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly
            820                 825                 830

Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu
        835                 840                 845

Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser
    850                 855                 860

Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly
865                 870                 875                 880
```

```
Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr
                885                 890                 895


Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp
            900                 905                 910


Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys
        915                 920                 925


Lys Glu Lys Lys
    930


<210>  114
<211>  923
<212>  PRT
<213>  Homo sapiens

<400>  114

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


Leu Phe Leu Phe Leu Leu Ser Leu Phe Cys Pro Ala Leu Cys Glu Gln
            20                  25                  30


Ile Arg Tyr Arg Ile Pro Glu Glu Met Pro Lys Gly Ser Val Val Gly
        35                  40                  45


Asn Leu Ala Thr Asp Leu Gly Phe Ser Val Gln Glu Leu Pro Thr Arg
    50                  55                  60


Lys Leu Arg Val Ser Ser Glu Lys Pro Tyr Phe Thr Val Ser Ala Glu
65                  70                  75                  80


Ser Gly Glu Leu Leu Val Ser Ser Arg Leu Asp Arg Glu Glu Ile Cys
                85                  90                  95


Gly Lys Lys Pro Ala Cys Ala Leu Glu Phe Glu Ala Val Ala Glu Asn
            100                 105                 110


Pro Leu Asn Phe Tyr His Val Asn Val Glu Ile Glu Asp Ile Asn Asp
        115                 120                 125


His Thr Pro Lys Phe Thr Gln Asn Ser Phe Glu Leu Gln Ile Ser Glu
    130                 135                 140
```

```
Ser Ala Gln Pro Gly Thr Arg Phe Ile Leu Gly Ser Ala His Asp Ala
145                 150                 155                 160

Asp Ile Gly Ser Asn Thr Leu Gln Asn Tyr Gln Leu Ser Pro Ser Asp
                165                 170                 175

His Phe Ser Leu Ile Asn Lys Glu Lys Ser Asp Gly Ser Lys Tyr Pro
            180                 185                 190

Glu Met Val Leu Lys Thr Pro Leu Asp Arg Glu Lys Gln Lys Ser Tyr
        195                 200                 205

His Leu Thr Leu Thr Ala Leu Asp Phe Gly Ala Pro Pro Leu Ser Ser
    210                 215                 220

Thr Ala Gln Ile His Val Leu Val Thr Asp Ala Asn Asp Asn Ala Pro
225                 230                 235                 240

Val Phe Ser Gln Asp Val Tyr Arg Val Ser Leu Ser Glu Asn Val Tyr
                245                 250                 255

Pro Gly Thr Thr Val Leu Gln Val Thr Ala Thr Asp Gln Asp Glu Gly
            260                 265                 270

Val Asn Ala Glu Ile Thr Phe Ser Phe Ser Glu Ala Ser Gln Ile Thr
        275                 280                 285

Gln Phe Asp Leu Asn Ser Asn Thr Gly Glu Ile Thr Val Leu Asn Thr
    290                 295                 300

Leu Asp Phe Glu Glu Val Lys Glu Tyr Ser Ile Val Leu Glu Ala Arg
305                 310                 315                 320

Asp Gly Gly Gly Met Ile Ala Gln Cys Thr Val Glu Val Glu Val Ile
                325                 330                 335

Asp Glu Asn Asp Asn Ala Pro Glu Val Ile Phe Gln Ser Leu Pro Asn
            340                 345                 350

Leu Ile Met Glu Asp Ala Glu Leu Gly Thr His Ile Ala Leu Leu Lys
        355                 360                 365

Val Arg Asp Lys Asp Ser Arg His Asn Gly Glu Val Thr Cys Lys Leu
    370                 375                 380
```

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

Lys Leu Val Thr Asp Ala Val Leu Asp Arg Glu Gln Asn Pro Glu Tyr
                405                 410                 415

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

Ser Ser Ser Ile Thr Leu His Ile Gly Asp Val Asn Asp Asn Ala Pro
        435                 440                 445

Val Phe Ser Gln Ser Ser Tyr Ile Val His Val Ala Glu Asn Asn Pro
    450                 455                 460

Pro Gly Ala Ser Ile Ser Gln Val Arg Ala Ser Asp Pro Asp Leu Gly
465                 470                 475                 480

Pro Asn Gly Gln Val Ser Tyr Cys Ile Met Ala Ser Asp Leu Glu Gln
                485                 490                 495

Arg Glu Leu Ser Ser Tyr Val Ser Ile Ser Ala Glu Ser Gly Val Val
            500                 505                 510

Phe Ala Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe Glu Leu
        515                 520                 525

Thr Leu Gln Ala Arg Asp Gln Gly Ser Pro Ala Leu Ser Ala Asn Val
    530                 535                 540

Ser Leu Arg Val Leu Val Asp Asp Arg Asn Asp Asn Ala Pro Arg Val
545                 550                 555                 560

Leu Tyr Pro Ala Leu Gly Pro Asp Gly Ser Ala Leu Phe Asp Met Val
                565                 570                 575

Pro His Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val Ala Val
            580                 585                 590

Asp Ala Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val Leu Gln
        595                 600                 605

Ala Ser Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly Glu Val
    610                 615                 620
```

```
Arg Thr Ala Arg Ala Leu Gly Asp Arg Asp Ala Val Arg Gln Arg Leu
625                 630                 635                 640

Leu Val Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala Thr Ala
                645                 650                 655

Thr Leu His Leu Val Phe Ala Asp Ser Leu Gln Glu Val Leu Pro Asp
            660                 665                 670

Ile Thr Asp Arg Pro Asp Pro Ser Asp Leu Gln Ala Glu Leu Gln Phe
        675                 680                 685

Tyr Leu Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu Val Ala
    690                 695                 700

Met Ile Leu Ala Ile Ala Leu Arg Leu Arg Arg Ser Ser Ser Pro Ala
705                 710                 715                 720

Ser Trp Ser Cys Phe Gln Pro Gly Leu Cys Val Lys Ser Glu Ser Val
                725                 730                 735

Val Pro Pro Asn Tyr Ser Glu Gly Thr Leu Pro Tyr Ser Tyr Asn Leu
            740                 745                 750

Cys Val Ala His Thr Gly Lys Thr Glu Phe Asn Phe Leu Lys Cys Ser
        755                 760                 765

Glu Gln Leu Ser Ser Gly Gln Asp Ile Leu Cys Gly Asp Ser Ser Gly
    770                 775                 780

Ala Leu Phe Pro Leu Cys Asn Ser Ser Glu Leu Thr Ser His Gln Gln
785                 790                 795                 800

Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser Gln Ala Gln Arg Pro Gly
                805                 810                 815

Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr Gly Thr Trp Pro Asn Asn
            820                 825                 830

Gln Phe Asp Thr Glu Met Leu Gln Ala Met Ile Leu Ala Ser Ala Ser
        835                 840                 845

Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly Gly Gly Ala Gly Thr Met
    850                 855                 860
```

```
Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe Thr Leu Gln His Val Pro
865                 870                 875                 880


Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly Ser Asn Ala Thr Leu Thr
                885                 890                 895


Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala Pro Ala Gly Gly Asn Gly
            900                 905                 910


Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys Lys
        915                 920


<210>  115
<211>  932
<212>  PRT
<213>  Homo sapiens

<400>  115

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


Cys Ala Leu Leu Gly Thr Leu Trp Glu Ile Gly Arg Gly Gln Ile Arg
            20                  25                  30


Tyr Ser Val Pro Glu Glu Thr Asp Lys Gly Ser Phe Val Gly Asn Ile
        35                  40                  45


Ser Lys Asp Leu Gly Leu Asp Pro Arg Lys Leu Ala Lys His Gly Val
    50                  55                  60


Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ala Leu Asn Pro Arg
65                  70                  75                  80


Ser Gly Ser Leu Ile Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys
                85                  90                  95


Ala Gln Ser Pro Arg Cys Leu Ile Asn Ile Asn Thr Leu Val Glu Asp
            100                 105                 110


Lys Gly Lys Leu Phe Gly Val Glu Ile Glu Ile Ile Asp Ile Asn Asp
        115                 120                 125


Asn Asn Pro Lys Phe Gln Val Glu Asp Leu Glu Val Lys Ile Asn Glu
    130                 135                 140
```

```
Ile Ala Val Pro Gly Ala Arg Tyr Pro Leu Pro Glu Ala Val Asp Pro
145                 150                 155                 160

Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn His
                165                 170                 175

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

Glu Leu Val Leu Glu Arg Ala Leu Asp Arg Glu Glu Glu Ala Ala His
        195                 200                 205

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

Thr Val Arg Ile His Val Thr Val Leu Asp Thr Asn Asp Asn Ala Pro
225                 230                 235                 240

Val Phe Pro His Pro Ile Tyr Arg Val Lys Val Leu Glu Asn Met Pro
                245                 250                 255

Pro Gly Thr Arg Leu Leu Thr Val Thr Ala Ser Asp Pro Asp Glu Gly
            260                 265                 270

Ile Asn Gly Lys Val Ala Tyr Lys Phe Arg Lys Ile Asn Glu Lys Gln
        275                 280                 285

Thr Pro Leu Phe Gln Leu Asn Glu Asn Thr Gly Glu Ile Ser Ile Ala
    290                 295                 300

Lys Ser Leu Asp Tyr Glu Glu Cys Ser Phe Tyr Glu Met Glu Ile Gln
305                 310                 315                 320

Ala Glu Asp Val Gly Ala Leu Leu Gly Arg Thr Lys Leu Leu Ile Ser
                325                 330                 335

Val Glu Asp Val Asn Asp Asn Arg Pro Glu Val Ile Ile Thr Ser Leu
            340                 345                 350

Phe Ser Pro Val Leu Glu Asn Ser Leu Pro Gly Thr Val Ile Ala Phe
        355                 360                 365

Leu Ser Val His Asp Gln Asp Ser Gly Lys Asn Gly Gln Val Val Cys
    370                 375                 380
```

```
Tyr Thr Arg Asp Asn Leu Pro Phe Lys Leu Glu Lys Ser Ile Gly Asn
385                 390                 395                 400

Tyr Tyr Arg Leu Val Thr Arg Lys Tyr Leu Asp Arg Glu Asn Val Ser
                405                 410                 415

Ile Tyr Asn Ile Thr Val Met Ala Ser Asp Leu Gly Thr Pro Pro Leu
            420                 425                 430

Ser Thr Glu Thr Gln Ile Ala Leu His Val Ala Asp Ile Asn Asp Asn
        435                 440                 445

Pro Pro Thr Phe Pro His Ala Ser Tyr Ser Ala Tyr Ile Leu Glu Asn
    450                 455                 460

Asn Leu Arg Gly Ala Ser Ile Phe Ser Leu Thr Ala His Asp Pro Asp
465                 470                 475                 480

Ser Gln Glu Asn Ala Gln Val Thr Tyr Ser Val Thr Glu Asp Thr Leu
                485                 490                 495

Gln Gly Ala Pro Leu Ser Ser Tyr Ile Ser Ile Asn Ser Asp Thr Gly
            500                 505                 510

Val Leu Tyr Ala Leu Gln Ser Phe Asp Tyr Glu Gln Ile Arg Asp Leu
        515                 520                 525

Gln Leu Leu Val Thr Ala Ser Asp Ser Gly Asp Pro Pro Leu Ser Ser
    530                 535                 540

Asn Met Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala Pro
545                 550                 555                 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu
                565                 570                 575

Leu Ala Pro Arg Ser Ala Glu Arg Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu
        595                 600                 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly
    610                 615                 620
```

```
Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln
625                 630                 635                 640

Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile Pro Glu Val Leu
            660                 665                 670

Thr Glu Leu Gly Ser Leu Lys Pro Ser Val Asp Pro Asn Asp Ser Ser
        675                 680                 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Ile Ser Cys Val Phe
    690                 695                 700

Leu Ala Phe Val Ala Val Leu Leu Gly Leu Arg Leu Arg Arg Trp His
705                 710                 715                 720

Lys Ser Arg Leu Leu Gln Asp Ser Gly Gly Arg Leu Val Gly Val Pro
                725                 730                 735

Ala Ser His Phe Val Gly Val Glu Glu Val Gln Ala Phe Leu Gln Thr
            740                 745                 750

Tyr Ser Gln Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu
        755                 760                 765

Ile Phe Pro Gln Pro Asn Tyr Ala Asp Met Leu Ile Ser Gln Glu Gly
    770                 775                 780

Cys Glu Lys Asn Asp Ser Leu Leu Thr Ser Val Asp Phe His Glu Tyr
785                 790                 795                 800

Lys Asn Glu Ala Asp His Gly Gln Gln Ala Pro Pro Asn Thr Asp Trp
                805                 810                 815

Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly
            820                 825                 830

Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu
        835                 840                 845

Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser
    850                 855                 860
```

```
Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly
865                 870                 875                 880


Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr
                885                 890                 895


Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp
            900                 905                 910


Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys
        915                 920                 925


Lys Glu Lys Lys
    930


<210>  116
<211>  923
<212>  PRT
<213>  Homo sapiens

<400>  116

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


Leu Phe Leu Phe Leu Leu Ser Leu Phe Cys Pro Ala Leu Cys Glu Gln
            20                  25                  30


Ile Arg Tyr Arg Ile Pro Glu Glu Met Pro Lys Gly Ser Val Val Gly
        35                  40                  45


Asn Leu Ala Thr Asp Leu Gly Phe Ser Val Gln Glu Leu Pro Thr Arg
    50                  55                  60


Lys Leu Arg Val Ser Ser Glu Lys Pro Tyr Phe Thr Val Ser Ala Glu
65                  70                  75                  80


Ser Gly Glu Leu Leu Val Ser Ser Arg Leu Asp Arg Glu Glu Ile Cys
                85                  90                  95


Gly Lys Lys Pro Ala Cys Ala Leu Glu Phe Glu Ala Val Ala Glu Asn
            100                 105                 110


Pro Leu Asn Phe Tyr His Val Asn Val Glu Ile Glu Asp Ile Asn Asp
        115                 120                 125
```

```
His Thr Pro Lys Phe Thr Gln Asn Ser Phe Glu Leu Gln Ile Ser Glu
    130                 135                 140

Ser Ala Gln Pro Gly Thr Arg Phe Ile Leu Glu Val Ala Glu Asp Ala
145                 150                 155                 160

Asp Ile Gly Leu Asn Ser Leu Gln Lys Tyr Lys Leu Ser Leu Asn Pro
                165                 170                 175

Ser Phe Ser Leu Ile Ile Lys Glu Lys Gln Asp Gly Ser Lys Tyr Pro
            180                 185                 190

Glu Leu Ala Leu Glu Lys Thr Leu Asp Arg Glu Gln Gln Ser Tyr His
        195                 200                 205

Arg Leu Val Leu Thr Ala Leu Asp Gly Gly His Pro Pro Leu Ser Gly
    210                 215                 220

Thr Thr Glu Leu Arg Ile Gln Val Thr Asp Ala Asn Asp Asn Pro Pro
225                 230                 235                 240

Val Phe Asn Arg Asp Val Tyr Arg Val Ser Leu Arg Glu Asn Val Pro
                245                 250                 255

Pro Gly Thr Thr Val Leu Gln Val Ser Ala Thr Asp Gln Asp Glu Gly
            260                 265                 270

Ile Asn Ser Glu Ile Thr Tyr Ser Phe Tyr Arg Thr Gly Gln Ile Phe
        275                 280                 285

Ser Leu Asn Ser Lys Ser Gly Glu Ile Thr Thr Gln Lys Lys Leu Asp
    290                 295                 300

Phe Glu Glu Thr Lys Glu Tyr Ser Met Val Val Glu Gly Arg Asp Gly
305                 310                 315                 320

Gly Gly Leu Val Ala Gln Cys Thr Val Glu Ile Asn Ile Gln Asp Glu
                325                 330                 335

Asn Asp Asn Ser Pro Glu Val Thr Phe His Ser Leu Leu Glu Met Ile
            340                 345                 350

Leu Glu Asn Ala Val Pro Gly Thr Leu Ile Ala Leu Ile Lys Ile His
        355                 360                 365
```

```
Asp Gln Asp Ser Gly Glu Asn Gly Glu Val Asn Cys Gln Leu Gln Gly
    370                 375                 380

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

Val Thr Asp Gly Thr Leu Asp Arg Glu Gln Thr Pro Glu Tyr Asn Val
                405                 410                 415

Thr Ile Thr Ala Thr Asp Arg Gly Lys Pro Pro Leu Ser Ser Ser Ile
            420                 425                 430

Ser Val Ile Leu His Ile Arg Asp Val Asn Asp Asn Ala Pro Val Phe
        435                 440                 445

His Gln Ala Ser Tyr Leu Val Ser Val Pro Glu Asn Asn Pro Pro Gly
    450                 455                 460

Ala Ser Ile Ala Gln Val Cys Ala Ser Asp Leu Asp Leu Gly Leu Asn
465                 470                 475                 480

Gly Gln Val Ser Tyr Ser Ile Met Ala Ser Asp Leu Glu Pro Leu Ala
                485                 490                 495

Leu Ala Ser Tyr Val Ser Met Ser Ala Gln Ser Gly Val Val Phe Ala
            500                 505                 510

Gln Arg Ala Phe Asp Tyr Glu Gln Leu Arg Thr Phe Glu Leu Thr Leu
        515                 520                 525

Gln Ala Arg Asp Gln Gly Ser Pro Ala Leu Ser Ala Asn Val Ser Leu
    530                 535                 540

Arg Val Leu Val Gly Asp Arg Asn Asp Asn Ala Pro Arg Val Leu Tyr
545                 550                 555                 560

Pro Ala Leu Gly Pro Asp Gly Ser Ala Leu Phe Asp Met Val Pro Arg
                565                 570                 575

Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val Ala Val Asp Ala
            580                 585                 590

Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val Leu Gln Ala Ser
        595                 600                 605
```

```
Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly Glu Val Arg Thr
    610                 615                 620


Ala Arg Ala Leu Gly Asp Arg Asp Ala Ala Arg Gln Arg Leu Leu Val
625                 630                 635                 640


Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala Thr Ala Thr Leu
                645                 650                 655


His Leu Val Phe Ala Asp Ser Leu Gln Glu Val Leu Pro Asp Ile Thr
            660                 665                 670


Asp Arg Pro Val Pro Ser Asp Pro Gln Ala Glu Leu Gln Phe Tyr Leu
        675                 680                 685


Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu Leu Ala Val Ile
    690                 695                 700


Leu Ala Val Ala Leu Arg Leu Arg Arg Ser Ser Ser Pro Ala Ala Trp
705                 710                 715                 720


Ser Cys Phe Gln Pro Gly Leu Cys Val Lys Ser Gly Pro Val Val Pro
                725                 730                 735


Pro Asn Tyr Ser Gln Gly Thr Leu Pro Tyr Ser Tyr Asn Leu Cys Val
            740                 745                 750


Ala His Thr Gly Lys Thr Glu Phe Asn Phe Leu Lys Cys Ser Glu Gln
        755                 760                 765


Leu Ser Ser Gly Gln Asp Ile Leu Cys Gly Asp Ser Ser Gly Ala Leu
    770                 775                 780


Phe Pro Leu Cys Asn Ser Ser Glu Ser Thr Ser His Pro Glu Leu Gln
785                 790                 795                 800


Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser Gln Ala Gln Arg Pro Gly
                805                 810                 815


Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr Gly Thr Trp Pro Asn Asn
            820                 825                 830


Gln Phe Asp Thr Glu Met Leu Gln Ala Met Ile Leu Ala Ser Ala Ser
        835                 840                 845
```

Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly Gly Gly Ala Gly Thr Met
    850   855   860

Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe Thr Leu Gln His Val Pro
865   870   875   880

Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly Ser Asn Ala Thr Leu Thr
                885   890   895

Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala Pro Ala Gly Gly Asn Gly
            900   905   910

Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys Lys
        915   920

<210> 117
<211> 932
<212> PRT
<213> Homo sapiens

<400> 117

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

Cys Ser Leu Leu Gly Met Leu Trp Glu Ala Arg Ala Ser Gln Ile Arg
            20   25   30

Tyr Ser Val Pro Glu Glu Thr Glu Lys Gly Tyr Ile Val Gly Asn Ile
        35   40   45

Ser Lys Asp Leu Ala Leu Glu Pro Arg Glu Leu Ala Glu Arg Arg Val
    50   55   60

Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ser Leu Asn Pro Arg
65   70   75   80

Ser Gly Thr Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys
                85   90   95

Ala Gln Ser Pro Arg Cys Leu Val Asn Phe Lys Val Leu Val Glu Asp
            100   105   110

Arg Val Lys Leu Tyr Gly Ile Glu Ile Glu Val Thr Asp Ile Asn Asp
        115   120   125

```
Ser Ala Pro Lys Phe Gln Ala Glu Ser Leu Glu Val Lys Ile Asn Glu
    130                 135                 140


Ile Ala Val Pro Gly Ala Arg Tyr Pro Leu Pro Glu Ala Ile Asp Pro
145                 150                 155                 160


Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn His
                165                 170                 175


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


Glu Leu Val Leu Glu Arg Ala Leu Asp Arg Glu Glu Ala Thr Ala His
        195                 200                 205


His Leu Val Leu Thr Ala Ser Asp Gly Gly Glu Pro Arg Arg Ser Ser
    210                 215                 220


Thr Val Arg Ile His Val Thr Val Leu Asp Thr Asn Asp Asn Ala Pro
225                 230                 235                 240


Val Phe Ala Gln Arg Ile Tyr Arg Val Lys Val Leu Glu Asn Val Pro
                245                 250                 255


Pro Gly Thr Trp Leu Leu Thr Ala Thr Ala Ser Asp Leu Asp Glu Gly
            260                 265                 270


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


Ser Leu Leu Phe Gln Leu Asn Glu Asn Thr Gly Glu Ile Ser Thr Ala
    290                 295                 300


Lys Ser Leu Asp Tyr Glu Glu Cys Ser Phe Tyr Glu Met Glu Ile Gln
305                 310                 315                 320


Ala Glu Asp Gly Gly Gly Leu Lys Gly Trp Thr Lys Val Leu Ile Ser
                325                 330                 335


Val Glu Asp Val Asn Asp Asn Arg Pro Glu Val Thr Ile Thr Ser Leu
            340                 345                 350


Phe Ser Pro Val Arg Glu Asp Ala Pro Gln Gly Thr Val Ile Leu Leu
        355                 360                 365
```

```
Phe Asn Ala His Asp Arg Asp Ser Gly Lys Asn Gly Gln Val Val Cys
    370                 375                 380

Ser Ile Gln Glu Asn Leu Ser Phe Thr Leu Glu Asn Ser Glu Glu Asp
385                 390                 395                 400

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

Glu Tyr Asn Ile Thr Val Thr Ala Thr Asp Arg Gly Thr Pro Pro Leu
            420                 425                 430

Ser Thr Glu Ile His Ile Thr Leu Gln Val Thr Asp Ile Asn Asp Asn
        435                 440                 445

Pro Pro Ala Phe Ser Gln Ala Ser Tyr Ser Val Tyr Leu Pro Glu Asn
    450                 455                 460

Asn Ala Arg Gly Thr Ser Ile Phe Ser Val Ile Ala Tyr Asp Pro Asp
465                 470                 475                 480

Ser Asn Glu Asn Ser Arg Val Ile Tyr Ser Leu Ala Glu Asp Thr Ile
                485                 490                 495

Gln Gly Ser Pro Leu Ser Thr Tyr Val Ser Ile Asn Ser Asp Thr Gly
            500                 505                 510

Val Leu Tyr Ala Leu Cys Ser Phe Asp Tyr Glu Gln Phe Arg Asp Leu
        515                 520                 525

Gln Met Gln Val Thr Ala Ser Asp Ser Gly Ser Pro Pro Leu Ser Ser
    530                 535                 540

Asn Val Ser Leu Arg Leu Phe Val Leu Asp Gln Asn Asp Asn Ala Pro
545                 550                 555                 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu
                565                 570                 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu
        595                 600                 605
```

```
Phe Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly
    610                 615                 620


Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln
625                 630                 635                 640


Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655


Thr Val Thr Leu Thr Val Ala Ile Ala Asp Ser Ile Pro Asp Ile Leu
            660                 665                 670


Ala Asp Leu Gly Ser Leu Gln Ile Pro Ala Asp Leu Glu Ala Ser Asp
        675                 680                 685


Leu Thr Leu Tyr Leu Val Val Ala Val Ala Val Val Ser Cys Val Phe
    690                 695                 700


Leu Thr Phe Val Ile Thr Leu Leu Ala Leu Arg Leu Arg His Trp His
705                 710                 715                 720


Ser Ser His Leu Leu Arg Ala Thr Ser Asp Gly Leu Ala Gly Val Pro
                725                 730                 735


Thr Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr
            740                 745                 750


Tyr Ser Gln Glu Phe Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu
        755                 760                 765


Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile Ser Gln Gln Ser
    770                 775                 780


Cys Glu Lys Asn Glu Pro Leu Cys Val Ser Val Asp Ser Lys Phe Pro
785                 790                 795                 800


Ile Glu Asp Thr Pro Leu Val Pro Gln Ala Pro Pro Asn Thr Asp Trp
                805                 810                 815


Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly
            820                 825                 830


Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu
        835                 840                 845
```

```
Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser
    850                 855                 860


Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly
865                 870                 875                 880


Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr
                885                 890                 895


Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp
            900                 905                 910


Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys
        915                 920                 925


Lys Glu Lys Lys
    930


<210>  118
<211>  930
<212>  PRT
<213>  Homo sapiens

<400>  118

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


Leu Phe Pro Leu Leu Leu Pro Leu Phe Tyr Pro Thr Leu Ser Glu Pro
            20                  25                  30


Ile Arg Tyr Ser Ile Pro Glu Glu Leu Ala Lys Gly Ser Val Val Gly
        35                  40                  45


Asn Leu Ala Lys Asp Leu Gly Leu Ser Val Leu Asp Val Ser Ala Arg
    50                  55                  60


Lys Leu Arg Val Ser Ala Glu Lys Leu His Phe Ser Val Asp Ala Glu
65                  70                  75                  80


Ser Gly Asp Leu Leu Val Lys Asn Arg Ile Asp Arg Glu Gln Ile Cys
                85                  90                  95


Lys Glu Arg Arg Arg Cys Glu Leu Gln Leu Glu Ala Val Val Glu Asn
            100                 105                 110
```

```
Pro Leu Asn Ile Phe His Val Ile Val Val Ile Glu Asp Val Asn Asp
        115                 120                 125

His Ala Pro Gln Phe Asp Lys Lys Glu Ile His Leu Glu Ile Phe Glu
    130                 135                 140

Ser Ala Ser Ala Gly Thr Arg Leu Ser Leu Asp Pro Ala Thr Asp Pro
145                 150                 155                 160

Asp Ile Asn Ile Asn Ser Ile Lys Asp Tyr Lys Ile Asn Ser Asn Pro
                165                 170                 175

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

Glu Leu Ser Leu Glu Lys Leu Leu Asp Arg Glu Glu Gln Arg Ser His
        195                 200                 205

Ser Leu Ile Leu Thr Ala Leu Asp Gly Gly Asp Pro Pro Arg Ser Ala
    210                 215                 220

Thr Ala His Ile Glu Ile Ser Val Lys Asp Thr Asn Asp Asn Pro Pro
225                 230                 235                 240

Val Phe Ser Arg Asp Glu Tyr Arg Ile Ser Leu Ser Glu Asn Leu Pro
                245                 250                 255

Pro Gly Ser Pro Val Leu Gln Val Thr Ala Thr Asp Gln Asp Glu Gly
            260                 265                 270

Val Asn Ala Glu Ile Asn Tyr Tyr Phe Arg Ser Thr Ala Gln Ser Thr
        275                 280                 285

Lys His Met Phe Ser Leu Asp Glu Lys Thr Gly Met Ile Lys Asn Asn
    290                 295                 300

Gln Ser Phe Asp Phe Glu Asp Val Glu Arg Tyr Thr Met Glu Val Glu
305                 310                 315                 320

Ala Lys Asp Gly Gly Gly Leu Ser Thr Gln Cys Lys Val Ile Ile Glu
                325                 330                 335

Ile Leu Asp Glu Asn Asp Asn Ser Pro Glu Ile Ile Ile Thr Ser Leu
            340                 345                 350
```

```
Ser Asp Gln Ile Leu Glu Asn Ser Pro Pro Gly Met Val Val Ala Leu
        355                 360                 365

Phe Lys Thr Arg Asp Leu Asp Phe Gly Gly Asn Gly Glu Val Arg Cys
    370                 375                 380

Asn Ile Glu Thr Asp Ile Pro Phe Lys Ile Tyr Ser Ser Ser Asn Asn
385                 390                 395                 400

Tyr Tyr Lys Leu Val Thr Asp Gly Ala Leu Asp Arg Glu Gln Thr Pro
                405                 410                 415

Glu Tyr Asn Val Thr Ile Val Ala Thr Asp Arg Gly Lys Pro Pro Leu
            420                 425                 430

Ser Ser Ser Arg Ser Ile Thr Leu Tyr Val Ala Asp Ile Asn Asp Asn
        435                 440                 445

Ala Pro Val Phe Asp Gln Thr Ser Tyr Val Val His Val Ala Glu Asn
    450                 455                 460

Asn Pro Pro Gly Ala Ser Ile Ala Gln Val Ser Ala Ser Asp Pro Asp
465                 470                 475                 480

Leu Gly Leu Asn Gly His Ile Ser Tyr Ser Ile Val Ala Ser Asp Leu
                485                 490                 495

Glu Pro Leu Ala Val Ser Ser Tyr Val Ser Val Ser Ala Gln Ser Gly
            500                 505                 510

Val Val Phe Ala Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe
        515                 520                 525

Ala Leu Thr Leu Gln Ala Arg Asp His Gly Ser Pro Thr Leu Ser Ala
    530                 535                 540

Asn Val Ser Leu Arg Val Leu Val Gly Asp Arg Asn Asp Asn Ala Pro
545                 550                 555                 560

Arg Val Leu Tyr Pro Ala Leu Gly Pro Asp Gly Ser Ala Phe Phe Asp
                565                 570                 575

Met Val Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val
            580                 585                 590
```

```
Ala Val Asp Ala Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val
        595                 600                 605


Leu Gln Ala Ser Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly
    610                 615                 620


Glu Val Arg Thr Ala Arg Ala Leu Gly Asp Arg Asp Ala Ala Arg Gln
625                 630                 635                 640


Arg Leu Leu Val Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala
                645                 650                 655


Thr Ala Thr Leu His Leu Val Phe Ala Asp Asn Leu Gln Glu Ile Leu
            660                 665                 670


Pro Asp Leu Ser Asp Arg Pro Val Leu Ser Asp Pro Gln Ala Glu Leu
        675                 680                 685


Gln Phe Tyr Leu Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu
    690                 695                 700


Leu Ala Val Ile Leu Ala Ile Ala Leu Arg Leu Arg Arg Ser Leu Ser
705                 710                 715                 720


Pro Ala Thr Trp Asp Cys Phe His Pro Gly Leu Cys Val Lys Ser Gly
                725                 730                 735


Pro Val Val Pro Pro Asn Tyr Ser Glu Gly Thr Leu Pro Tyr Ser Tyr
            740                 745                 750


Asn Leu Cys Ile Ala His Thr Gly Thr Lys Glu Phe Asn Phe Leu Lys
        755                 760                 765


Cys Ser Val Pro Leu His Ser Asn Glu Asp Met Val Cys Ser Val Ser
    770                 775                 780


Pro Gly Ala Leu Ile Pro Pro His Gly Gly Glu Asp Leu Thr Ser His
785                 790                 795                 800


Pro Glu Thr Leu Thr Ser Gln Ala Pro Pro Asn Thr Asp Trp Arg Phe
                805                 810                 815


Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp Asp
            820                 825                 830
```

```
Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln Ala
        835                 840                 845


Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr Leu
    850                 855                 860


Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro Gln
865                 870                 875                 880


Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile Pro
                885                 890                 895


Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly Lys
            900                 905                 910


Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys Glu
        915                 920                 925


Lys Lys
    930


<210>  119
<211>  936
<212>  PRT
<213>  Homo sapiens

<400>  119

Met Ala Ala Gln Arg Asn Arg Ser Lys Glu Ser Lys Asp Cys Ser Gly
1               5                   10                  15


Leu Val Leu Leu Cys Leu Phe Phe Gly Ile Pro Trp Glu Ala Gly Ala
            20                  25                  30


Arg Gln Ile Ser Tyr Ser Ile Pro Glu Glu Leu Glu Lys Gly Ser Phe
        35                  40                  45


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


Glu Arg Gly Val Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ser
65                  70                  75                  80


Leu Asn Pro Arg Ser Gly Ser Leu Ile Thr Ala Gly Arg Ile Asp Arg
                85                  90                  95
```

```
Glu Glu Leu Cys Ala Gln Ser Ala Arg Cys Val Val Ser Phe Asn Ile
            100                 105                 110


Leu Val Glu Asp Arg Val Lys Leu Phe Gly Ile Glu Ile Glu Val Thr
        115                 120                 125


Asp Ile Asn Asp Asn Ala Pro Lys Phe Gln Ala Glu Asn Leu Asp Val
    130                 135                 140


Lys Ile Asn Glu Asn Val Ala Ala Gly Met Arg Phe Pro Leu Pro Glu
145                 150                 155                 160


Ala Ile Asp Pro Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu
                165                 170                 175


Ser Pro Asn Lys His Phe Ser Leu Arg Val Gln Ser Arg Ala Asn Gly
            180                 185                 190


Val Lys Tyr Pro Glu Leu Val Leu Glu His Ser Leu Asp Arg Glu Glu
        195                 200                 205


Glu Ala Ile His His Leu Val Leu Thr Ala Ser Asp Gly Gly Asp Pro
    210                 215                 220


Leu Arg Ser Gly Thr Val Leu Val Ser Val Thr Val Phe Asp Ala Asn
225                 230                 235                 240


Asp Asn Ala Pro Val Phe Thr Leu Pro Glu Tyr Arg Val Ser Val Pro
                245                 250                 255


Glu Asn Leu Pro Val Gly Thr Gln Leu Leu Thr Val Thr Ala Thr Asp
            260                 265                 270


Arg Asp Glu Gly Ala Asn Gly Glu Val Thr Tyr Ser Phe Arg Lys Leu
        275                 280                 285


Pro Asp Thr Gln Leu Leu Lys Phe Gln Leu Asn Lys Tyr Thr Gly Glu
    290                 295                 300


Ile Lys Ile Ser Glu Asn Leu Asp Tyr Glu Glu Thr Gly Phe Tyr Glu
305                 310                 315                 320


Ile Glu Ile Gln Ala Glu Asp Gly Gly Ala Tyr Leu Ala Thr Ala Lys
                325                 330                 335
```

```
Val Leu Ile Thr Val Glu Asp Val Asn Asp Asn Ser Pro Glu Leu Thr
            340                 345                 350

Ile Thr Ser Leu Phe Ser Pro Val Thr Glu Asp Ser Pro Leu Gly Thr
        355                 360                 365

Val Val Ala Leu Leu Asn Val His Asp Leu Asp Ser Glu Gln Asn Gly
    370                 375                 380

Gln Val Thr Cys Ser Ile Leu Ala Tyr Leu Pro Phe Lys Leu Glu Lys
385                 390                 395                 400

Ser Ile Asp Ser Tyr Tyr Arg Leu Val Ile His Arg Ala Leu Asp Arg
                405                 410                 415

Glu Gln Val Ser Ser Tyr Asn Ile Thr Val Thr Ala Thr Asp Gly Gly
            420                 425                 430

Ser Pro Pro Leu Ser Thr Glu Ala His Phe Met Leu Gln Val Ala Asp
        435                 440                 445

Ile Asn Asp Asn Pro Pro Thr Phe Ser Gln Val Ser Tyr Phe Thr Tyr
    450                 455                 460

Ile Pro Glu Asn Asn Ala Arg Gly Ala Ser Ile Phe Ser Val Thr Ala
465                 470                 475                 480

Leu Asp Pro Asp Ser Lys Glu Asn Ala Gln Ile Ile Tyr Ser Leu Ala
                485                 490                 495

Glu Asp Thr Ile Gln Gly Val Pro Leu Ser Ser Tyr Ile Ser Ile Asn
            500                 505                 510

Ser Asp Thr Gly Val Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln
        515                 520                 525

Phe His Glu Leu Gln Met Gln Val Thr Ala Ser Asp Ser Gly Asp Pro
    530                 535                 540

Pro Leu Ser Ser Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn
545                 550                 555                 560

Asp Asn Ala Pro Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser
                565                 570                 575
```

```
Thr Gly Val Glu Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val
            580                 585                 590

Thr Lys Val Val Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu
        595                 600                 605

Ser Tyr Arg Leu Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly
    610                 615                 620

Glu His Thr Gly Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp
625                 630                 635                 640

Ala Leu Lys Gln Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro
                645                 650                 655

Pro Leu Ser Ala Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile
            660                 665                 670

Pro Gln Val Leu Ala Asp Leu Gly Ser Phe Glu Ser Pro Ala Asn Ser
        675                 680                 685

Glu Thr Ser Asp Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val
    690                 695                 700

Ser Cys Val Phe Leu Ala Phe Val Ile Val Leu Leu Ala His Arg Leu
705                 710                 715                 720

Arg Arg Trp His Lys Ser Arg Leu Leu Gln Ala Ser Gly Gly Gly Leu
                725                 730                 735

Thr Gly Val Ser Gly Ser His Phe Val Gly Val Asp Gly Val Arg Ala
            740                 745                 750

Phe Leu Gln Thr Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg
        755                 760                 765

Lys Ser His Leu Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile
    770                 775                 780

Ser Gln Glu Ser Cys Glu Lys Asn Asp Pro Leu Ser Leu Leu Asp Asp
785                 790                 795                 800

Ser Lys Phe Pro Ile Glu Asp Thr Pro Leu Val Pro Gln Ala Pro Pro
                805                 810                 815
```

```
Asn Thr Asp Trp Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly
            820                 825                 830


Ser Gln Asn Gly Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp
        835                 840                 845


Thr Glu Met Leu Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala
    850                 855                 860


Asp Gly Ser Ser Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser
865                 870                 875                 880


Ala Arg Tyr Gly Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg
                885                 890                 895


Gln Asn Val Tyr Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala
            900                 905                 910


Gly Lys Arg Asp Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys
        915                 920                 925


Lys Ser Gly Lys Lys Glu Lys Lys
    930                 935


<210>  120
<211>  935
<212>  PRT
<213>  Homo sapiens

<400>  120

Met Ala Asn Arg Leu Gln Arg Gly Asp Arg Ser Arg Leu Leu Leu Leu
1               5                   10                  15


Leu Cys Ile Phe Leu Gly Thr Leu Arg Gly Phe Arg Ala Arg Gln Ile
            20                  25                  30


Arg Tyr Ser Val Pro Glu Glu Thr Glu Lys Gly Ser Phe Val Gly Asn
        35                  40                  45


Ile Ser Lys Asp Leu Gly Leu Glu Pro Arg Glu Leu Ala Lys Arg Gly
    50                  55                  60


Val Arg Ile Val Ser Arg Gly Lys Thr Gln Leu Phe Ala Val Asn Pro
65                  70                  75                  80
```

```
Arg Ser Gly Ser Leu Ile Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu
                85                  90                  95

Cys Glu Thr Val Ser Ser Cys Phe Leu Asn Met Glu Leu Leu Val Glu
            100                 105                 110

Asp Thr Leu Lys Ile Tyr Gly Val Glu Val Glu Ile Ile Asp Ile Asn
        115                 120                 125

Asp Asn Ala Pro Ser Phe Gln Glu Asp Glu Val Glu Ile Lys Val Ser
    130                 135                 140

Glu His Ala Ile Pro Gly Ala Arg Phe Ala Leu Pro Asn Ala Arg Asp
145                 150                 155                 160

Pro Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn
                165                 170                 175

Asn Tyr Phe Ser Leu Gln Leu Arg Gly Arg Thr Asp Gly Ala Lys Asn
            180                 185                 190

Pro Glu Leu Val Leu Glu Gly Ser Leu Asp Arg Glu Lys Glu Ala Ala
        195                 200                 205

His Leu Leu Leu Leu Thr Ala Leu Asp Gly Gly Asp Pro Ile Arg Lys
    210                 215                 220

Gly Ala Val Pro Ile Arg Val Val Val Leu Asp Val Asn Asp His Ile
225                 230                 235                 240

Pro Met Phe Thr Gln Ser Val Tyr Arg Val Ser Val Pro Glu Asn Ile
                245                 250                 255

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

Gly Ile Asn Gly Glu Val Met Tyr Ser Phe Arg Asn Met Glu Ser Lys
        275                 280                 285

Ala Ser Glu Ile Phe Gln Leu Asp Ser Gln Thr Gly Glu Val Gln Val
    290                 295                 300

Arg Gly Ser Leu Asp Phe Glu Lys Tyr Arg Phe Tyr Glu Met Glu Ile
305                 310                 315                 320
```

Gln Gly Gln Asp Gly Gly Gly Leu Phe Thr Thr Thr Thr Met Leu Ile
325 330 335

Thr Val Val Asp Val Asn Asp Asn Ala Pro Glu Ile Thr Ile Thr Ser
340 345 350

Ser Ile Asn Ser Ile Leu Glu Asn Ser Pro Pro Gly Thr Val Ile Ala
355 360 365

Leu Leu Asn Val Gln Asp Gln Asp Ser Gly Glu Asn Gly Gln Val Ser
370 375 380

Cys Phe Ile Pro Asn His Leu Pro Phe Lys Leu Glu Lys Thr Tyr Gly
385 390 395 400

Asn Tyr Tyr Lys Leu Ile Thr Ser Arg Val Leu Asp Arg Glu Leu Val
405 410 415

Gln Ser Tyr Asn Ile Thr Leu Thr Ala Thr Asp Gln Gly Ser Pro Pro
420 425 430

Leu Ser Ala Glu Thr His Val Trp Leu Asn Val Ala Asp Asp Asn Asp
435 440 445

Asn Pro Pro Val Phe Pro His Ser Ser Tyr Ser Ala Tyr Ile Pro Glu
450 455 460

Asn Asn Pro Arg Gly Ala Ser Ile Phe Ser Val Thr Ala Leu Asp Pro
465 470 475 480

Asp Ser Lys Gln Asn Ala Leu Val Thr Tyr Ser Leu Thr Asp Asp Thr
485 490 495

Val Gln Gly Val Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asn Thr
500 505 510

Gly Val Leu Tyr Ala Leu Gln Ser Phe Asp Tyr Glu Gln Phe Arg Asp
515 520 525

Leu Glu Leu Arg Val Ile Ala Arg Asp Ser Gly Asp Pro Pro Leu Ser
530 535 540

Ser Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala
545 550 555 560

```
Pro Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val
                565                 570                 575

Glu Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val
            580                 585                 590

Val Ala Val Asp Lys Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg
        595                 600                 605

Leu Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly Glu His Thr
    610                 615                 620

Gly Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys
625                 630                 635                 640

Gln Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser
                645                 650                 655

Ala Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile Pro Glu Val
            660                 665                 670

Leu Ala Asp Leu Gly Ser Leu Glu Ser Leu Ala Asn Ser Glu Thr Ser
        675                 680                 685

Asp Leu Ser Leu Tyr Leu Val Val Ala Val Ala Ala Val Ser Cys Ile
    690                 695                 700

Phe Leu Val Phe Val Ile Val Leu Leu Ala Leu Arg Leu Trp Arg Trp
705                 710                 715                 720

His Lys Ser Arg Leu Leu Gln Ala Ser Glu Gly Gly Leu Ala Gly Met
                725                 730                 735

Pro Thr Ser His Phe Val Gly Val Asp Gly Val Gln Ala Phe Leu Gln
            740                 745                 750

Thr Tyr Ser His Glu Val Ser Leu Ile Ala Asp Ser Gln Lys Ser His
        755                 760                 765

Leu Ile Phe Pro Gln Pro Asn Tyr Gly Asp Thr Leu Ile Ser Gln Glu
    770                 775                 780

Ser Cys Glu Lys Ser Glu Pro Leu Leu Ile Ala Glu Asp Ser Ala Ile
785                 790                 795                 800
```

```
Ile Leu Gly Lys Cys Asp Pro Thr Ser Asn Gln Gln Ala Pro Pro Asn
                805                 810                 815


Thr Asp Trp Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser
            820                 825                 830


Gln Asn Gly Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr
        835                 840                 845


Glu Met Leu Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp
    850                 855                 860


Gly Ser Ser Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala
865                 870                 875                 880


Arg Tyr Gly Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln
                885                 890                 895


Asn Val Tyr Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly
            900                 905                 910


Lys Arg Asp Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys
        915                 920                 925


Ser Gly Lys Lys Glu Lys Lys
    930                 935


<210>  121
<211>  750
<212>  PRT
<213>  Homo sapiens

<400>  121

Met Ala Asn Arg Leu Gln Arg Gly Asp Arg Ser Arg Leu Leu Leu Leu
1               5                   10                  15


Leu Cys Ile Phe Leu Gly Thr Leu Arg Gly Phe Arg Ala Arg Gln Ile
            20                  25                  30


Arg Tyr Ser Val Pro Glu Glu Thr Glu Lys Gly Ser Phe Val Gly Asn
        35                  40                  45


Ile Ser Lys Asp Leu Gly Leu Glu Pro Arg Glu Leu Ala Lys Arg Gly
    50                  55                  60
```

```
Val Arg Ile Val Ser Arg Gly Lys Thr Gln Leu Phe Ala Val Asn Pro
65                  70                  75                  80


Arg Ser Gly Ser Leu Ile Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu
                85                  90                  95


Cys Glu Thr Val Ser Ser Cys Phe Leu Asn Met Glu Leu Leu Val Glu
            100                 105                 110


Asp Thr Leu Lys Ile Tyr Gly Val Glu Val Glu Ile Ile Asp Ile Asn
        115                 120                 125


Asp Asn Ala Pro Ser Phe Gln Glu Asp Glu Val Glu Ile Lys Val Ser
    130                 135                 140


Glu His Ala Ile Pro Gly Ala Arg Phe Ala Leu Pro Asn Ala Arg Asp
145                 150                 155                 160


Pro Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn
                165                 170                 175


Asn Tyr Phe Ser Leu Gln Leu Arg Gly Arg Thr Asp Gly Ala Lys Asn
            180                 185                 190


Pro Glu Leu Val Leu Glu Gly Ser Leu Asp Arg Glu Lys Glu Ala Ala
        195                 200                 205


His Leu Leu Leu Leu Thr Ala Leu Asp Gly Gly Asp Pro Ile Arg Lys
    210                 215                 220


Gly Ala Val Pro Ile Arg Val Val Val Leu Asp Val Asn Asp His Ile
225                 230                 235                 240


Pro Met Phe Thr Gln Ser Val Tyr Arg Val Ser Val Pro Glu Asn Ile
                245                 250                 255


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


Gly Ile Asn Gly Glu Val Met Tyr Ser Phe Arg Asn Met Glu Ser Lys
        275                 280                 285


Ala Ser Glu Ile Phe Gln Leu Asp Ser Gln Thr Gly Glu Val Gln Val
    290                 295                 300
```

```
Arg Gly Ser Leu Asp Phe Glu Lys Tyr Arg Phe Tyr Glu Met Glu Ile
305                 310                 315                 320

Gln Gly Gln Asp Gly Gly Gly Leu Phe Thr Thr Thr Thr Met Leu Ile
                325                 330                 335

Thr Val Val Asp Val Asn Asp Asn Ala Pro Glu Ile Thr Ile Thr Ser
            340                 345                 350

Ser Ile Asn Ser Ile Leu Glu Asn Ser Pro Pro Gly Thr Val Ile Ala
        355                 360                 365

Leu Leu Asn Val Gln Asp Gln Asp Ser Gly Glu Asn Gly Gln Val Ser
    370                 375                 380

Cys Phe Ile Pro Asn His Leu Pro Phe Lys Leu Glu Lys Thr Tyr Gly
385                 390                 395                 400

Asn Tyr Tyr Lys Leu Ile Thr Ser Arg Val Leu Asp Arg Glu Leu Val
                405                 410                 415

Gln Ser Tyr Asn Ile Thr Leu Thr Ala Thr Asp Gln Gly Ser Pro Pro
            420                 425                 430

Leu Ser Ala Glu Thr His Val Trp Leu Asn Val Ala Asp Asp Asn Asp
        435                 440                 445

Asn Pro Pro Val Phe Pro His Ser Ser Tyr Ser Ala Tyr Ile Pro Glu
    450                 455                 460

Asn Asn Pro Arg Gly Ala Ser Ile Phe Ser Val Thr Ala Leu Asp Pro
465                 470                 475                 480

Asp Ser Lys Gln Asn Ala Leu Val Thr Tyr Ser Leu Thr Asp Asp Thr
                485                 490                 495

Val Gln Gly Val Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asn Thr
            500                 505                 510

Gly Val Leu Tyr Ala Leu Gln Ser Phe Asp Tyr Glu Gln Phe Arg Asp
        515                 520                 525

Leu Glu Leu Arg Val Ile Ala Arg Asp Ser Gly Asp Pro Pro Leu Ser
    530                 535                 540
```

```
Ser Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala
545                 550                 555                 560

Pro Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val
                565                 570                 575

Glu Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val
            580                 585                 590

Val Ala Val Asp Lys Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg
        595                 600                 605

Leu Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly Glu His Thr
    610                 615                 620

Gly Glu Gln Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser Gln Ala Gln
625                 630                 635                 640

Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr Gly Thr Trp
                645                 650                 655

Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln Ala Met Ile Leu Ala
            660                 665                 670

Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly Gly Gly Ala
        675                 680                 685

Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe Thr Leu Gln
    690                 695                 700

His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly Ser Asn Ala
705                 710                 715                 720

Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala Pro Ala Gly
                725                 730                 735

Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys Lys
            740                 745                 750


<210>  122
<211>  462
<212>  PRT
<213>  Homo sapiens

<400>  122
```

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


Asn Gly Tyr Pro Val Pro Pro Tyr Ala Phe Phe Phe Pro Pro Met Leu
            20                  25                  30


Gly Gly Leu Ser Pro Pro Gly Ala Leu Thr Thr Leu Gln His Gln Leu
        35                  40                  45


Pro Val Ser Gly Tyr Ser Thr Pro Ser Pro Ala Thr Ile Glu Thr Gln
    50                  55                  60


Ser Ser Ser Ser Glu Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro
65                  70                  75                  80


Leu Pro Arg Ile Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser
                85                  90                  95


Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe
            100                 105                 110


Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys
        115                 120                 125


Asn Cys Ile Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg
    130                 135                 140


Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn
145                 150                 155                 160


Asp Arg Asn Lys Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu
                165                 170                 175


Ser Tyr Thr Leu Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg
            180                 185                 190


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


Thr Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu
    210                 215                 220


Trp Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val
225                 230                 235                 240
```

```
Glu Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp
                245                 250                 255

Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg
            260                 265                 270

Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp
        275                 280                 285

Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro
    290                 295                 300

Leu Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu
305                 310                 315                 320

Met Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys
                325                 330                 335

Gly Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln
            340                 345                 350

Glu Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro
        355                 360                 365

Ser Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu
    370                 375                 380

Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met
385                 390                 395                 400

Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn
                405                 410                 415

Ser Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg
            420                 425                 430

Asp Gly Gly Gly Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu
        435                 440                 445

Ser Pro Ser Ser Asn Arg Ser Ser Pro Ala Thr His Ser Pro
    450                 455                 460

<210>  123
<211>  462
```

```
<212>  PRT
<213>  Homo sapiens

<400>  123

Met Ala Ser Asn Ser Ser Ser Cys Pro Thr Pro Gly Gly Gly His Leu
1               5                   10                  15


Asn Gly Tyr Pro Val Pro Pro Tyr Ala Phe Phe Phe Pro Pro Met Leu
            20                  25                  30


Gly Gly Leu Ser Pro Pro Gly Ala Leu Thr Thr Leu Gln His Gln Leu
        35                  40                  45


Pro Val Ser Gly Tyr Ser Thr Pro Ser Pro Ala Thr Ile Glu Thr Gln
    50                  55                  60


Ser Ser Ser Ser Glu Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro
65                  70                  75                  80


Leu Pro Arg Ile Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser
                85                  90                  95


Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe
            100                 105                 110


Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys
        115                 120                 125


Asn Cys Ile Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg
    130                 135                 140


Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn
145                 150                 155                 160


Asp Arg Asn Lys Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu
                165                 170                 175


Ser Tyr Thr Leu Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg
            180                 185                 190


Lys Ala His Gln Glu Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr
        195                 200                 205
```

```
Thr Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu
    210                 215                 220

Trp Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val
225                 230                 235                 240

Glu Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp
                245                 250                 255

Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg
            260                 265                 270

Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp
        275                 280                 285

Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro
    290                 295                 300

Leu Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu
305                 310                 315                 320

Met Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys
                325                 330                 335

Gly Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln
            340                 345                 350

Glu Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro
        355                 360                 365

Ser Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu
    370                 375                 380

Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met
385                 390                 395                 400

Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn
                405                 410                 415

Ser Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg
            420                 425                 430

Asp Gly Gly Gly Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu
        435                 440                 445
```

```
Ser Pro Ser Ser Asn Arg Ser Ser Pro Ala Thr His Ser Pro
    450                 455                 460


<210>  124
<211>  365
<212>  PRT
<213>  Homo sapiens

<400>  124

Met Ala Ser Asn Ser Ser Ser Cys Pro Thr Pro Gly Gly Gly His Leu
1               5                   10                  15


Asn Gly Tyr Pro Val Pro Pro Tyr Ala Phe Phe Phe Pro Pro Met Leu
            20                  25                  30


Gly Gly Leu Ser Pro Pro Gly Ala Leu Thr Thr Leu Gln His Gln Leu
        35                  40                  45


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


Arg Asn Lys Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu Ser
65                  70                  75                  80


Tyr Thr Leu Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg Lys
                85                  90                  95


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


Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu Trp
        115                 120                 125


Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val Glu
    130                 135                 140


Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp Gln
145                 150                 155                 160


Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg Ile
                165                 170                 175


Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp Gly
            180                 185                 190
```

```
Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro Leu
        195                 200                 205


Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu Met
    210                 215                 220


Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys Gly
225                 230                 235                 240


Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln Glu
                245                 250                 255


Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro Ser
            260                 265                 270


Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu Arg
        275                 280                 285


Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met Glu
    290                 295                 300


Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn Ser
305                 310                 315                 320


Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg Asp
                325                 330                 335


Gly Gly Gly Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu Ser
            340                 345                 350


Pro Ser Ser Asn Arg Ser Ser Pro Ala Thr His Ser Pro
        355                 360                 365


<210>  125
<211>  457
<212>  PRT
<213>  Homo sapiens

<400>  125

Met Tyr Glu Ser Val Glu Val Gly Gly Pro Thr Pro Asn Pro Phe Leu
1               5                   10                  15


Val Val Asp Phe Tyr Asn Gln Asn Arg Ala Cys Leu Leu Pro Glu Lys
            20                  25                  30
```

```
Gly Leu Pro Ala Pro Gly Pro Tyr Ser Thr Pro Leu Arg Thr Pro Leu
        35                  40                  45

Trp Asn Gly Ser Asn His Ser Ile Glu Thr Gln Ser Ser Ser Ser Glu
    50                  55                  60

Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro Leu Pro Arg Ile Tyr
65                  70                  75                  80

Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser Gly Tyr His Tyr Gly
                85                  90                  95

Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile Gln
            100                 105                 110

Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys Asn Cys Ile Ile Asn
        115                 120                 125

Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg Leu Gln Lys Cys Phe
    130                 135                 140

Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn Asp Arg Asn Lys Lys
145                 150                 155                 160

Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu Ser Tyr Thr Leu Thr
                165                 170                 175

Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg Lys Ala His Gln Glu
            180                 185                 190

Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr Thr Thr Asn Asn Ser
        195                 200                 205

Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu Trp Asp Lys Phe Ser
    210                 215                 220

Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val Glu Phe Ala Lys Gln
225                 230                 235                 240

Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp Gln Ile Thr Leu Leu
                245                 250                 255

Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg Ile Cys Thr Arg Tyr
            260                 265                 270
```

```
Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp Gly Leu Thr Leu Asn
        275                 280                 285


Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro Leu Thr Asp Leu Val
    290                 295                 300


Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu Met Asp Asp Ala Glu
305                 310                 315                 320


Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys Gly Asp Arg Gln Asp
                325                 330                 335


Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln Glu Pro Leu Leu Glu
            340                 345                 350


Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro Ser Arg Pro His Met
        355                 360                 365


Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu Arg Ser Ile Ser Ala
    370                 375                 380


Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met Glu Ile Pro Gly Ser
385                 390                 395                 400


Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn Ser Glu Gly Leu Asp
                405                 410                 415


Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg Asp Gly Gly Gly Leu
            420                 425                 430


Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu Ser Pro Ser Ser Asn
        435                 440                 445


Arg Ser Ser Pro Ala Thr His Ser Pro
    450                 455


<210>  126
<211>  1441
<212>  PRT
<213>  Homo sapiens

<400>  126

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

```
Pro Gly Ser Cys Pro Asn Phe Ala Val Val Cys Ser Phe Leu Glu Arg
            20                  25                  30

Tyr Gly Pro Leu Leu Asp Leu Pro Glu Leu Pro Phe Pro Glu Leu Glu
        35                  40                  45

Arg Val Leu Gln Ala Pro Pro Pro Asp Val Gly Asn Gly Glu Val Pro
    50                  55                  60

Lys Glu Leu Val Glu Leu His Leu Lys Leu Met Arg Lys Ile Gly Lys
65                  70                  75                  80

Ser Val Thr Ala Asp Arg Trp Glu Lys Tyr Leu Ile Lys Ile Cys Gln
                85                  90                  95

Glu Phe Asn Ser Thr Trp Ala Trp Glu Met Glu Lys Lys Gly Tyr Leu
            100                 105                 110

Glu Met Ser Val Glu Cys Lys Leu Ala Leu Leu Lys Tyr Leu Cys Glu
        115                 120                 125

Cys Gln Phe Asp Asp Asn Leu Lys Phe Lys Asn Ile Ile Asn Glu Glu
    130                 135                 140

Asp Ala Asp Thr Met Arg Leu Gln Pro Ile Gly Arg Asp Lys Asp Gly
145                 150                 155                 160

Leu Met Tyr Trp Tyr Gln Leu Asp Gln Asp His Asn Val Arg Met Tyr
                165                 170                 175

Ile Glu Glu Gln Asp Asp Gln Asp Gly Ser Ser Trp Lys Cys Ile Val
            180                 185                 190

Arg Asn Arg Asn Glu Leu Ala Glu Thr Leu Ala Leu Leu Lys Ala Gln
        195                 200                 205

Ile Asp Pro Val Leu Leu Lys Asn Ser Ser Gln Gln Asp Asn Ser Ser
    210                 215                 220

Arg Glu Ser Pro Ser Leu Glu Asp Glu Glu Thr Lys Lys Glu Glu Glu
225                 230                 235                 240

Thr Pro Lys Gln Glu Glu Gln Lys Glu Ser Glu Lys Met Lys Ser Glu
                245                 250                 255
```

```
Glu Gln Pro Met Asp Leu Glu Asn Arg Ser Thr Ala Asn Val Leu Glu
            260                 265                 270

Glu Thr Thr Val Lys Lys Glu Lys Glu Asp Glu Lys Glu Leu Val Lys
        275                 280                 285

Leu Pro Val Ile Val Lys Leu Glu Lys Pro Leu Pro Glu Asn Glu Glu
    290                 295                 300

Lys Lys Ile Ile Lys Glu Glu Ser Asp Ser Phe Lys Glu Asn Val Lys
305                 310                 315                 320

Pro Ile Lys Val Glu Val Lys Glu Cys Arg Ala Asp Pro Lys Asp Thr
                325                 330                 335

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

Phe Gly Gly Asn Ile Lys Ser Ser His Glu Ile Thr Glu Lys Ser Thr
        355                 360                 365

Glu Glu Thr Glu Lys Leu Lys Asn Asp Gln Gln Ala Lys Ile Pro Leu
    370                 375                 380

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

Gly Pro Leu Cys Lys Ser Val Thr Pro Thr Lys Glu Phe Leu Lys Asp
                405                 410                 415

Glu Ile Lys Gln Glu Glu Glu Thr Cys Lys Arg Ile Ser Thr Ile Thr
            420                 425                 430

Ala Leu Gly His Glu Gly Lys Gln Leu Val Asn Gly Glu Val Ser Asp
        435                 440                 445

Glu Arg Val Ala Pro Asn Phe Lys Thr Glu Pro Ile Glu Thr Lys Phe
    450                 455                 460

Tyr Glu Thr Lys Glu Glu Ser Tyr Ser Pro Ser Lys Asp Arg Asn Ile
465                 470                 475                 480

Ile Thr Glu Gly Asn Gly Thr Glu Ser Leu Asn Ser Val Ile Thr Ser
                485                 490                 495
```

```
Met Lys Thr Gly Glu Leu Glu Lys Glu Thr Ala Pro Leu Arg Lys Asp
            500                 505                 510


Ala Asp Ser Ser Ile Ser Val Leu Glu Ile His Ser Gln Lys Ala Gln
        515                 520                 525


Ile Glu Glu Pro Asp Pro Pro Glu Met Glu Thr Ser Leu Asp Ser Ser
    530                 535                 540


Glu Met Ala Lys Asp Leu Ser Ser Lys Thr Ala Leu Ser Ser Thr Glu
545                 550                 555                 560


Ser Cys Thr Met Lys Gly Glu Glu Lys Ser Pro Lys Thr Lys Lys Asp
                565                 570                 575


Lys Arg Pro Pro Ile Leu Glu Cys Leu Glu Lys Leu Glu Lys Ser Lys
            580                 585                 590


Lys Thr Phe Leu Asp Lys Asp Ala Gln Arg Leu Ser Pro Ile Pro Glu
        595                 600                 605


Glu Val Pro Lys Ser Thr Leu Glu Ser Glu Lys Pro Gly Ser Pro Glu
    610                 615                 620


Ala Ala Glu Thr Ser Pro Pro Ser Asn Ile Ile Asp His Cys Glu Lys
625                 630                 635                 640


Leu Ala Ser Glu Lys Glu Val Val Glu Cys Gln Ser Thr Ser Thr Val
                645                 650                 655


Gly Gly Gln Ser Val Lys Lys Val Asp Leu Glu Thr Leu Lys Glu Asp
            660                 665                 670


Ser Glu Phe Thr Lys Val Glu Met Asp Asn Leu Asp Asn Ala Gln Thr
        675                 680                 685


Ser Gly Ile Glu Glu Pro Ser Glu Thr Lys Gly Ser Met Gln Lys Ser
    690                 695                 700


Lys Phe Lys Tyr Lys Leu Val Pro Glu Glu Glu Thr Thr Ala Ser Glu
705                 710                 715                 720


Asn Thr Glu Ile Thr Ser Glu Arg Gln Lys Glu Gly Ile Lys Leu Thr
                725                 730                 735
```

```
Ile Arg Ile Ser Ser Arg Lys Lys Lys Pro Asp Ser Pro Pro Lys Val
            740                 745                 750

Leu Glu Pro Glu Asn Lys Gln Glu Lys Thr Glu Lys Glu Glu Glu Lys
        755                 760                 765

Thr Asn Val Gly Arg Thr Leu Arg Arg Ser Pro Arg Ile Ser Arg Pro
    770                 775                 780

Thr Ala Lys Val Ala Glu Ile Arg Asp Gln Lys Ala Asp Lys Lys Arg
785                 790                 795                 800

Gly Glu Gly Glu Asp Glu Val Glu Glu Glu Ser Thr Ala Leu Gln Lys
                805                 810                 815

Thr Asp Lys Lys Glu Ile Leu Lys Lys Ser Glu Lys Asp Thr Asn Ser
            820                 825                 830

Lys Val Ser Lys Val Lys Pro Lys Gly Lys Val Arg Trp Thr Gly Ser
        835                 840                 845

Arg Thr Arg Gly Arg Trp Lys Tyr Ser Ser Asn Asp Glu Ser Glu Gly
    850                 855                 860

Ser Gly Ser Glu Lys Ser Ser Ala Ala Ser Glu Glu Glu Glu Glu Lys
865                 870                 875                 880

Glu Ser Glu Glu Ala Ile Leu Ala Asp Asp Asp Glu Pro Cys Lys Lys
                885                 890                 895

Cys Gly Leu Pro Asn His Pro Glu Leu Ile Leu Leu Cys Asp Ser Cys
            900                 905                 910

Asp Ser Gly Tyr His Thr Ala Cys Leu Arg Pro Pro Leu Met Ile Ile
        915                 920                 925

Pro Asp Gly Glu Trp Phe Cys Pro Pro Cys Gln His Lys Leu Leu Cys
    930                 935                 940

Glu Lys Leu Glu Glu Gln Leu Gln Asp Leu Asp Val Ala Leu Lys Lys
945                 950                 955                 960

Lys Glu Arg Ala Glu Arg Arg Lys Glu Arg Leu Val Tyr Val Gly Ile
                965                 970                 975
```

```
Ser Ile Glu Asn Ile Ile Pro Pro Gln Glu Pro Asp Phe Ser Glu Asp
            980                 985                 990


Gln Glu Glu Lys Lys Lys Asp Ser  Lys Lys Ser Lys Ala  Asn Leu Leu
        995                 1000                 1005


Glu Arg  Arg Ser Thr Arg Thr  Arg Lys Cys Ile Ser  Tyr Arg Phe
    1010                 1015                 1020


Asp Glu  Phe Asp Glu Ala Ile  Asp Glu Ala Ile Glu  Asp Asp Ile
    1025                 1030                 1035


Lys Glu  Ala Asp Gly Gly Gly  Val Gly Arg Gly Lys  Asp Ile Ser
    1040                 1045                 1050


Thr Ile  Thr Gly His Arg Gly  Lys Asp Ile Ser Thr  Ile Leu Asp
    1055                 1060                 1065


Glu Glu  Arg Lys Glu Asn Lys  Arg Pro Gln Arg Ala  Ala Ala Ala
    1070                 1075                 1080


Arg Arg  Lys Lys Arg Arg Arg  Leu Asn Asp Leu Asp  Ser Asp Ser
    1085                 1090                 1095


Asn Leu  Asp Glu Glu Glu Ser  Glu Asp Glu Phe Lys  Ile Ser Asp
    1100                 1105                 1110


Gly Ser  Gln Asp Glu Phe Val  Val Ser Asp Glu Asn  Pro Asp Glu
    1115                 1120                 1125


Ser Glu  Glu Asp Pro Pro Ser  Asn Asp Asp Ser Asp  Thr Asp Phe
    1130                 1135                 1140


Cys Ser  Arg Arg Leu Arg Arg  His Pro Ser Arg Pro  Met Arg Gln
    1145                 1150                 1155


Ser Arg  Arg Leu Arg Arg Lys  Thr Pro Lys Lys Lys  Tyr Ser Asp
    1160                 1165                 1170


Asp Asp  Glu Glu Glu Glu Ser  Glu Glu Asn Ser Arg  Asp Ser Glu
    1175                 1180                 1185


Ser Asp  Phe Ser Asp Asp Phe  Ser Asp Asp Phe Val  Glu Thr Arg
    1190                 1195                 1200
```

```
Arg Arg  Arg Ser Arg Arg Asn  Gln Lys Arg Gln Ile  Asn Tyr Lys
    1205                 1210                 1215

Glu Asp  Ser Glu Ser Asp Gly  Ser Gln Lys Ser Leu  Arg Arg Gly
    1220                 1225                 1230

Lys Glu  Ile Arg Arg Val His  Lys Arg Arg Leu Ser  Ser Ser Glu
    1235                 1240                 1245

Ser Glu  Glu Ser Tyr Leu Ser  Lys Asn Ser Glu Asp  Asp Glu Leu
    1250                 1255                 1260

Ala Lys  Glu Ser Lys Arg Ser  Val Arg Lys Arg Gly  Arg Ser Thr
    1265                 1270                 1275

Asp Glu  Tyr Ser Glu Ala Asp  Glu Glu Glu Glu Glu  Glu Glu Gly
    1280                 1285                 1290

Lys Pro  Ser Arg Lys Arg Leu  His Arg Ile Glu Thr  Asp Glu Glu
    1295                 1300                 1305

Glu Ser  Cys Asp Asn Ala His  Gly Asp Ala Asn Gln  Pro Ala Arg
    1310                 1315                 1320

Asp Ser  Gln Pro Arg Val Leu  Pro Ser Glu Gln Glu  Ser Thr Lys
    1325                 1330                 1335

Lys Pro  Tyr Arg Ile Glu Ser  Asp Glu Glu Glu Asp  Phe Glu Asn
    1340                 1345                 1350

Val Gly  Lys Val Gly Ser Pro  Leu Asp Tyr Ser Leu  Val Asp Leu
    1355                 1360                 1365

Pro Ser  Thr Asn Gly Gln Ser  Pro Gly Lys Ala Ile  Glu Asn Leu
    1370                 1375                 1380

Ile Gly  Lys Pro Thr Glu Lys  Ser Gln Thr Pro Lys  Asp Asn Ser
    1385                 1390                 1395

Thr Ala  Ser Ala Ser Leu Ala  Ser Asn Gly Thr Ser  Gly Gly Gln
    1400                 1405                 1410

Glu Ala  Gly Ala Pro Glu Glu  Glu Glu Asp Glu Leu  Leu Arg Val
    1415                 1420                 1425
```

```
Thr Asp  Leu Val Asp Tyr Val  Cys Asn Ser Glu Gln  Leu
    1430                 1435                 1440


<210>  127
<211>  1285
<212>  PRT
<213>  Homo sapiens

<400>  127

Met Glu Arg Arg Trp Asp Leu Asp Leu Thr Tyr Val Thr Glu Arg Ile
1               5                   10                  15


Leu Ala Ala Ala Phe Pro Ala Arg Pro Asp Glu Gln Arg His Arg Gly
            20                  25                  30


His Leu Arg Glu Leu Ala His Val Leu Gln Ser Lys His Arg Asp Lys
        35                  40                  45


Tyr Leu Leu Phe Asn Leu Ser Glu Lys Arg His Asp Leu Thr Arg Leu
    50                  55                  60


Asn Pro Lys Val Gln Asp Phe Gly Trp Pro Glu Leu His Ala Pro Pro
65                  70                  75                  80


Leu Asp Lys Leu Cys Ser Ile Cys Lys Ala Met Glu Thr Trp Leu Ser
                85                  90                  95


Ala Asp Pro Gln His Val Val Val Leu Tyr Cys Lys Gly Asn Lys Gly
            100                 105                 110


Lys Leu Gly Val Ile Val Ser Ala Tyr Met His Tyr Ser Lys Ile Ser
        115                 120                 125


Ala Gly Ala Asp Gln Ala Leu Ala Thr Leu Thr Met Arg Lys Phe Cys
    130                 135                 140


Glu Asp Lys Val Ala Thr Glu Leu Gln Pro Ser Gln Arg Arg Tyr Ile
145                 150                 155                 160


Ser Tyr Phe Ser Gly Leu Leu Ser Gly Ser Ile Arg Met Asn Ser Ser
                165                 170                 175


Pro Leu Phe Leu His Tyr Val Leu Ile Pro Met Leu Pro Ala Phe Glu
            180                 185                 190
```

Pro Gly Thr Gly Phe Gln Pro Phe Leu Lys Ile Tyr Gln Ser Met Gln
        195   200   205

Leu Val Tyr Thr Ser Gly Val Tyr His Ile Ala Gly Pro Gly Pro Gln
    210   215   220

Gln Leu Cys Ile Ser Leu Glu Pro Ala Leu Leu Leu Lys Gly Asp Val
225   230   235   240

Met Val Thr Cys Tyr His Lys Gly Gly Arg Gly Thr Asp Arg Thr Leu
                245   250   255

Val Phe Arg Val Gln Phe His Thr Cys Thr Ile His Gly Pro Gln Leu
            260   265   270

Thr Phe Pro Lys Asp Gln Leu Asp Glu Ala Trp Thr Asp Glu Arg Phe
        275   280   285

Pro Phe Gln Ala Ser Val Glu Phe Val Phe Ser Ser Ser Pro Glu Lys
    290   295   300

Ile Lys Gly Ser Thr Pro Arg Asn Asp Pro Ser Val Ser Val Asp Tyr
305   310   315   320

Asn Thr Thr Glu Pro Ala Val Arg Trp Asp Ser Tyr Glu Asn Phe Asn
                325   330   335

Gln His His Glu Asp Ser Val Asp Gly Ser Leu Thr His Thr Arg Gly
            340   345   350

Pro Leu Asp Gly Ser Pro Tyr Ala Gln Val Gln Arg Pro Pro Arg Gln
        355   360   365

Thr Pro Pro Ala Pro Ser Pro Glu Pro Pro Pro Pro Pro Met Leu Ser
    370   375   380

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

Ala Glu Ser Pro Gly Arg Pro Pro Pro Thr Ala Ala Glu Arg Gln Glu
                405   410   415

Leu Asp Arg Leu Leu Gly Gly Cys Gly Val Ala Ser Gly Gly Arg Gly
            420   425   430

```
Ala Gly Arg Glu Thr Ala Ile Leu Asp Asp Glu Glu Gln Pro Thr Val
        435                 440                 445

Gly Gly Gly Pro His Leu Gly Val Tyr Pro Gly His Arg Pro Gly Leu
    450                 455                 460

Ser Arg His Cys Ser Cys Arg Gln Gly Tyr Arg Glu Pro Cys Gly Val
465                 470                 475                 480

Pro Asn Gly Gly Tyr Tyr Arg Pro Glu Gly Thr Leu Glu Arg Arg Arg
                485                 490                 495

Leu Ala Tyr Gly Gly Tyr Glu Gly Ser Pro Gln Gly Tyr Ala Glu Ala
            500                 505                 510

Ser Met Glu Lys Arg Arg Leu Cys Arg Ser Leu Ser Glu Gly Leu Tyr
        515                 520                 525

Pro Tyr Pro Pro Glu Met Gly Lys Pro Ala Thr Gly Asp Phe Gly Tyr
    530                 535                 540

Arg Ala Pro Gly Tyr Arg Glu Val Val Ile Leu Glu Asp Pro Gly Leu
545                 550                 555                 560

Pro Ala Leu Tyr Pro Cys Pro Ala Cys Glu Glu Lys Leu Ala Leu Pro
                565                 570                 575

Thr Ala Ala Leu Tyr Gly Leu Arg Leu Glu Arg Glu Ala Gly Glu Gly
            580                 585                 590

Trp Ala Ser Glu Ala Gly Lys Pro Leu Leu His Pro Val Arg Pro Gly
        595                 600                 605

His Pro Leu Pro Leu Leu Leu Pro Ala Cys Gly His His His Ala Pro
    610                 615                 620

Met Pro Asp Tyr Ser Cys Leu Lys Pro Pro Lys Ala Gly Glu Glu Gly
625                 630                 635                 640

His Glu Gly Cys Ser Tyr Thr Met Cys Pro Glu Gly Arg Tyr Gly His
                645                 650                 655

Pro Gly Tyr Pro Ala Leu Val Thr Tyr Ser Tyr Gly Gly Ala Val Pro
            660                 665                 670
```

```
Ser Tyr Cys Pro Ala Tyr Gly Arg Val Pro His Ser Cys Gly Ser Pro
        675                 680                 685

Gly Glu Gly Arg Gly Tyr Pro Ser Pro Gly Ala His Ser Pro Arg Ala
    690                 695                 700

Gly Ser Ile Ser Pro Gly Ser Pro Pro Tyr Pro Gln Ser Arg Lys Leu
705                 710                 715                 720

Ser Tyr Glu Ile Pro Thr Glu Glu Gly Gly Asp Arg Tyr Pro Leu Pro
                725                 730                 735

Gly His Leu Ala Ser Ala Gly Pro Leu Ala Ser Ala Glu Ser Leu Glu
            740                 745                 750

Pro Val Ser Trp Arg Glu Gly Pro Ser Gly His Ser Thr Leu Pro Arg
        755                 760                 765

Ser Pro Arg Asp Ala Pro Cys Ser Ala Ser Ser Glu Leu Ser Gly Pro
    770                 775                 780

Ser Thr Pro Leu His Thr Ser Ser Pro Val Gln Gly Lys Glu Ser Thr
785                 790                 795                 800

Arg Arg Gln Asp Thr Arg Ser Pro Thr Ser Ala Pro Thr Gln Arg Leu
                805                 810                 815

Ser Pro Gly Glu Ala Leu Pro Pro Val Ser Gln Ala Gly Thr Gly Lys
            820                 825                 830

Ala Pro Glu Leu Pro Ser Gly Ser Gly Pro Glu Pro Leu Ala Pro Ser
        835                 840                 845

Pro Val Ser Pro Thr Phe Pro Pro Ser Ser Pro Ser Asp Trp Pro Gln
    850                 855                 860

Glu Arg Ser Pro Gly Gly His Ser Asp Gly Ala Ser Pro Arg Ser Pro
865                 870                 875                 880

Val Pro Thr Thr Leu Pro Gly Leu Arg His Ala Pro Trp Gln Gly Pro
                885                 890                 895

Arg Gly Pro Pro Asp Ser Pro Asp Gly Ser Pro Leu Thr Pro Val Pro
            900                 905                 910
```

```
Ser Gln Met Pro Trp Leu Val Ala Ser Pro Glu Pro Pro Gln Ser Ser
        915                 920                 925

Pro Thr Pro Ala Phe Pro Leu Ala Ala Ser Tyr Asp Thr Asn Gly Leu
    930                 935                 940

Ser Gln Pro Pro Leu Pro Glu Lys Arg His Leu Pro Gly Pro Gly Gln
945                 950                 955                 960

Gln Pro Gly Pro Trp Gly Pro Glu Gln Ala Ser Ser Pro Ala Arg Gly
                965                 970                 975

Ile Ser His His Val Thr Phe Ala Pro Leu Leu Ser Asp Asn Val Pro
            980                 985                 990

Gln Thr Pro Glu Pro Pro Thr Gln  Glu Ser Gln Ser Asn  Val Lys Phe
        995                 1000                 1005

Val Gln  Asp Thr Ser Lys Phe  Trp Tyr Lys Pro His  Leu Ser Arg
    1010                 1015                 1020

Asp Gln  Ala Ile Ala Leu Leu  Lys Asp Lys Asp Pro  Gly Ala Phe
    1025                 1030                 1035

Leu Ile  Arg Asp Ser His Ser  Phe Gln Gly Ala Tyr  Gly Leu Ala
    1040                 1045                 1050

Leu Lys  Val Ala Thr Pro Pro  Pro Ser Ala Gln Pro  Trp Lys Gly
    1055                 1060                 1065

Asp Pro  Val Glu Gln Leu Val  Arg His Phe Leu Ile  Glu Thr Gly
    1070                 1075                 1080

Pro Lys  Gly Val Lys Ile Lys  Gly Cys Pro Ser Glu  Pro Tyr Phe
    1085                 1090                 1095

Gly Ser  Leu Ser Ala Leu Val  Ser Gln His Ser Ile  Ser Pro Ile
    1100                 1105                 1110

Ser Leu  Pro Cys Cys Leu Arg  Ile Pro Ser Lys Asp  Pro Leu Glu
    1115                 1120                 1125

Glu Thr  Pro Glu Ala Pro Val  Pro Thr Asn Met Ser  Thr Ala Ala
    1130                 1135                 1140
```

Asp Leu Leu Arg Gln Gly Ala Ala Cys Ser Val Leu Tyr Leu Thr
1145 1150 1155

Ser Val Glu Thr Glu Ser Leu Thr Gly Pro Gln Ala Val Ala Arg
1160 1165 1170

Ala Ser Ser Ala Ala Leu Ser Cys Ser Pro Arg Pro Thr Pro Ala
1175 1180 1185

Val Val His Phe Lys Val Ser Ala Gln Gly Ile Thr Leu Thr Asp
1190 1195 1200

Asn Gln Arg Lys Leu Phe Phe Arg Arg His Tyr Pro Val Asn Ser
1205 1210 1215

Ile Thr Phe Ser Ser Thr Asp Pro Gln Asp Arg Arg Trp Thr Asn
1220 1225 1230

Pro Asp Gly Thr Thr Ser Lys Ile Phe Gly Phe Val Ala Lys Lys
1235 1240 1245

Pro Gly Ser Pro Trp Glu Asn Val Cys His Leu Phe Ala Glu Leu
1250 1255 1260

Asp Pro Asp Gln Pro Ala Gly Ala Ile Val Thr Phe Ile Thr Lys
1265 1270 1275

Val Leu Leu Gly Gln Arg Lys
1280 1285

<210> 128
<211> 1419
<212> PRT
<213> Homo sapiens

<400> 128

Met Asp Gly Gly Gly Val Cys Val Gly Arg Gly Asp Leu Leu Ser Ser
1 5 10 15

Pro Gln Ala Leu Gly Gln Leu Leu Arg Lys Glu Ser Arg Pro Arg Arg
20 25 30

Ala Met Lys Pro Arg Lys Ala Glu Pro His Ser Phe Arg Glu Lys Val
35 40 45

```
Phe Arg Lys Lys Pro Pro Val Cys Ala Val Cys Lys Val Thr Ile Asp
    50                  55                  60


Gly Thr Gly Val Ser Cys Arg Val Cys Lys Val Ala Thr His Arg Lys
65                  70                  75                  80


Cys Glu Ala Lys Val Thr Ser Ala Cys Gln Ala Leu Pro Pro Val Glu
                85                  90                  95


Leu Arg Arg Asn Thr Ala Pro Val Arg Arg Ile Glu His Leu Gly Ser
            100                 105                 110


Thr Lys Ser Leu Asn His Ser Lys Gln Arg Ser Thr Leu Pro Arg Ser
        115                 120                 125


Phe Ser Leu Asp Pro Leu Met Glu Arg Arg Trp Asp Leu Asp Leu Thr
    130                 135                 140


Tyr Val Thr Glu Arg Ile Leu Ala Ala Ala Phe Pro Ala Arg Pro Asp
145                 150                 155                 160


Glu Gln Arg His Arg Gly His Leu Arg Glu Leu Ala His Val Leu Gln
                165                 170                 175


Ser Lys His Arg Asp Lys Tyr Leu Leu Phe Asn Leu Ser Glu Lys Arg
            180                 185                 190


His Asp Leu Thr Arg Leu Asn Pro Lys Val Gln Asp Phe Gly Trp Pro
        195                 200                 205


Glu Leu His Ala Pro Pro Leu Asp Lys Leu Cys Ser Ile Cys Lys Ala
    210                 215                 220


Met Glu Thr Trp Leu Ser Ala Asp Pro Gln His Val Val Val Leu Tyr
225                 230                 235                 240


Cys Lys Gly Asn Lys Gly Lys Leu Gly Val Ile Val Ser Ala Tyr Met
                245                 250                 255


His Tyr Ser Lys Ile Ser Ala Gly Ala Asp Gln Ala Leu Ala Thr Leu
            260                 265                 270


Thr Met Arg Lys Phe Cys Glu Asp Lys Val Ala Thr Glu Leu Gln Pro
        275                 280                 285
```

```
Ser Gln Arg Arg Tyr Ile Ser Tyr Phe Ser Gly Leu Leu Ser Gly Ser
    290                 295                 300


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


Met Leu Pro Ala Phe Glu Pro Gly Thr Gly Phe Gln Pro Phe Leu Lys
                325                 330                 335


Ile Tyr Gln Ser Met Gln Leu Val Tyr Thr Ser Gly Val Tyr His Ile
            340                 345                 350


Ala Gly Pro Gly Pro Gln Gln Leu Cys Ile Ser Leu Glu Pro Ala Leu
        355                 360                 365


Leu Leu Lys Gly Asp Val Met Val Thr Cys Tyr His Lys Gly Gly Arg
    370                 375                 380


Gly Thr Asp Arg Thr Leu Val Phe Arg Val Gln Phe His Thr Cys Thr
385                 390                 395                 400


Ile His Gly Pro Gln Leu Thr Phe Pro Lys Asp Gln Leu Asp Glu Ala
                405                 410                 415


Trp Thr Asp Glu Arg Phe Pro Phe Gln Ala Ser Val Glu Phe Val Phe
            420                 425                 430


Ser Ser Ser Pro Glu Lys Ile Lys Gly Ser Thr Pro Arg Asn Asp Pro
        435                 440                 445


Ser Val Ser Val Asp Tyr Asn Thr Thr Glu Pro Ala Val Arg Trp Asp
    450                 455                 460


Ser Tyr Glu Asn Phe Asn Gln His His Glu Asp Ser Val Asp Gly Ser
465                 470                 475                 480


Leu Thr His Thr Arg Gly Pro Leu Asp Gly Ser Pro Tyr Ala Gln Val
                485                 490                 495


Gln Arg Pro Pro Arg Gln Thr Pro Pro Ala Pro Ser Pro Glu Pro Pro
            500                 505                 510


Pro Pro Pro Met Leu Ser Val Ser Ser Asp Ser Gly His Ser Ser Thr
        515                 520                 525
```

```
Leu Thr Thr Glu Pro Ala Ala Glu Ser Pro Gly Arg Pro Pro Pro Thr
    530                 535                 540

Ala Ala Glu Arg Gln Glu Leu Asp Arg Leu Leu Gly Gly Cys Gly Val
545                 550                 555                 560

Ala Ser Gly Gly Arg Gly Ala Gly Arg Glu Thr Ala Ile Leu Asp Asp
                565                 570                 575

Glu Glu Gln Pro Thr Val Gly Gly Gly Pro His Leu Gly Val Tyr Pro
            580                 585                 590

Gly His Arg Pro Gly Leu Ser Arg His Cys Ser Cys Arg Gln Gly Tyr
        595                 600                 605

Arg Glu Pro Cys Gly Val Pro Asn Gly Gly Tyr Tyr Arg Pro Glu Gly
    610                 615                 620

Thr Leu Glu Arg Arg Arg Leu Ala Tyr Gly Gly Tyr Glu Gly Ser Pro
625                 630                 635                 640

Gln Gly Tyr Ala Glu Ala Ser Met Glu Lys Arg Arg Leu Cys Arg Ser
                645                 650                 655

Leu Ser Glu Gly Leu Tyr Pro Tyr Pro Pro Glu Met Gly Lys Pro Ala
            660                 665                 670

Thr Gly Asp Phe Gly Tyr Arg Ala Pro Gly Tyr Arg Glu Val Val Ile
        675                 680                 685

Leu Glu Asp Pro Gly Leu Pro Ala Leu Tyr Pro Cys Pro Ala Cys Glu
    690                 695                 700

Glu Lys Leu Ala Leu Pro Thr Ala Ala Leu Tyr Gly Leu Arg Leu Glu
705                 710                 715                 720

Arg Glu Ala Gly Glu Gly Trp Ala Ser Glu Ala Gly Lys Pro Leu Leu
                725                 730                 735

His Pro Val Arg Pro Gly His Pro Leu Pro Leu Leu Leu Pro Ala Cys
            740                 745                 750

Gly His His His Ala Pro Met Pro Asp Tyr Ser Cys Leu Lys Pro Pro
        755                 760                 765
```

```
Lys Ala Gly Glu Glu Gly His Glu Gly Cys Ser Tyr Thr Met Cys Pro
    770                 775                 780


Glu Gly Arg Tyr Gly His Pro Gly Tyr Pro Ala Leu Val Thr Tyr Ser
785                 790                 795                 800


Tyr Gly Gly Ala Val Pro Ser Tyr Cys Pro Ala Tyr Gly Arg Val Pro
                805                 810                 815


His Ser Cys Gly Ser Pro Gly Glu Gly Arg Gly Tyr Pro Ser Pro Gly
            820                 825                 830


Ala His Ser Pro Arg Ala Gly Ser Ile Ser Pro Gly Ser Pro Pro Tyr
        835                 840                 845


Pro Gln Ser Arg Lys Leu Ser Tyr Glu Ile Pro Thr Glu Glu Gly Gly
    850                 855                 860


Asp Arg Tyr Pro Leu Pro Gly His Leu Ala Ser Ala Gly Pro Leu Ala
865                 870                 875                 880


Ser Ala Glu Ser Leu Glu Pro Val Ser Trp Arg Glu Gly Pro Ser Gly
                885                 890                 895


His Ser Thr Leu Pro Arg Ser Pro Arg Asp Ala Pro Cys Ser Ala Ser
            900                 905                 910


Ser Glu Leu Ser Gly Pro Ser Thr Pro Leu His Thr Ser Ser Pro Val
        915                 920                 925


Gln Gly Lys Glu Ser Thr Arg Arg Gln Asp Thr Arg Ser Pro Thr Ser
    930                 935                 940


Ala Pro Thr Gln Arg Leu Ser Pro Gly Glu Ala Leu Pro Pro Val Ser
945                 950                 955                 960


Gln Ala Gly Thr Gly Lys Ala Pro Glu Leu Pro Ser Gly Ser Gly Pro
                965                 970                 975


Glu Pro Leu Ala Pro Ser Pro Val Ser Pro Thr Phe Pro Pro Ser Ser
            980                 985                 990


Pro Ser Asp Trp Pro Gln Glu Arg  Ser Pro Gly Gly His  Ser Asp Gly
        995                 1000                 1005
```

```
Ala Ser  Pro Arg Ser Pro Val  Pro Thr Thr Leu Pro  Gly Leu Arg
    1010                 1015                 1020


His Ala  Pro Trp Gln Gly Pro  Arg Gly Pro Pro Asp  Ser Pro Asp
    1025                 1030                 1035


Gly Ser  Pro Leu Thr Pro Val  Pro Ser Gln Met Pro  Trp Leu Val
    1040                 1045                 1050


Ala Ser  Pro Glu Pro Pro Gln  Ser Ser Pro Thr Pro  Ala Phe Pro
    1055                 1060                 1065


Leu Ala  Ala Ser Tyr Asp Thr  Asn Gly Leu Ser Gln  Pro Pro Leu
    1070                 1075                 1080


Pro Glu  Lys Arg His Leu Pro  Gly Pro Gly Gln Gln  Pro Gly Pro
    1085                 1090                 1095


Trp Gly  Pro Glu Gln Ala Ser  Ser Pro Ala Arg Gly  Ile Ser His
    1100                 1105                 1110


His Val  Thr Phe Ala Pro Leu  Leu Ser Asp Asn Val  Pro Gln Thr
    1115                 1120                 1125


Pro Glu  Pro Pro Thr Gln Glu  Ser Gln Ser Asn Val  Lys Phe Val
    1130                 1135                 1140


Gln Asp  Thr Ser Lys Phe Trp  Tyr Lys Pro His Leu  Ser Arg Asp
    1145                 1150                 1155


Gln Ala  Ile Ala Leu Leu Lys  Asp Lys Asp Pro Gly  Ala Phe Leu
    1160                 1165                 1170


Ile Arg  Asp Ser His Ser Phe  Gln Gly Ala Tyr Gly  Leu Ala Leu
    1175                 1180                 1185


Lys Val  Ala Thr Pro Pro Pro  Ser Ala Gln Pro Trp  Lys Gly Asp
    1190                 1195                 1200


Pro Val  Glu Gln Leu Val Arg  His Phe Leu Ile Glu  Thr Gly Pro
    1205                 1210                 1215


Lys Gly  Val Lys Ile Lys Gly  Cys Pro Ser Glu Pro  Tyr Phe Gly
    1220                 1225                 1230
```

Ser Leu Ser Ala Leu Val Ser Gln His Ser Ile Ser Pro Ile Ser
1235 1240 1245

Leu Pro Cys Cys Leu Arg Ile Pro Ser Lys Asp Pro Leu Glu Glu
1250 1255 1260

Thr Pro Glu Ala Pro Val Pro Thr Asn Met Ser Thr Ala Ala Asp
1265 1270 1275

Leu Leu Arg Gln Gly Ala Ala Cys Ser Val Leu Tyr Leu Thr Ser
1280 1285 1290

Val Glu Thr Glu Ser Leu Thr Gly Pro Gln Ala Val Ala Arg Ala
1295 1300 1305

Ser Ser Ala Ala Leu Ser Cys Ser Pro Arg Pro Thr Pro Ala Val
1310 1315 1320

Val His Phe Lys Val Ser Ala Gln Gly Ile Thr Leu Thr Asp Asn
1325 1330 1335

Gln Arg Lys Leu Phe Phe Arg Arg His Tyr Pro Val Asn Ser Ile
1340 1345 1350

Thr Phe Ser Ser Thr Asp Pro Gln Asp Arg Arg Trp Thr Asn Pro
1355 1360 1365

Asp Gly Thr Thr Ser Lys Ile Phe Gly Phe Val Ala Lys Lys Pro
1370 1375 1380

Gly Ser Pro Trp Glu Asn Val Cys His Leu Phe Ala Glu Leu Asp
1385 1390 1395

Pro Asp Gln Pro Ala Gly Ala Ile Val Thr Phe Ile Thr Lys Val
1400 1405 1410

Leu Leu Gly Gln Arg Lys
1415

<210> 129
<211> 1409
<212> PRT
<213> Homo sapiens

<400> 129

```
Met Lys Ser Ser Gly Pro Val Glu Arg Leu Leu Arg Ala Leu Gly Arg
1               5                   10                  15

Arg Asp Ser Ser Arg Ala Ala Ser Arg Pro Arg Lys Ala Glu Pro His
            20                  25                  30

Ser Phe Arg Glu Lys Val Phe Arg Lys Lys Pro Pro Val Cys Ala Val
        35                  40                  45

Cys Lys Val Thr Ile Asp Gly Thr Gly Val Ser Cys Arg Val Cys Lys
    50                  55                  60

Val Ala Thr His Arg Lys Cys Glu Ala Lys Val Thr Ser Ala Cys Gln
65                  70                  75                  80

Ala Leu Pro Pro Val Glu Leu Arg Arg Asn Thr Ala Pro Val Arg Arg
                85                  90                  95

Ile Glu His Leu Gly Ser Thr Lys Ser Leu Asn His Ser Lys Gln Arg
            100                 105                 110

Ser Thr Leu Pro Arg Ser Phe Ser Leu Asp Pro Leu Met Glu Arg Arg
        115                 120                 125

Trp Asp Leu Asp Leu Thr Tyr Val Thr Glu Arg Ile Leu Ala Ala Ala
    130                 135                 140

Phe Pro Ala Arg Pro Asp Glu Gln Arg His Arg Gly His Leu Arg Glu
145                 150                 155                 160

Leu Ala His Val Leu Gln Ser Lys His Arg Asp Lys Tyr Leu Leu Phe
                165                 170                 175

Asn Leu Ser Glu Lys Arg His Asp Leu Thr Arg Leu Asn Pro Lys Val
            180                 185                 190

Gln Asp Phe Gly Trp Pro Glu Leu His Ala Pro Pro Leu Asp Lys Leu
        195                 200                 205

Cys Ser Ile Cys Lys Ala Met Glu Thr Trp Leu Ser Ala Asp Pro Gln
    210                 215                 220

His Val Val Val Leu Tyr Cys Lys Gly Asn Lys Gly Lys Leu Gly Val
225                 230                 235                 240
```

```
Ile Val Ser Ala Tyr Met His Tyr Ser Lys Ile Ser Ala Gly Ala Asp
                245                 250                 255

Gln Ala Leu Ala Thr Leu Thr Met Arg Lys Phe Cys Glu Asp Lys Val
            260                 265                 270

Ala Thr Glu Leu Gln Pro Ser Gln Arg Arg Tyr Ile Ser Tyr Phe Ser
        275                 280                 285

Gly Leu Leu Ser Gly Ser Ile Arg Met Asn Ser Ser Pro Leu Phe Leu
    290                 295                 300

His Tyr Val Leu Ile Pro Met Leu Pro Ala Phe Glu Pro Gly Thr Gly
305                 310                 315                 320

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

Ser Gly Val Tyr His Ile Ala Gly Pro Gly Pro Gln Gln Leu Cys Ile
            340                 345                 350

Ser Leu Glu Pro Ala Leu Leu Leu Lys Gly Asp Val Met Val Thr Cys
        355                 360                 365

Tyr His Lys Gly Gly Arg Gly Thr Asp Arg Thr Leu Val Phe Arg Val
    370                 375                 380

Gln Phe His Thr Cys Thr Ile His Gly Pro Gln Leu Thr Phe Pro Lys
385                 390                 395                 400

Asp Gln Leu Asp Glu Ala Trp Thr Asp Glu Arg Phe Pro Phe Gln Ala
                405                 410                 415

Ser Val Glu Phe Val Phe Ser Ser Ser Pro Glu Lys Ile Lys Gly Ser
            420                 425                 430

Thr Pro Arg Asn Asp Pro Ser Val Ser Val Asp Tyr Asn Thr Thr Glu
        435                 440                 445

Pro Ala Val Arg Trp Asp Ser Tyr Glu Asn Phe Asn Gln His His Glu
    450                 455                 460

Asp Ser Val Asp Gly Ser Leu Thr His Thr Arg Gly Pro Leu Asp Gly
465                 470                 475                 480
```

```
Ser Pro Tyr Ala Gln Val Gln Arg Pro Pro Arg Gln Thr Pro Pro Ala
                485                 490                 495

Pro Ser Pro Glu Pro Pro Pro Pro Pro Met Leu Ser Val Ser Ser Asp
            500                 505                 510

Ser Gly His Ser Ser Thr Leu Thr Thr Glu Pro Ala Ala Glu Ser Pro
        515                 520                 525

Gly Arg Pro Pro Pro Thr Ala Ala Glu Arg Gln Glu Leu Asp Arg Leu
    530                 535                 540

Leu Gly Gly Cys Gly Val Ala Ser Gly Gly Arg Gly Ala Gly Arg Glu
545                 550                 555                 560

Thr Ala Ile Leu Asp Asp Glu Glu Gln Pro Thr Val Gly Gly Gly Pro
                565                 570                 575

His Leu Gly Val Tyr Pro Gly His Arg Pro Gly Leu Ser Arg His Cys
            580                 585                 590

Ser Cys Arg Gln Gly Tyr Arg Glu Pro Cys Gly Val Pro Asn Gly Gly
        595                 600                 605

Tyr Tyr Arg Pro Glu Gly Thr Leu Glu Arg Arg Arg Leu Ala Tyr Gly
    610                 615                 620

Gly Tyr Glu Gly Ser Pro Gln Gly Tyr Ala Glu Ala Ser Met Glu Lys
625                 630                 635                 640

Arg Arg Leu Cys Arg Ser Leu Ser Glu Gly Leu Tyr Pro Tyr Pro Pro
                645                 650                 655

Glu Met Gly Lys Pro Ala Thr Gly Asp Phe Gly Tyr Arg Ala Pro Gly
            660                 665                 670

Tyr Arg Glu Val Val Ile Leu Glu Asp Pro Gly Leu Pro Ala Leu Tyr
        675                 680                 685

Pro Cys Pro Ala Cys Glu Glu Lys Leu Ala Leu Pro Thr Ala Ala Leu
    690                 695                 700

Tyr Gly Leu Arg Leu Glu Arg Glu Ala Gly Glu Gly Trp Ala Ser Glu
705                 710                 715                 720
```

```
Ala Gly Lys Pro Leu Leu His Pro Val Arg Pro Gly His Pro Leu Pro
                725                 730                 735

Leu Leu Leu Pro Ala Cys Gly His His His Ala Pro Met Pro Asp Tyr
            740                 745                 750

Ser Cys Leu Lys Pro Pro Lys Ala Gly Glu Glu Gly His Glu Gly Cys
        755                 760                 765

Ser Tyr Thr Met Cys Pro Glu Gly Arg Tyr Gly His Pro Gly Tyr Pro
    770                 775                 780

Ala Leu Val Thr Tyr Ser Tyr Gly Gly Ala Val Pro Ser Tyr Cys Pro
785                 790                 795                 800

Ala Tyr Gly Arg Val Pro His Ser Cys Gly Ser Pro Gly Glu Gly Arg
                805                 810                 815

Gly Tyr Pro Ser Pro Gly Ala His Ser Pro Arg Ala Gly Ser Ile Ser
            820                 825                 830

Pro Gly Ser Pro Pro Tyr Pro Gln Ser Arg Lys Leu Ser Tyr Glu Ile
        835                 840                 845

Pro Thr Glu Glu Gly Gly Asp Arg Tyr Pro Leu Pro Gly His Leu Ala
    850                 855                 860

Ser Ala Gly Pro Leu Ala Ser Ala Glu Ser Leu Glu Pro Val Ser Trp
865                 870                 875                 880

Arg Glu Gly Pro Ser Gly His Ser Thr Leu Pro Arg Ser Pro Arg Asp
                885                 890                 895

Ala Pro Cys Ser Ala Ser Ser Glu Leu Ser Gly Pro Ser Thr Pro Leu
            900                 905                 910

His Thr Ser Ser Pro Val Gln Gly Lys Glu Ser Thr Arg Arg Gln Asp
        915                 920                 925

Thr Arg Ser Pro Thr Ser Ala Pro Thr Gln Arg Leu Ser Pro Gly Glu
    930                 935                 940

Ala Leu Pro Pro Val Ser Gln Ala Gly Thr Gly Lys Ala Pro Glu Leu
945                 950                 955                 960
```

```
Pro Ser Gly Ser Gly Pro Glu Pro Leu Ala Pro Ser Pro Val Ser Pro
                965                 970                 975


Thr Phe Pro Pro Ser Ser Pro Ser Asp Trp Pro Gln Glu Arg Ser Pro
            980                 985                 990


Gly Gly His Ser Asp Gly Ala Ser  Pro Arg Ser Pro Val  Pro Thr Thr
        995                 1000                1005


Leu Pro  Gly Leu Arg His Ala  Pro Trp Gln Gly Pro  Arg Gly Pro
    1010                 1015                 1020


Pro Asp  Ser Pro Asp Gly Ser  Pro Leu Thr Pro Val  Pro Ser Gln
    1025                 1030                 1035


Met Pro  Trp Leu Val Ala Ser  Pro Glu Pro Pro Gln  Ser Ser Pro
    1040                 1045                 1050


Thr Pro  Ala Phe Pro Leu Ala  Ala Ser Tyr Asp Thr  Asn Gly Leu
    1055                 1060                 1065


Ser Gln  Pro Pro Leu Pro Glu  Lys Arg His Leu Pro  Gly Pro Gly
    1070                 1075                 1080


Gln Gln  Pro Gly Pro Trp Gly  Pro Glu Gln Ala Ser  Ser Pro Ala
    1085                 1090                 1095


Arg Gly  Ile Ser His His Val  Thr Phe Ala Pro Leu  Leu Ser Asp
    1100                 1105                 1110


Asn Val  Pro Gln Thr Pro Glu  Pro Pro Thr Gln Glu  Ser Gln Ser
    1115                 1120                 1125


Asn Val  Lys Phe Val Gln Asp  Thr Ser Lys Phe Trp  Tyr Lys Pro
    1130                 1135                 1140


His Leu  Ser Arg Asp Gln Ala  Ile Ala Leu Leu Lys  Asp Lys Asp
    1145                 1150                 1155


Pro Gly  Ala Phe Leu Ile Arg  Asp Ser His Ser Phe  Gln Gly Ala
    1160                 1165                 1170


Tyr Gly  Leu Ala Leu Lys Val  Ala Thr Pro Pro Pro  Ser Ala Gln
    1175                 1180                 1185
```

```
Pro Trp  Lys Gly Asp Pro Val  Glu Gln Leu Val Arg  His Phe Leu
    1190                 1195                 1200

Ile Glu  Thr Gly Pro Lys Gly  Val Lys Ile Lys Gly  Cys Pro Ser
    1205                 1210                 1215

Glu Pro  Tyr Phe Gly Ser Leu  Ser Ala Leu Val Ser  Gln His Ser
    1220                 1225                 1230

Ile Ser  Pro Ile Ser Leu Pro  Cys Cys Leu Arg Ile  Pro Ser Lys
    1235                 1240                 1245

Asp Pro  Leu Glu Glu Thr Pro  Glu Ala Pro Val Pro  Thr Asn Met
    1250                 1255                 1260

Ser Thr  Ala Ala Asp Leu Leu  Arg Gln Gly Ala Ala  Cys Ser Val
    1265                 1270                 1275

Leu Tyr  Leu Thr Ser Val Glu  Thr Glu Ser Leu Thr  Gly Pro Gln
    1280                 1285                 1290

Ala Val  Ala Arg Ala Ser Ser  Ala Ala Leu Ser Cys  Ser Pro Arg
    1295                 1300                 1305

Pro Thr  Pro Ala Val Val His  Phe Lys Val Ser Ala  Gln Gly Ile
    1310                 1315                 1320

Thr Leu  Thr Asp Asn Gln Arg  Lys Leu Phe Phe Arg  Arg His Tyr
    1325                 1330                 1335

Pro Val  Asn Ser Ile Thr Phe  Ser Ser Thr Asp Pro  Gln Asp Arg
    1340                 1345                 1350

Arg Trp  Thr Asn Pro Asp Gly  Thr Thr Ser Lys Ile  Phe Gly Phe
    1355                 1360                 1365

Val Ala  Lys Lys Pro Gly Ser  Pro Trp Glu Asn Val  Cys His Leu
    1370                 1375                 1380

Phe Ala  Glu Leu Asp Pro Asp  Gln Pro Ala Gly Ala  Ile Val Thr
    1385                 1390                 1395

Phe Ile  Thr Lys Val Leu Leu  Gly Gln Arg Lys
    1400                 1405
```

```
<210>  130
<211>  914
<212>  PRT
<213>  Homo sapiens

<400>  130

Met Ser Gln Ser Gln Asn Ala Ile Phe Thr Ser Pro Thr Gly Glu Glu
1               5                   10                  15

Asn Leu Met Asn Ser Asn His Arg Asp Ser Glu Ser Ile Thr Asp Val
            20                  25                  30

Cys Ser Asn Glu Asp Leu Pro Glu Val Glu Leu Val Ser Leu Leu Glu
        35                  40                  45

Glu Gln Leu Pro Gln Tyr Arg Leu Lys Val Asp Thr Leu Phe Leu Tyr
    50                  55                  60

Glu Asn Gln Asp Trp Thr Gln Ser Pro His Gln Arg Gln His Ala Ser
65                  70                  75                  80

Asp Ala Leu Ser Pro Val Leu Ala Glu Glu Thr Phe Arg Tyr Met Ile
                85                  90                  95

Leu Gly Thr Asp Arg Val Glu Gln Met Thr Lys Thr Tyr Asn Asp Ile
            100                 105                 110

Asp Met Val Thr His Leu Leu Ala Glu Arg Asp Arg Asp Leu Glu Leu
        115                 120                 125

Ala Ala Arg Ile Gly Gln Ala Leu Leu Lys Arg Asn His Val Leu Ser
    130                 135                 140

Glu Gln Asn Glu Ser Leu Glu Glu Gln Leu Gly Gln Ala Phe Asp Gln
145                 150                 155                 160

Val Asn Gln Leu Gln His Glu Leu Cys Lys Lys Asp Glu Leu Leu Arg
                165                 170                 175

Ile Val Ser Ile Ala Ser Glu Glu Ser Glu Thr Asp Ser Ser Cys Ser
            180                 185                 190

Thr Pro Leu Arg Phe Asn Glu Ser Phe Ser Leu Ser Gln Gly Leu Leu
        195                 200                 205
```

```
Gln Leu Glu Met Leu Gln Glu Lys Leu Lys Glu Leu Glu Glu Glu Asn
    210                 215                 220

Met Ala Leu Arg Ser Lys Ala Cys His Ile Lys Thr Glu Thr Val Thr
225                 230                 235                 240

Tyr Glu Glu Lys Glu Gln Gln Leu Val Ser Asp Cys Val Lys Glu Leu
                245                 250                 255

Arg Glu Thr Asn Ala Gln Met Ser Arg Met Thr Glu Glu Leu Ser Gly
            260                 265                 270

Lys Ser Asp Glu Leu Ile Arg Tyr Gln Glu Glu Leu Ser Ser Leu Leu
        275                 280                 285

Ser Gln Ile Val Asp Leu Gln His Lys Leu Lys Glu His Val Ile Glu
    290                 295                 300

Lys Glu Glu Leu Lys Leu His Leu Gln Ala Ser Lys Asp Ala Gln Arg
305                 310                 315                 320

Gln Leu Thr Met Glu Leu His Glu Leu Gln Asp Arg Asn Met Glu Cys
                325                 330                 335

Leu Gly Met Leu His Glu Ser Gln Glu Glu Ile Lys Glu Leu Arg Ser
            340                 345                 350

Arg Ser Gly Pro Thr Ala His Leu Tyr Phe Ser Gln Ser Tyr Gly Ala
        355                 360                 365

Phe Thr Gly Glu Ser Leu Ala Ala Glu Ile Glu Gly Thr Met Arg Lys
    370                 375                 380

Lys Leu Ser Leu Asp Glu Glu Ser Ser Leu Phe Lys Gln Lys Ala Gln
385                 390                 395                 400

Gln Lys Arg Val Phe Asp Thr Val Arg Ile Ala Asn Asp Thr Arg Gly
                405                 410                 415

Arg Ser Ile Ser Phe Pro Ala Leu Leu Pro Ile Pro Gly Ser Asn Arg
            420                 425                 430

Ser Ser Val Ile Met Thr Ala Lys Pro Phe Glu Ser Gly Leu Gln Gln
        435                 440                 445
```

```
Thr Glu Asp Lys Ser Leu Leu Asn Gln Gly Ser Ser Ser Glu Glu Val
    450                 455                 460

Ala Gly Ser Ser Gln Lys Met Gly Gln Pro Gly Pro Ser Gly Asp Ser
465                 470                 475                 480

Asp Leu Ala Thr Ala Leu His Arg Leu Ser Leu Arg Arg Gln Asn Tyr
                485                 490                 495

Leu Ser Glu Lys Gln Phe Phe Ala Glu Glu Trp Gln Arg Lys Ile Gln
            500                 505                 510

Val Leu Ala Asp Gln Lys Glu Gly Val Ser Gly Cys Val Thr Pro Thr
        515                 520                 525

Glu Ser Leu Ala Ser Leu Cys Thr Thr Gln Ser Glu Ile Thr Asp Leu
    530                 535                 540

Ser Ser Ala Ser Cys Leu Arg Gly Phe Met Pro Glu Lys Leu Gln Ile
545                 550                 555                 560

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

Ala Gln Pro Asn Leu Gly Thr Ile Leu Asp Pro Arg Pro Gly Val Ile
            580                 585                 590

Thr Lys Gly Phe Thr Gln Leu Pro Gly Asp Ala Ile Tyr His Ile Ser
        595                 600                 605

Asp Leu Glu Glu Asp Glu Glu Glu Gly Ile Thr Phe Gln Val Gln Gln
    610                 615                 620

Pro Leu Glu Val Glu Glu Lys Leu Ser Thr Ser Lys Pro Val Thr Gly
625                 630                 635                 640

Ile Phe Leu Pro Pro Ile Thr Ser Ala Gly Gly Pro Val Thr Val Ala
                645                 650                 655

Thr Ala Asn Pro Gly Lys Cys Leu Ser Cys Thr Asn Ser Thr Phe Thr
            660                 665                 670

Phe Thr Thr Cys Arg Ile Leu His Pro Ser Asp Ile Thr Gln Val Thr
        675                 680                 685
```

```
Pro Ser Ser Gly Phe Pro Ser Leu Ser Cys Gly Ser Ser Gly Ser Ser
    690                 695                 700

Ser Ser Asn Thr Ala Val Asn Ser Pro Ala Leu Ser Tyr Arg Leu Ser
705                 710                 715                 720

Ile Gly Glu Ser Ile Thr Asn Arg Arg Asp Ser Thr Thr Thr Phe Ser
                725                 730                 735

Ser Thr Met Ser Leu Ala Lys Leu Leu Gln Glu Arg Gly Ile Ser Ala
            740                 745                 750

Lys Val Tyr His Ser Pro Ile Ser Glu Asn Pro Leu Gln Pro Leu Pro
        755                 760                 765

Lys Ser Leu Ala Ile Pro Ser Thr Pro Pro Asn Ser Pro Ser His Ser
    770                 775                 780

Pro Cys Pro Ser Pro Leu Pro Phe Glu Pro Arg Val His Leu Ser Glu
785                 790                 795                 800

Asn Phe Leu Ala Ser Arg Pro Ala Glu Thr Phe Leu Gln Glu Met Tyr
                805                 810                 815

Gly Leu Arg Pro Ser Arg Asn Pro Pro Asp Val Gly Gln Leu Lys Met
            820                 825                 830

Asn Leu Val Asp Arg Leu Lys Arg Leu Gly Ile Ala Arg Val Val Lys
        835                 840                 845

Asn Pro Gly Ala Gln Glu Asn Gly Arg Cys Gln Glu Ala Glu Ile Gly
    850                 855                 860

Pro Gln Lys Pro Asp Ser Ala Val Tyr Leu Asn Ser Gly Ser Ser Leu
865                 870                 875                 880

Leu Gly Gly Leu Arg Arg Asn Gln Ser Leu Pro Val Ile Met Gly Ser
                885                 890                 895

Phe Ala Ala Pro Val Cys Thr Ser Ser Pro Lys Met Gly Val Leu Lys
            900                 905                 910

Glu Asp
```

```
<210>  131
<211>  94
<212>  PRT
<213>  Homo sapiens

<400>  131

Met Arg Thr Ile Ala Ile Leu Ala Ala Ile Leu Leu Val Ala Leu Gln
1               5                   10                  15


Ala Gln Ala Glu Ser Leu Gln Glu Arg Ala Asp Glu Ala Thr Thr Gln
            20                  25                  30


Lys Gln Ser Gly Glu Asp Asn Gln Asp Leu Ala Ile Ser Phe Ala Gly
        35                  40                  45


Asn Gly Leu Ser Ala Leu Arg Thr Ser Gly Ser Gln Ala Arg Ala Thr
    50                  55                  60


Cys Tyr Cys Arg Thr Gly Arg Cys Ala Thr Arg Glu Ser Leu Ser Gly
65                  70                  75                  80


Val Cys Glu Ile Ser Gly Arg Leu Tyr Arg Leu Cys Cys Arg
                85                  90


<210>  132
<211>  504
<212>  PRT
<213>  Homo sapiens

<400>  132

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


Phe Leu Leu Val Leu Val Asp Leu Gln Tyr Glu Gly Ala Glu Cys Gly
            20                  25                  30


Val Asn Ala Asp Val Glu Lys His Leu Glu Leu Gly Lys Lys Leu Leu
        35                  40                  45


Ala Ala Gly Gln Leu Ala Asp Ala Leu Ser Gln Phe His Ala Ala Val
    50                  55                  60


Asp Gly Asp Pro Asp Asn Tyr Ile Ala Tyr Tyr Arg Arg Ala Thr Val
65                  70                  75                  80
```

```
Phe Leu Ala Met Gly Lys Ser Lys Ala Ala Leu Pro Asp Leu Thr Lys
                85                  90                  95

Val Ile Gln Leu Lys Met Asp Phe Thr Ala Ala Arg Leu Gln Arg Gly
            100                 105                 110

His Leu Leu Leu Lys Gln Gly Lys Leu Asp Glu Ala Glu Asp Asp Phe
        115                 120                 125

Lys Lys Val Leu Lys Ser Asn Pro Ser Glu Asn Glu Glu Lys Glu Ala
    130                 135                 140

Gln Ser Gln Leu Ile Lys Ser Asp Glu Met Gln Arg Leu Arg Ser Gln
145                 150                 155                 160

Ala Leu Asn Ala Phe Gly Ser Gly Asp Tyr Thr Ala Ala Ile Ala Phe
                165                 170                 175

Leu Asp Lys Ile Leu Glu Val Cys Val Trp Asp Ala Glu Leu Arg Glu
            180                 185                 190

Leu Arg Ala Glu Cys Phe Ile Lys Glu Gly Glu Pro Arg Lys Ala Ile
        195                 200                 205

Ser Asp Leu Lys Ala Ala Ser Lys Leu Lys Asn Asp Asn Thr Glu Ala
    210                 215                 220

Phe Tyr Lys Ile Ser Thr Leu Tyr Tyr Gln Leu Gly Asp His Glu Leu
225                 230                 235                 240

Ser Leu Ser Glu Val Arg Glu Cys Leu Lys Leu Asp Gln Asp His Lys
                245                 250                 255

Arg Cys Phe Ala His Tyr Lys Gln Val Lys Lys Leu Asn Lys Leu Ile
            260                 265                 270

Glu Ser Ala Glu Glu Leu Ile Arg Asp Gly Arg Tyr Thr Asp Ala Thr
        275                 280                 285

Ser Lys Tyr Glu Ser Val Met Lys Thr Glu Pro Ser Ile Ala Glu Tyr
    290                 295                 300

Thr Val Arg Ser Lys Glu Arg Ile Cys His Cys Phe Ser Lys Asp Glu
305                 310                 315                 320
```

```
Lys Pro Val Glu Ala Ile Arg Val Cys Ser Glu Val Leu Gln Met Glu
                325                 330                 335

Pro Asp Asn Val Asn Ala Leu Lys Asp Arg Ala Glu Ala Tyr Leu Ile
            340                 345                 350

Glu Glu Met Tyr Asp Glu Ala Ile Gln Asp Tyr Glu Thr Ala Gln Glu
        355                 360                 365

His Asn Glu Asn Asp Gln Gln Ile Arg Glu Gly Leu Glu Lys Ala Gln
    370                 375                 380

Arg Leu Leu Lys Gln Ser Gln Lys Arg Asp Tyr Tyr Lys Ile Leu Gly
385                 390                 395                 400

Val Lys Arg Asn Ala Lys Lys Gln Glu Ile Ile Lys Ala Tyr Arg Lys
                405                 410                 415

Leu Ala Leu Gln Trp His Pro Asp Asn Phe Gln Asn Glu Glu Glu Lys
            420                 425                 430

Lys Lys Ala Glu Lys Lys Phe Ile Asp Ile Ala Ala Ala Lys Glu Val
        435                 440                 445

Leu Ser Asp Pro Glu Met Arg Lys Lys Phe Asp Asp Gly Glu Asp Pro
    450                 455                 460

Leu Asp Ala Glu Ser Gln Gln Gly Gly Gly Gly Asn Pro Phe His Arg
465                 470                 475                 480

Ser Trp Asn Ser Trp Gln Gly Phe Asn Pro Phe Ser Ser Gly Gly Pro
                485                 490                 495

Phe Arg Phe Lys Phe His Phe Asn
            500


<210>  133
<211>  762
<212>  PRT
<213>  Homo sapiens

<400>  133

Met Asn Glu Ala Lys Val Lys Glu Thr Leu Arg Arg Cys Gly Ala Ser
1               5                   10                  15
```

```
Gly Asp Glu Cys Gly Arg Leu Gln Tyr Ala Leu Thr Cys Leu Arg Lys
            20                  25                  30


Val Thr Gly Leu Gly Gly Glu His Lys Glu Asp Ser Ser Trp Ser Ser
        35                  40                  45


Leu Asp Ala Arg Arg Glu Ser Gly Ser Gly Pro Ser Thr Asp Thr Leu
    50                  55                  60


Ser Ala Ala Ser Leu Pro Trp Pro Pro Gly Ser Ser Gln Leu Gly Arg
65                  70                  75                  80


Ala Gly Asn Ser Ala Gln Gly Pro Arg Ser Ile Ser Val Ser Ala Leu
                85                  90                  95


Pro Ala Ser Asp Ser Pro Thr Pro Ser Phe Ser Glu Gly Leu Ser Asp
            100                 105                 110


Thr Cys Ile Pro Leu His Ala Ser Gly Arg Leu Thr Pro Arg Ala Leu
        115                 120                 125


His Ser Phe Ile Thr Pro Pro Thr Thr Pro Gln Leu Arg Arg His Thr
    130                 135                 140


Lys Leu Lys Pro Pro Arg Thr Pro Pro Pro Pro Ser Arg Lys Val Phe
145                 150                 155                 160


Gln Leu Leu Pro Ser Phe Pro Thr Leu Thr Arg Ser Lys Ser His Glu
                165                 170                 175


Ser Gln Leu Gly Asn Arg Ile Asp Asp Val Ser Ser Met Arg Phe Asp
            180                 185                 190


Leu Ser His Gly Ser Pro Gln Met Val Arg Arg Asp Ile Gly Leu Ser
        195                 200                 205


Val Thr His Arg Phe Ser Thr Lys Ser Trp Leu Ser Gln Val Cys His
    210                 215                 220


Val Cys Gln Lys Ser Met Ile Phe Gly Val Lys Cys Lys His Cys Arg
225                 230                 235                 240


Leu Lys Cys His Asn Lys Cys Thr Lys Glu Ala Pro Ala Cys Arg Ile
                245                 250                 255
```

```
Ser Phe Leu Pro Leu Thr Arg Leu Arg Arg Thr Glu Ser Val Pro Ser
            260                 265                 270


Asp Ile Asn Asn Pro Val Asp Arg Ala Ala Glu Pro His Phe Gly Thr
        275                 280                 285


Leu Pro Lys Ala Leu Thr Lys Lys Glu His Pro Pro Ala Met Asn His
    290                 295                 300


Leu Asp Ser Ser Ser Asn Pro Ser Ser Thr Thr Ser Ser Thr Pro Ser
305                 310                 315                 320


Ser Pro Ala Pro Phe Pro Thr Ser Ser Asn Pro Ser Ser Ala Thr Thr
                325                 330                 335


Pro Pro Asn Pro Ser Pro Gly Gln Arg Asp Ser Arg Phe Asn Phe Pro
            340                 345                 350


Ala Ala Tyr Phe Ile His His Arg Gln Gln Phe Ile Phe Pro Val Pro
        355                 360                 365


Ser Ala Gly His Cys Trp Lys Cys Leu Leu Ile Ala Glu Ser Leu Lys
    370                 375                 380


Glu Asn Ala Phe Asn Ile Ser Ala Phe Ala His Ala Ala Pro Leu Pro
385                 390                 395                 400


Glu Ala Ala Asp Gly Thr Arg Leu Asp Asp Gln Pro Lys Ala Asp Val
                405                 410                 415


Leu Glu Ala His Glu Ala Glu Ala Glu Glu Pro Glu Ala Gly Lys Ser
            420                 425                 430


Glu Ala Glu Asp Asp Glu Asp Glu Val Asp Asp Leu Pro Ser Ser Arg
        435                 440                 445


Arg Pro Trp Arg Gly Pro Ile Ser Arg Lys Ala Ser Gln Thr Ser Val
    450                 455                 460


Tyr Leu Gln Glu Trp Asp Ile Pro Phe Glu Gln Val Glu Leu Gly Glu
465                 470                 475                 480


Pro Ile Gly Gln Gly Arg Trp Gly Arg Val His Arg Gly Arg Trp His
                485                 490                 495
```

```
Gly Glu Val Ala Ile Arg Leu Leu Glu Met Asp Gly His Asn Gln Asp
            500                 505                 510

His Leu Lys Leu Phe Lys Lys Glu Val Met Asn Tyr Arg Gln Thr Arg
        515                 520                 525

His Glu Asn Val Val Leu Phe Met Gly Ala Cys Met Asn Pro Pro His
    530                 535                 540

Leu Ala Ile Ile Thr Ser Phe Cys Lys Gly Arg Thr Leu His Ser Phe
545                 550                 555                 560

Val Arg Asp Pro Lys Thr Ser Leu Asp Ile Asn Lys Thr Arg Gln Ile
                565                 570                 575

Ala Gln Glu Ile Ile Lys Gly Met Gly Tyr Leu His Ala Lys Gly Ile
            580                 585                 590

Val His Lys Asp Leu Lys Ser Lys Asn Val Phe Tyr Asp Asn Gly Lys
        595                 600                 605

Val Val Ile Thr Asp Phe Gly Leu Phe Gly Ile Ser Gly Val Val Arg
    610                 615                 620

Glu Gly Arg Arg Glu Asn Gln Leu Lys Leu Ser His Asp Trp Leu Cys
625                 630                 635                 640

Tyr Leu Ala Pro Glu Ile Val Arg Glu Met Thr Pro Gly Lys Asp Glu
                645                 650                 655

Asp Gln Leu Pro Phe Ser Lys Ala Ala Asp Val Tyr Ala Phe Gly Thr
            660                 665                 670

Val Trp Tyr Glu Leu Gln Ala Arg Asp Trp Pro Leu Lys Asn Gln Ala
        675                 680                 685

Ala Glu Ala Ser Ile Trp Gln Ile Gly Ser Gly Glu Gly Met Lys Arg
    690                 695                 700

Val Leu Thr Ser Val Ser Leu Gly Lys Glu Val Ser Glu Ile Leu Ser
705                 710                 715                 720

Ala Cys Trp Ala Phe Asp Leu Gln Glu Arg Pro Ser Phe Ser Leu Leu
                725                 730                 735
```

```
Met Asp Met Leu Glu Lys Leu Pro Lys Leu Asn Arg Arg Leu Ser His
            740                 745                 750


Pro Gly His Phe Trp Lys Ser Ala Glu Leu
        755                 760


<210>  134
<211>  959
<212>  PRT
<213>  Homo sapiens

<400>  134

Met Ala Ala Ser Thr Gly Tyr Val Arg Leu Trp Gly Ala Ala Arg Cys
1               5                   10                  15


Trp Val Leu Arg Arg Pro Met Leu Ala Ala Ala Gly Gly Arg Val Pro
            20                  25                  30


Thr Ala Ala Gly Ala Trp Leu Leu Arg Gly Gln Arg Thr Cys Asp Ala
        35                  40                  45


Ser Pro Pro Trp Ala Leu Trp Gly Arg Gly Pro Ala Ile Gly Gly Gln
    50                  55                  60


Trp Arg Gly Phe Trp Glu Ala Ser Ser Arg Gly Gly Gly Ala Phe Ser
65                  70                  75                  80


Gly Gly Glu Asp Ala Ser Glu Gly Gly Ala Glu Glu Gly Ala Gly Gly
                85                  90                  95


Ala Gly Gly Ser Ala Gly Ala Gly Glu Gly Pro Val Ile Thr Ala Leu
            100                 105                 110


Thr Pro Met Thr Ile Pro Asp Val Phe Pro His Leu Pro Leu Ile Ala
        115                 120                 125


Ile Thr Arg Asn Pro Val Phe Pro Arg Phe Ile Lys Ile Ile Glu Val
    130                 135                 140


Lys Asn Lys Lys Leu Val Glu Leu Leu Arg Arg Lys Val Arg Leu Ala
145                 150                 155                 160


Gln Pro Tyr Val Gly Val Phe Leu Lys Arg Asp Asp Ser Asn Glu Ser
                165                 170                 175
```

```
Asp Val Val Glu Ser Leu Asp Glu Ile Tyr His Thr Gly Thr Phe Ala
            180                 185                 190

Gln Ile His Glu Met Gln Asp Leu Gly Asp Lys Leu Arg Met Ile Val
        195                 200                 205

Met Gly His Arg Arg Val His Ile Ser Arg Gln Leu Glu Val Glu Pro
    210                 215                 220

Glu Glu Pro Glu Ala Glu Asn Lys His Lys Pro Arg Arg Lys Ser Lys
225                 230                 235                 240

Arg Gly Lys Lys Glu Ala Glu Asp Glu Leu Ser Ala Arg His Pro Ala
                245                 250                 255

Glu Leu Ala Met Glu Pro Thr Pro Glu Leu Pro Ala Glu Val Leu Met
            260                 265                 270

Val Glu Val Glu Asn Val Val His Glu Asp Phe Gln Val Thr Glu Glu
        275                 280                 285

Val Lys Ala Leu Thr Ala Glu Ile Val Lys Thr Ile Arg Asp Ile Ile
    290                 295                 300

Ala Leu Asn Pro Leu Tyr Arg Glu Ser Val Leu Gln Met Met Gln Ala
305                 310                 315                 320

Gly Gln Arg Val Val Asp Asn Pro Ile Tyr Leu Ser Asp Met Gly Ala
                325                 330                 335

Ala Leu Thr Gly Ala Glu Ser His Glu Leu Gln Asp Val Leu Glu Glu
            340                 345                 350

Thr Asn Ile Pro Lys Arg Leu Tyr Lys Ala Leu Ser Leu Leu Lys Lys
        355                 360                 365

Glu Phe Glu Leu Ser Lys Leu Gln Gln Arg Leu Gly Arg Glu Val Glu
    370                 375                 380

Glu Lys Ile Lys Gln Thr His Arg Lys Tyr Leu Leu Gln Glu Gln Leu
385                 390                 395                 400

Lys Ile Ile Lys Lys Glu Leu Gly Leu Glu Lys Asp Asp Lys Asp Ala
                405                 410                 415
```

```
Ile Glu Glu Lys Phe Arg Glu Arg Leu Lys Glu Leu Val Val Pro Lys
            420                 425                 430

His Val Met Asp Val Val Asp Glu Glu Leu Ser Lys Leu Gly Leu Leu
        435                 440                 445

Asp Asn His Ser Ser Glu Phe Asn Val Thr Arg Asn Tyr Leu Asp Trp
    450                 455                 460

Leu Thr Ser Ile Pro Trp Gly Lys Tyr Ser Asn Glu Asn Leu Asp Leu
465                 470                 475                 480

Ala Arg Ala Gln Ala Val Leu Glu Glu Asp His Tyr Gly Met Glu Asp
                485                 490                 495

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

Ser Thr Gln Gly Lys Ile Leu Cys Phe Tyr Gly Pro Pro Gly Val Gly
        515                 520                 525

Lys Thr Ser Ile Ala Arg Ser Ile Ala Arg Ala Leu Asn Arg Glu Tyr
    530                 535                 540

Phe Arg Phe Ser Val Gly Gly Met Thr Asp Val Ala Glu Ile Lys Gly
545                 550                 555                 560

His Arg Arg Thr Tyr Val Gly Ala Met Pro Gly Lys Ile Ile Gln Cys
                565                 570                 575

Leu Lys Lys Thr Lys Thr Glu Asn Pro Leu Ile Leu Ile Asp Glu Val
            580                 585                 590

Asp Lys Ile Gly Arg Gly Tyr Gln Gly Asp Pro Ser Ser Ala Leu Leu
        595                 600                 605

Glu Leu Leu Asp Pro Glu Gln Asn Ala Asn Phe Leu Asp His Tyr Leu
    610                 615                 620

Asp Val Pro Val Asp Leu Ser Lys Val Leu Phe Ile Cys Thr Ala Asn
625                 630                 635                 640

Val Thr Asp Thr Ile Pro Glu Pro Leu Arg Asp Arg Met Glu Met Ile
                645                 650                 655
```

```
Asn Val Ser Gly Tyr Val Ala Gln Glu Lys Leu Ala Ile Ala Glu Arg
            660                 665                 670

Tyr Leu Val Pro Gln Ala Arg Ala Leu Cys Gly Leu Asp Glu Ser Lys
        675                 680                 685

Ala Lys Leu Ser Ser Asp Val Leu Thr Leu Leu Ile Lys Gln Tyr Cys
    690                 695                 700

Arg Glu Ser Gly Val Arg Asn Leu Gln Lys Gln Val Glu Lys Val Leu
705                 710                 715                 720

Arg Lys Ser Ala Tyr Lys Ile Val Ser Gly Glu Ala Glu Ser Val Glu
                725                 730                 735

Val Thr Pro Glu Asn Leu Gln Asp Phe Val Gly Lys Pro Val Phe Thr
            740                 745                 750

Val Glu Arg Met Tyr Asp Val Thr Pro Pro Gly Val Val Met Gly Leu
        755                 760                 765

Ala Trp Thr Ala Met Gly Gly Ser Thr Leu Phe Val Glu Thr Ser Leu
    770                 775                 780

Arg Arg Pro Gln Asp Lys Asp Ala Lys Gly Asp Lys Asp Gly Ser Leu
785                 790                 795                 800

Glu Val Thr Gly Gln Leu Gly Glu Val Met Lys Glu Ser Ala Arg Ile
                805                 810                 815

Ala Tyr Thr Phe Ala Arg Ala Phe Leu Met Gln His Ala Pro Ala Asn
            820                 825                 830

Asp Tyr Leu Val Thr Ser His Ile His Leu His Val Pro Glu Gly Ala
        835                 840                 845

Thr Pro Lys Asp Gly Pro Ser Ala Gly Cys Thr Ile Val Thr Ala Leu
    850                 855                 860

Leu Ser Leu Ala Met Gly Arg Pro Val Arg Gln Asn Leu Ala Met Thr
865                 870                 875                 880

Gly Glu Val Ser Leu Thr Gly Lys Ile Leu Pro Val Gly Gly Ile Lys
                885                 890                 895
```

```
Glu Lys Thr Ile Ala Ala Lys Arg Ala Gly Val Thr Cys Ile Val Leu
            900                 905                 910


Pro Ala Glu Asn Lys Lys Asp Phe Tyr Asp Leu Ala Ala Phe Ile Thr
        915                 920                 925


Glu Gly Leu Glu Val His Phe Val Glu His Tyr Arg Glu Ile Phe Asp
    930                 935                 940


Ile Ala Phe Pro Asp Glu Gln Ala Glu Ala Leu Ala Val Glu Arg
945                 950                 955


<210>  135
<211>  979
<212>  PRT
<213>  Homo sapiens

<400>  135

Met Gly Thr Arg Leu Pro Leu Val Leu Arg Gln Leu Arg Arg Pro Pro
1               5                   10                  15


Gln Pro Pro Gly Pro Pro Arg Arg Leu Arg Val Pro Cys Arg Ala Ser
            20                  25                  30


Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Arg Glu Gly Leu Leu Gly
        35                  40                  45


Gln Arg Arg Pro Gln Asp Gly Gln Ala Arg Ser Ser Cys Ser Pro Gly
    50                  55                  60


Gly Arg Thr Pro Ala Ala Arg Asp Ser Ile Val Arg Glu Val Ile Gln
65                  70                  75                  80


Asn Ser Lys Glu Val Leu Ser Leu Leu Gln Glu Lys Asn Pro Ala Phe
                85                  90                  95


Lys Pro Val Leu Ala Ile Ile Gln Ala Gly Asp Asp Asn Leu Met Gln
            100                 105                 110


Glu Ile Asn Gln Asn Leu Ala Glu Glu Ala Gly Leu Asn Ile Thr His
        115                 120                 125


Ile Cys Leu Pro Pro Asp Ser Ser Glu Ala Glu Ile Ile Asp Glu Ile
    130                 135                 140
```

```
Leu Lys Ile Asn Glu Asp Thr Arg Val His Gly Leu Ala Leu Gln Ile
145                 150                 155                 160

Ser Glu Asn Leu Phe Ser Asn Lys Val Leu Asn Ala Leu Lys Pro Glu
                165                 170                 175

Lys Asp Val Asp Gly Val Thr Asp Ile Asn Leu Gly Lys Leu Val Arg
            180                 185                 190

Gly Asp Ala His Glu Cys Phe Val Ser Pro Val Ala Lys Ala Val Ile
        195                 200                 205

Glu Leu Leu Glu Lys Ser Val Gly Val Asn Leu Asp Gly Lys Lys Ile
    210                 215                 220

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

Phe Gln Arg Lys Gly Ser Met Thr Met Ser Ile Gln Trp Lys Thr Arg
                245                 250                 255

Gln Leu Gln Ser Lys Leu His Glu Ala Asp Ile Val Val Leu Gly Ser
            260                 265                 270

Pro Lys Pro Glu Glu Ile Pro Leu Thr Trp Ile Gln Pro Gly Thr Thr
        275                 280                 285

Val Leu Asn Cys Ser His Asp Phe Leu Ser Gly Lys Val Gly Cys Gly
    290                 295                 300

Ser Pro Arg Ile His Phe Gly Gly Leu Ile Glu Glu Asp Asp Val Ile
305                 310                 315                 320

Leu Leu Ala Ala Ala Leu Arg Ile Gln Asn Met Val Ser Ser Gly Arg
                325                 330                 335

Arg Trp Leu Arg Glu Gln Gln His Arg Arg Trp Arg Leu His Cys Leu
            340                 345                 350

Lys Leu Gln Pro Leu Ser Pro Val Pro Ser Asp Ile Glu Ile Ser Arg
        355                 360                 365

Gly Gln Thr Pro Lys Ala Val Asp Val Leu Ala Lys Glu Ile Gly Leu
    370                 375                 380
```

```
Leu Ala Asp Glu Ile Glu Ile Tyr Gly Lys Ser Lys Ala Lys Val Arg
385                 390                 395                 400


Leu Ser Val Leu Glu Arg Leu Lys Asp Gln Ala Asp Gly Lys Tyr Val
                405                 410                 415


Leu Val Ala Gly Ile Thr Pro Thr Pro Leu Gly Glu Gly Lys Ser Thr
            420                 425                 430


Val Thr Ile Gly Leu Val Gln Ala Leu Thr Ala His Leu Asn Val Asn
        435                 440                 445


Ser Phe Ala Cys Leu Arg Gln Pro Ser Gln Gly Pro Thr Phe Gly Val
    450                 455                 460


Lys Gly Gly Ala Ala Gly Gly Gly Tyr Ala Gln Val Ile Pro Met Glu
465                 470                 475                 480


Glu Phe Asn Leu His Leu Thr Gly Asp Ile His Ala Ile Thr Ala Ala
                485                 490                 495


Asn Asn Leu Leu Ala Ala Ala Ile Asp Thr Arg Ile Leu His Glu Asn
            500                 505                 510


Thr Gln Thr Asp Lys Ala Leu Tyr Asn Arg Leu Val Pro Leu Val Asn
        515                 520                 525


Gly Val Arg Glu Phe Ser Glu Ile Gln Leu Ala Arg Leu Lys Lys Leu
    530                 535                 540


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


Lys Phe Ala Arg Leu Asp Ile Asp Pro Ser Thr Ile Thr Trp Gln Arg
                565                 570                 575


Val Leu Asp Thr Asn Asp Arg Phe Leu Arg Lys Ile Thr Ile Gly Gln
            580                 585                 590


Gly Asn Thr Glu Lys Gly His Tyr Arg Gln Ala Gln Phe Asp Ile Ala
        595                 600                 605


Val Ala Ser Glu Ile Met Ala Val Leu Ala Leu Thr Asp Ser Leu Ala
    610                 615                 620
```

```
Asp Met Lys Ala Arg Leu Gly Arg Met Val Val Ala Ser Asp Lys Ser
625                 630                 635                 640

Gly Gln Pro Val Thr Ala Asp Asp Leu Gly Val Thr Gly Ala Leu Thr
                645                 650                 655

Val Leu Met Lys Asp Ala Ile Lys Pro Asn Leu Met Gln Thr Leu Glu
            660                 665                 670

Gly Thr Pro Val Phe Val His Ala Gly Pro Phe Ala Asn Ile Ala His
        675                 680                 685

Gly Asn Ser Ser Val Leu Ala Asp Lys Ile Ala Leu Lys Leu Val Gly
    690                 695                 700

Glu Glu Gly Phe Val Val Thr Glu Ala Gly Phe Gly Ala Asp Ile Gly
705                 710                 715                 720

Met Glu Lys Phe Phe Asn Ile Lys Cys Arg Ala Ser Gly Leu Val Pro
                725                 730                 735

Asn Val Val Val Leu Val Ala Thr Val Arg Ala Leu Lys Met His Gly
            740                 745                 750

Gly Gly Pro Ser Val Thr Ala Gly Val Pro Leu Lys Lys Glu Tyr Thr
        755                 760                 765

Glu Glu Asn Ile Gln Leu Val Ala Asp Gly Cys Cys Asn Leu Gln Lys
    770                 775                 780

Gln Ile Gln Ile Thr Gln Leu Phe Gly Val Pro Val Val Val Ala Leu
785                 790                 795                 800

Asn Val Phe Lys Thr Asp Thr Arg Ala Glu Ile Asp Leu Val Cys Glu
                805                 810                 815

Leu Ala Lys Arg Ala Gly Ala Phe Asp Ala Val Pro Cys Tyr His Trp
            820                 825                 830

Ser Val Gly Gly Lys Gly Ser Val Asp Leu Ala Arg Ala Val Arg Glu
        835                 840                 845

Ala Ala Ser Lys Arg Ser Arg Phe Gln Phe Leu Tyr Asp Val Gln Val
    850                 855                 860
```

```
Pro Ile Val Asp Lys Ile Arg Thr Ile Ala Gln Ala Val Tyr Gly Ala
865                 870                 875                 880


Lys Asp Ile Glu Leu Ser Pro Glu Ala Gln Ala Lys Ile Asp Arg Tyr
                885                 890                 895


Thr Gln Gln Gly Phe Gly Asn Leu Pro Ile Cys Met Ala Lys Thr His
            900                 905                 910


Leu Ser Leu Ser His Gln Pro Asp Lys Lys Gly Val Pro Arg Asp Phe
        915                 920                 925


Ile Leu Pro Ile Ser Asp Val Arg Ala Ser Ile Gly Ala Gly Phe Ile
    930                 935                 940


Tyr Pro Leu Val Gly Thr Met Ser Thr Met Pro Gly Leu Pro Thr Arg
945                 950                 955                 960


Pro Cys Phe Tyr Asp Ile Asp Leu Asp Thr Glu Thr Glu Gln Val Lys
                965                 970                 975


Gly Leu Phe



<210>  136
<211>  978
<212>  PRT
<213>  Homo sapiens

<400>  136

Met Gly Thr Arg Leu Pro Leu Val Leu Arg Gln Leu Arg Arg Pro Pro
1               5                   10                  15


Gln Pro Pro Gly Pro Pro Arg Arg Leu Arg Val Pro Cys Arg Ala Ser
            20                  25                  30


Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Arg Glu Gly Leu Leu Gly
        35                  40                  45


Gln Arg Arg Pro Gln Asp Gly Gln Ala Arg Ser Ser Cys Ser Pro Gly
    50                  55                  60


Gly Arg Thr Pro Ala Ala Arg Asp Ser Ile Val Arg Glu Val Ile Gln
65                  70                  75                  80
```

```
Asn Ser Lys Glu Val Leu Ser Leu Leu Gln Glu Lys Asn Pro Ala Phe
                85                  90                  95

Lys Pro Val Leu Ala Ile Ile Gln Ala Gly Asp Asp Asn Leu Met Gln
            100                 105                 110

Glu Ile Asn Gln Asn Leu Ala Glu Glu Ala Gly Leu Asn Ile Thr His
        115                 120                 125

Ile Cys Leu Pro Pro Asp Ser Ser Glu Ala Glu Ile Ile Asp Glu Ile
    130                 135                 140

Leu Lys Ile Asn Glu Asp Thr Arg Val His Gly Leu Ala Leu Gln Ile
145                 150                 155                 160

Ser Glu Asn Leu Phe Ser Asn Lys Val Leu Asn Ala Leu Lys Pro Glu
                165                 170                 175

Lys Asp Val Asp Gly Val Thr Asp Ile Asn Leu Gly Lys Leu Val Arg
            180                 185                 190

Gly Asp Ala His Glu Cys Phe Val Ser Pro Val Ala Lys Ala Val Ile
        195                 200                 205

Glu Leu Leu Glu Lys Ser Gly Val Asn Leu Asp Gly Lys Lys Ile Leu
    210                 215                 220

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

Gln Arg Lys Gly Ser Met Thr Met Ser Ile Gln Trp Lys Thr Arg Gln
                245                 250                 255

Leu Gln Ser Lys Leu His Glu Ala Asp Ile Val Val Leu Gly Ser Pro
            260                 265                 270

Lys Pro Glu Glu Ile Pro Leu Thr Trp Ile Gln Pro Gly Thr Thr Val
        275                 280                 285

Leu Asn Cys Ser His Asp Phe Leu Ser Gly Lys Val Gly Cys Gly Ser
    290                 295                 300

Pro Arg Ile His Phe Gly Gly Leu Ile Glu Glu Asp Asp Val Ile Leu
305                 310                 315                 320
```

```
Leu Ala Ala Ala Leu Arg Ile Gln Asn Met Val Ser Ser Gly Arg Arg
                325                 330                 335

Trp Leu Arg Glu Gln Gln His Arg Arg Trp Arg Leu His Cys Leu Lys
            340                 345                 350

Leu Gln Pro Leu Ser Pro Val Pro Ser Asp Ile Glu Ile Ser Arg Gly
        355                 360                 365

Gln Thr Pro Lys Ala Val Asp Val Leu Ala Lys Glu Ile Gly Leu Leu
    370                 375                 380

Ala Asp Glu Ile Glu Ile Tyr Gly Lys Ser Lys Ala Lys Val Arg Leu
385                 390                 395                 400

Ser Val Leu Glu Arg Leu Lys Asp Gln Ala Asp Gly Lys Tyr Val Leu
                405                 410                 415

Val Ala Gly Ile Thr Pro Thr Pro Leu Gly Glu Gly Lys Ser Thr Val
            420                 425                 430

Thr Ile Gly Leu Val Gln Ala Leu Thr Ala His Leu Asn Val Asn Ser
        435                 440                 445

Phe Ala Cys Leu Arg Gln Pro Ser Gln Gly Pro Thr Phe Gly Val Lys
    450                 455                 460

Gly Gly Ala Ala Gly Gly Gly Tyr Ala Gln Val Ile Pro Met Glu Glu
465                 470                 475                 480

Phe Asn Leu His Leu Thr Gly Asp Ile His Ala Ile Thr Ala Ala Asn
                485                 490                 495

Asn Leu Leu Ala Ala Ala Ile Asp Thr Arg Ile Leu His Glu Asn Thr
            500                 505                 510

Gln Thr Asp Lys Ala Leu Tyr Asn Arg Leu Val Pro Leu Val Asn Gly
        515                 520                 525

Val Arg Glu Phe Ser Glu Ile Gln Leu Ala Arg Leu Lys Lys Leu Gly
    530                 535                 540

Ile Asn Lys Thr Asp Pro Ser Thr Leu Thr Glu Glu Glu Val Ser Lys
545                 550                 555                 560
```

```
Phe Ala Arg Leu Asp Ile Asp Pro Ser Thr Ile Thr Trp Gln Arg Val
                565                 570                 575

Leu Asp Thr Asn Asp Arg Phe Leu Arg Lys Ile Thr Ile Gly Gln Gly
            580                 585                 590

Asn Thr Glu Lys Gly His Tyr Arg Gln Ala Gln Phe Asp Ile Ala Val
        595                 600                 605

Ala Ser Glu Ile Met Ala Val Leu Ala Leu Thr Asp Ser Leu Ala Asp
    610                 615                 620

Met Lys Ala Arg Leu Gly Arg Met Val Val Ala Ser Asp Lys Ser Gly
625                 630                 635                 640

Gln Pro Val Thr Ala Asp Asp Leu Gly Val Thr Gly Ala Leu Thr Val
                645                 650                 655

Leu Met Lys Asp Ala Ile Lys Pro Asn Leu Met Gln Thr Leu Glu Gly
            660                 665                 670

Thr Pro Val Phe Val His Ala Gly Pro Phe Ala Asn Ile Ala His Gly
        675                 680                 685

Asn Ser Ser Val Leu Ala Asp Lys Ile Ala Leu Lys Leu Val Gly Glu
    690                 695                 700

Glu Gly Phe Val Val Thr Glu Ala Gly Phe Gly Ala Asp Ile Gly Met
705                 710                 715                 720

Glu Lys Phe Phe Asn Ile Lys Cys Arg Ala Ser Gly Leu Val Pro Asn
                725                 730                 735

Val Val Val Leu Val Ala Thr Val Arg Ala Leu Lys Met His Gly Gly
            740                 745                 750

Gly Pro Ser Val Thr Ala Gly Val Pro Leu Lys Lys Glu Tyr Thr Glu
        755                 760                 765

Glu Asn Ile Gln Leu Val Ala Asp Gly Cys Cys Asn Leu Gln Lys Gln
    770                 775                 780

Ile Gln Ile Thr Gln Leu Phe Gly Val Pro Val Val Val Ala Leu Asn
785                 790                 795                 800
```

```
Val Phe Lys Thr Asp Thr Arg Ala Glu Ile Asp Leu Val Cys Glu Leu
                805                 810                 815


Ala Lys Arg Ala Gly Ala Phe Asp Ala Val Pro Cys Tyr His Trp Ser
            820                 825                 830


Val Gly Gly Lys Gly Ser Val Asp Leu Ala Arg Ala Val Arg Glu Ala
        835                 840                 845


Ala Ser Lys Arg Ser Arg Phe Gln Phe Leu Tyr Asp Val Gln Val Pro
    850                 855                 860


Ile Val Asp Lys Ile Arg Thr Ile Ala Gln Ala Val Tyr Gly Ala Lys
865                 870                 875                 880


Asp Ile Glu Leu Ser Pro Glu Ala Gln Ala Lys Ile Asp Arg Tyr Thr
                885                 890                 895


Gln Gln Gly Phe Gly Asn Leu Pro Ile Cys Met Ala Lys Thr His Leu
            900                 905                 910


Ser Leu Ser His Gln Pro Asp Lys Lys Gly Val Pro Arg Asp Phe Ile
        915                 920                 925


Leu Pro Ile Ser Asp Val Arg Ala Ser Ile Gly Ala Gly Phe Ile Tyr
    930                 935                 940


Pro Leu Val Gly Thr Met Ser Thr Met Pro Gly Leu Pro Thr Arg Pro
945                 950                 955                 960


Cys Phe Tyr Asp Ile Asp Leu Asp Thr Glu Thr Glu Gln Val Lys Gly
                965                 970                 975


Leu Phe



<210>  137
<211>  275
<212>  PRT
<213>  Homo sapiens

<400>  137

Met Gly Thr Arg Leu Pro Leu Val Leu Arg Gln Leu Arg Arg Pro Pro
1               5                   10                  15
```

```
Gln Pro Pro Gly Pro Pro Arg Arg Leu Arg Val Pro Cys Arg Ala Ser
            20                  25                  30

Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Arg Glu Gly Leu Leu Gly
        35                  40                  45

Gln Arg Arg Pro Gln Asp Gly Gln Ala Arg Ser Ser Cys Ser Pro Gly
    50                  55                  60

Gly Arg Thr Pro Ala Ala Arg Asp Ser Ile Val Arg Glu Val Ile Gln
65                  70                  75                  80

Asn Ser Lys Glu Val Leu Ser Leu Leu Gln Glu Lys Asn Pro Ala Phe
                85                  90                  95

Lys Pro Val Leu Ala Ile Ile Gln Ala Gly Asp Asp Asn Leu Met Gln
            100                 105                 110

Glu Ile Asn Gln Asn Leu Ala Glu Glu Ala Gly Leu Asn Ile Thr His
        115                 120                 125

Ile Cys Leu Pro Pro Asp Ser Ser Glu Ala Glu Ile Ile Asp Glu Ile
    130                 135                 140

Leu Lys Ile Asn Glu Asp Thr Arg Val His Gly Leu Ala Leu Gln Ile
145                 150                 155                 160

Ser Glu Asn Leu Phe Ser Asn Lys Val Leu Asn Ala Leu Lys Pro Glu
                165                 170                 175

Lys Asp Val Asp Gly Val Thr Asp Ile Asn Leu Gly Lys Leu Val Arg
            180                 185                 190

Gly Asp Ala His Glu Cys Phe Val Ser Pro Val Ala Lys Ala Val Ile
        195                 200                 205

Glu Leu Leu Glu Lys Ser Gly Val Asn Leu Asp Gly Lys Lys Ile Leu
    210                 215                 220

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

Gln Arg Lys Gly Ser Met Thr Met Ser Ile Gln Trp Lys Thr Arg Gln
                245                 250                 255
```

```
Leu Gln Ser Lys Thr Glu Ser Arg Ser Val Thr Arg Leu Glu Cys Arg
            260                 265                 270


Arg Val Ile
        275


<210>  138
<211>  913
<212>  PRT
<213>  Homo sapiens

<400>  138

Met Gln Ser Arg Arg Ala Arg Pro Arg Arg Glu Val Ile Gln Asn Ser
1               5                   10                  15


Lys Glu Val Leu Ser Leu Leu Gln Glu Lys Asn Pro Ala Phe Lys Pro
            20                  25                  30


Val Leu Ala Ile Ile Gln Ala Gly Asp Asp Asn Leu Met Gln Glu Ile
        35                  40                  45


Asn Gln Asn Leu Ala Glu Glu Ala Gly Leu Asn Ile Thr His Ile Cys
    50                  55                  60


Leu Pro Pro Asp Ser Ser Glu Ala Glu Ile Ile Asp Glu Ile Leu Lys
65                  70                  75                  80


Ile Asn Glu Asp Thr Arg Val His Gly Leu Ala Leu Gln Ile Ser Glu
                85                  90                  95


Asn Leu Phe Ser Asn Lys Val Leu Asn Ala Leu Lys Pro Glu Lys Asp
            100                 105                 110


Val Asp Gly Val Thr Asp Ile Asn Leu Gly Lys Leu Val Arg Gly Asp
        115                 120                 125


Ala His Glu Cys Phe Val Ser Pro Val Ala Lys Ala Val Ile Glu Leu
    130                 135                 140


Leu Glu Lys Ser Val Gly Val Asn Leu Asp Gly Lys Lys Ile Leu Val
145                 150                 155                 160


Val Gly Ala His Gly Ser Leu Glu Ala Ala Leu Gln Cys Leu Phe Gln
                165                 170                 175
```

```
Arg Lys Gly Ser Met Thr Met Ser Ile Gln Trp Lys Thr Arg Gln Leu
            180                 185                 190

Gln Ser Lys Leu His Glu Ala Asp Ile Val Val Leu Gly Ser Pro Lys
        195                 200                 205

Pro Glu Glu Ile Pro Leu Thr Trp Ile Gln Pro Gly Thr Thr Val Leu
    210                 215                 220

Asn Cys Ser His Asp Phe Leu Ser Gly Lys Val Gly Cys Gly Ser Pro
225                 230                 235                 240

Arg Ile His Phe Gly Gly Leu Ile Glu Glu Asp Asp Val Ile Leu Leu
                245                 250                 255

Ala Ala Ala Leu Arg Ile Gln Asn Met Val Ser Ser Gly Arg Arg Trp
            260                 265                 270

Leu Arg Glu Gln Gln His Arg Arg Trp Arg Leu His Cys Leu Lys Leu
        275                 280                 285

Gln Pro Leu Ser Pro Val Pro Ser Asp Ile Glu Ile Ser Arg Gly Gln
    290                 295                 300

Thr Pro Lys Ala Val Asp Val Leu Ala Lys Glu Ile Gly Leu Leu Ala
305                 310                 315                 320

Asp Glu Ile Glu Ile Tyr Gly Lys Ser Lys Ala Lys Val Arg Leu Ser
                325                 330                 335

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

Ala Gly Ile Thr Pro Thr Pro Leu Gly Glu Gly Lys Ser Thr Val Thr
        355                 360                 365

Ile Gly Leu Val Gln Ala Leu Thr Ala His Leu Asn Val Asn Ser Phe
    370                 375                 380

Ala Cys Leu Arg Gln Pro Ser Gln Gly Pro Thr Phe Gly Val Lys Gly
385                 390                 395                 400

Gly Ala Ala Gly Gly Gly Tyr Ala Gln Val Ile Pro Met Glu Glu Phe
                405                 410                 415
```

```
Asn Leu His Leu Thr Gly Asp Ile His Ala Ile Thr Ala Ala Asn Asn
            420                 425                 430

Leu Leu Ala Ala Ala Ile Asp Thr Arg Ile Leu His Glu Asn Thr Gln
        435                 440                 445

Thr Asp Lys Ala Leu Tyr Asn Arg Leu Val Pro Leu Val Asn Gly Val
    450                 455                 460

Arg Glu Phe Ser Glu Ile Gln Leu Ala Arg Leu Lys Lys Leu Gly Ile
465                 470                 475                 480

Asn Lys Thr Asp Pro Ser Thr Leu Thr Glu Glu Glu Val Ser Lys Phe
                485                 490                 495

Ala Arg Leu Asp Ile Asp Pro Ser Thr Ile Thr Trp Gln Arg Val Leu
            500                 505                 510

Asp Thr Asn Asp Arg Phe Leu Arg Lys Ile Thr Ile Gly Gln Gly Asn
        515                 520                 525

Thr Glu Lys Gly His Tyr Arg Gln Ala Gln Phe Asp Ile Ala Val Ala
    530                 535                 540

Ser Glu Ile Met Ala Val Leu Ala Leu Thr Asp Ser Leu Ala Asp Met
545                 550                 555                 560

Lys Ala Arg Leu Gly Arg Met Val Val Ala Ser Asp Lys Ser Gly Gln
                565                 570                 575

Pro Val Thr Ala Asp Asp Leu Gly Val Thr Gly Ala Leu Thr Val Leu
            580                 585                 590

Met Lys Asp Ala Ile Lys Pro Asn Leu Met Gln Thr Leu Glu Gly Thr
        595                 600                 605

Pro Val Phe Val His Ala Gly Pro Phe Ala Asn Ile Ala His Gly Asn
    610                 615                 620

Ser Ser Val Leu Ala Asp Lys Ile Ala Leu Lys Leu Val Gly Glu Glu
625                 630                 635                 640

Gly Phe Val Val Thr Glu Ala Gly Phe Gly Ala Asp Ile Gly Met Glu
                645                 650                 655
```

```
Lys Phe Phe Asn Ile Lys Cys Arg Ala Ser Gly Leu Val Pro Asn Val
            660                 665                 670

Val Val Leu Val Ala Thr Val Arg Ala Leu Lys Met His Gly Gly Gly
        675                 680                 685

Pro Ser Val Thr Ala Gly Val Pro Leu Lys Lys Glu Tyr Thr Glu Glu
    690                 695                 700

Asn Ile Gln Leu Val Ala Asp Gly Cys Cys Asn Leu Gln Lys Gln Ile
705                 710                 715                 720

Gln Ile Thr Gln Leu Phe Gly Val Pro Val Val Val Ala Leu Asn Val
                725                 730                 735

Phe Lys Thr Asp Thr Arg Ala Glu Ile Asp Leu Val Cys Glu Leu Ala
            740                 745                 750

Lys Arg Ala Gly Ala Phe Asp Ala Val Pro Cys Tyr His Trp Ser Val
        755                 760                 765

Gly Gly Lys Gly Ser Val Asp Leu Ala Arg Ala Val Arg Glu Ala Ala
    770                 775                 780

Ser Lys Arg Ser Arg Phe Gln Phe Leu Tyr Asp Val Gln Val Pro Ile
785                 790                 795                 800

Val Asp Lys Ile Arg Thr Ile Ala Gln Ala Val Tyr Gly Ala Lys Asp
                805                 810                 815

Ile Glu Leu Ser Pro Glu Ala Gln Ala Lys Ile Asp Arg Tyr Thr Gln
            820                 825                 830

Gln Gly Phe Gly Asn Leu Pro Ile Cys Met Ala Lys Thr His Leu Ser
        835                 840                 845

Leu Ser His Gln Pro Asp Lys Lys Gly Val Pro Arg Asp Phe Ile Leu
    850                 855                 860

Pro Ile Ser Asp Val Arg Ala Ser Ile Gly Ala Gly Phe Ile Tyr Pro
865                 870                 875                 880

Leu Val Gly Thr Met Ser Thr Met Pro Gly Leu Pro Thr Arg Pro Cys
                885                 890                 895
```

```
Phe Tyr Asp Ile Asp Leu Asp Thr Glu Thr Glu Gln Val Lys Gly Leu
            900                 905                 910


Phe




<210>  139
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<212>  PRT
<213>  Homo sapiens

<400>  139

Met Asn Gly Asp Met Pro His Val Pro Ile Thr Thr Leu Ala Gly Ile
1               5                   10                  15


Ala Ser Leu Thr Asp Leu Leu Asn Gln Leu Pro Leu Pro Ser Pro Leu
            20                  25                  30


Pro Ala Thr Thr Thr Lys Ser Leu Leu Phe Asn Ala Arg Ile Ala Glu
        35                  40                  45


Glu Val Asn Cys Leu Leu Ala Cys Arg Asp Asp Asn Leu Val Ser Gln
    50                  55                  60


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


Asp Asn Leu Gly Ser Asp Asp Pro Glu Gly Asp Ile Pro Val Leu Leu
                85                  90                  95


Gln Ala Val Leu Ala Arg Ser Pro Asn Val Phe Arg Glu Lys Ser Met
            100                 105                 110


Gln Asn Arg Tyr Val Gln Ser Gly Met Met Met Ser Gln Tyr Lys Leu
        115                 120                 125


Ser Gln Asn Ser Met His Ser Ser Pro Ala Ser Ser Asn Tyr Gln Gln
    130                 135                 140


Thr Thr Ile Ser His Ser Pro Ser Ser Arg Phe Val Pro Pro Gln Thr
145                 150                 155                 160


Ser Ser Gly Asn Arg Phe Met Pro Gln Gln Asn Ser Pro Val Pro Ser
                165                 170                 175
```

```
Pro Tyr Ala Pro Gln Ser Pro Ala Gly Tyr Met Pro Tyr Ser His Pro
            180                 185                 190

Ser Ser Tyr Thr Thr His Pro Gln Met Gln Gln Ala Ser Val Ser Ser
    195                 200                 205

Pro Ile Val Ala Gly Gly Leu Arg Asn Ile His Asp Asn Lys Val Ser
    210                 215                 220

Gly Pro Leu Ser Gly Asn Ser Ala Asn His His Ala Asp Asn Pro Arg
225                 230                 235                 240

His Gly Ser Ser Glu Asp Tyr Leu His Met Val His Arg Leu Ser Ser
                245                 250                 255

Asp Asp Gly Asp Ser Ser Thr Met Arg Asn Ala Ala Ser Phe Pro Leu
            260                 265                 270

Arg Ser Pro Gln Pro Val Cys Ser Pro Ala Gly Ser Glu Gly Thr Pro
    275                 280                 285

Lys Gly Ser Arg Pro Pro Leu Ile Leu Gln Ser Gln Ser Leu Pro Cys
    290                 295                 300

Ser Ser Pro Arg Asp Val Pro Pro Asp Ile Leu Leu Asp Ser Pro Glu
305                 310                 315                 320

Arg Lys Gln Lys Lys Gln Lys Lys Met Lys Leu Gly Lys Asp Glu Lys
                325                 330                 335

Glu Gln Ser Glu Lys Ala Ala Met Tyr Asp Ile Ile Ser Ser Pro Ser
            340                 345                 350

Lys Asp Ser Thr Lys Leu Thr Leu Arg Leu Ser Arg Val Arg Ser Ser
    355                 360                 365

Asp Met Asp Gln Gln Glu Asp Met Ile Ser Gly Val Glu Asn Ser Asn
    370                 375                 380

Val Ser Glu Asn Asp Ile Pro Phe Asn Val Gln Tyr Pro Gly Gln Thr
385                 390                 395                 400

Ser Lys Thr Pro Ile Thr Pro Gln Asp Ile Asn Arg Pro Leu Asn Ala
                405                 410                 415
```

```
Ala Gln Cys Leu Ser Gln Gln Glu Gln Thr Ala Phe Leu Pro Ala Asn
            420                 425                 430

Gln Val Pro Val Leu Gln Gln Asn Thr Ser Val Ala Ala Lys Gln Pro
        435                 440                 445

Gln Thr Ser Val Val Gln Asn Gln Gln Gln Ile Ser Gln Gln Gly Pro
    450                 455                 460

Ile Tyr Asp Glu Val Glu Leu Asp Ala Leu Ala Glu Ile Glu Arg Ile
465                 470                 475                 480

Glu Arg Glu Ser Ala Ile Glu Arg Glu Arg Phe Ser Lys Glu Val Gln
                485                 490                 495

Asp Lys Asp Lys Pro Leu Lys Lys Arg Lys Gln Asp Ser Tyr Pro Gln
            500                 505                 510

Glu Ala Gly Gly Ala Thr Gly Gly Asn Arg Pro Ala Ser Gln Glu Thr
        515                 520                 525

Gly Ser Thr Gly Asn Gly Ser Arg Pro Ala Leu Met Val Ser Ile Asp
    530                 535                 540

Leu His Gln Ala Gly Arg Val Asp Ser Gln Ala Ser Ile Thr Gln Asp
545                 550                 555                 560

Ser Asp Ser Ile Lys Lys Pro Glu Glu Ile Lys Gln Cys Asn Asp Ala
                565                 570                 575

Pro Val Ser Val Leu Gln Glu Asp Ile Val Gly Ser Leu Lys Ser Thr
            580                 585                 590

Pro Glu Asn His Pro Glu Thr Pro Lys Lys Lys Ser Asp Pro Glu Leu
        595                 600                 605

Ser Lys Ser Glu Met Lys Gln Ser Glu Ser Arg Leu Ala Glu Ser Lys
    610                 615                 620

Pro Asn Glu Asn Arg Leu Val Glu Thr Lys Ser Ser Glu Asn Lys Leu
625                 630                 635                 640

Glu Thr Lys Val Glu Thr Gln Thr Glu Glu Leu Lys Gln Asn Glu Ser
                645                 650                 655
```

Arg Thr Thr Glu Cys Lys Gln Asn Glu Ser Thr Ile Val Glu Pro Lys
660 665 670

Gln Asn Glu Asn Arg Leu Ser Asp Thr Lys Pro Asn Asp Asn Lys Gln
675 680 685

Asn Asn Gly Arg Ser Glu Thr Thr Lys Ser Arg Pro Glu Thr Pro Lys
690 695 700

Gln Lys Gly Glu Ser Arg Pro Glu Thr Pro Lys Gln Lys Ser Asp Gly
705 710 715 720

His Pro Glu Thr Pro Lys Gln Lys Gly Asp Gly Arg Pro Glu Thr Pro
725 730 735

Lys Gln Lys Gly Glu Ser Arg Pro Glu Thr Pro Lys Gln Lys Asn Glu
740 745 750

Gly Arg Pro Glu Thr Pro Lys His Arg His Asp Asn Arg Arg Asp Ser
755 760 765

Gly Lys Pro Ser Thr Glu Lys Lys Pro Glu Val Ser Lys His Lys Gln
770 775 780

Asp Thr Lys Ser Asp Ser Pro Arg Leu Lys Ser Glu Arg Ala Glu Ala
785 790 795 800

Leu Lys Gln Arg Pro Asp Gly Arg Ser Val Ser Glu Ser Leu Arg Arg
805 810 815

Asp His Asp Asn Lys Gln Lys Ser Asp Asp Arg Gly Glu Ser Glu Arg
820 825 830

His Arg Gly Asp Gln Ser Arg Val Arg Arg Pro Glu Thr Leu Arg Ser
835 840 845

Ser Ser Arg Asn Glu His Gly Ile Lys Ser Asp Ser Ser Lys Thr Asp
850 855 860

Lys Leu Glu Arg Lys His Arg His Glu Ser Gly Asp Ser Arg Glu Arg
865 870 875 880

Pro Ser Ser Gly Glu Gln Lys Ser Arg Pro Asp Ser Pro Arg Val Lys
885 890 895

```
Gln Gly Asp Ser Asn Lys Ser Arg Ser Asp Lys Leu Gly Phe Lys Ser
            900                 905                 910

Pro Thr Ser Lys Asp Asp Lys Arg Thr Glu Gly Asn Lys Ser Lys Val
        915                 920                 925

Asp Thr Asn Lys Ala His Pro Asp Asn Lys Ala Glu Phe Pro Ser Tyr
    930                 935                 940

Leu Leu Gly Gly Arg Ser Gly Ala Leu Lys Asn Phe Val Ile Pro Lys
945                 950                 955                 960

Ile Lys Arg Asp Lys Asp Gly Asn Val Thr Gln Glu Thr Lys Lys Met
                965                 970                 975

Glu Met Lys Gly Glu Pro Lys Asp Lys Val Glu Lys Ile Gly Leu Val
            980                 985                 990

Glu Asp Leu Asn Lys Gly Ala Lys  Pro Val Val Val Leu  Gln Lys Leu
        995                 1000                1005

Ser Leu  Asp Asp Val Gln Lys  Leu Ile Lys Asp Arg  Glu Asp Lys
    1010                 1015                 1020

Ser Arg  Ser Ser Leu Lys Pro  Ile Lys Asn Lys Pro  Ser Lys Ser
    1025                 1030                 1035

Asn Lys  Gly Ser Ile Asp Gln  Ser Val Leu Lys Glu  Leu Pro Pro
    1040                 1045                 1050

Glu Leu  Leu Ala Glu Ile Glu  Ser Thr Met Pro Leu  Cys Glu Arg
    1055                 1060                 1065

Val Lys  Met Asn Lys Arg Lys  Arg Ser Thr Val Asn  Glu Lys Pro
    1070                 1075                 1080

Lys Tyr  Ala Glu Ile Ser Ser  Asp Glu Asp Asn Asp  Ser Asp Glu
    1085                 1090                 1095

Ala Phe  Glu Ser Ser Arg Lys  Arg His Lys Lys Asp  Asp Asp Lys
    1100                 1105                 1110

Ala Trp  Glu Tyr Glu Glu Arg  Asp Arg Arg Ser Ser  Gly Asp His
    1115                 1120                 1125
```

```
Arg Arg  Ser Gly His Ser His  Glu Gly Arg Arg Ser  Ser Gly Gly
    1130                 1135                 1140

Gly Arg  Tyr Arg Asn Arg Ser  Pro Ser Asp Ser Asp  Met Glu Asp
    1145                 1150                 1155

Tyr Ser  Pro Pro Pro Ser Leu  Ser Glu Val Ala Arg  Lys Met Lys
    1160                 1165                 1170

Lys Lys  Glu Lys Gln Lys Lys  Arg Lys Ala Tyr Glu  Pro Lys Leu
    1175                 1180                 1185

Thr Pro  Glu Glu Met Met Asp  Ser Ser Thr Phe Lys  Arg Phe Thr
    1190                 1195                 1200

Ala Ser  Ile Glu Asn Ile Leu  Asp Asn Leu Glu Asp  Met Asp Phe
    1205                 1210                 1215

Thr Ala  Phe Gly Asp Asp Asp  Glu Ile Pro Gln Glu  Leu Leu Leu
    1220                 1225                 1230

Gly Lys  His Gln Leu Asn Glu  Leu Gly Ser Glu Ser  Ala Lys Ile
    1235                 1240                 1245

Lys Ala  Met Gly Ile Met Asp  Lys Leu Ser Thr Asp  Lys Thr Val
    1250                 1255                 1260

Lys Val  Leu Asn Ile Leu Glu  Lys Asn Ile Gln Asp  Gly Ser Lys
    1265                 1270                 1275

Leu Ser  Thr Leu Leu Asn His  Asn Asn Asp Thr Glu  Glu Glu Glu
    1280                 1285                 1290

Arg Leu  Trp Arg Asp Leu Ile  Met Glu Arg Val Thr  Lys Ser Ala
    1295                 1300                 1305

Asp Ala  Cys Leu Thr Thr Ile  Asn Ile Met Thr Ser  Pro Asn Met
    1310                 1315                 1320

Pro Lys  Ala Val Tyr Ile Glu  Asp Val Ile Glu Arg  Val Ile Gln
    1325                 1330                 1335

Tyr Thr  Lys Phe His Leu Gln  Asn Thr Leu Tyr Pro  Gln Tyr Asp
    1340                 1345                 1350
```

```
Pro Val  Tyr Arg Leu Asp Pro  His Gly Gly Gly Leu  Leu Ser Ser
    1355                 1360                 1365

Lys Ala  Lys Arg Ala Lys Cys  Ser Thr His Lys Gln  Arg Val Ile
    1370                 1375                 1380

Val Met  Leu Tyr Asn Lys Val  Cys Asp Ile Val Ser  Ser Leu Ser
    1385                 1390                 1395

Glu Leu  Leu Glu Ile Gln Leu  Leu Thr Asp Thr Thr  Ile Leu Gln
    1400                 1405                 1410

Val Ser  Ser Met Gly Ile Thr  Pro Phe Phe Val Glu  Asn Val Ser
    1415                 1420                 1425

Glu Leu  Gln Leu Cys Ala Ile  Lys Leu Val Thr Ala  Val Phe Ser
    1430                 1435                 1440

Arg Tyr  Glu Lys His Arg Gln  Leu Ile Leu Glu Glu  Ile Phe Thr
    1445                 1450                 1455

Ser Leu  Ala Arg Leu Pro Thr  Ser Lys Arg Ser Leu  Arg Asn Phe
    1460                 1465                 1470

Arg Leu  Asn Ser Ser Asp Met  Asp Gly Glu Pro Met  Tyr Ile Gln
    1475                 1480                 1485

Met Val  Thr Ala Leu Val Leu  Gln Leu Ile Gln Cys  Val Val His
    1490                 1495                 1500

Leu Pro  Ser Ser Glu Lys Asp  Ser Asn Ala Glu Glu  Asp Ser Asn
    1505                 1510                 1515

Lys Lys  Ile Asp Gln Asp Val  Val Ile Thr Asn Ser  Tyr Glu Thr
    1520                 1525                 1530

Ala Met  Arg Thr Ala Gln Asn  Phe Leu Ser Ile Phe  Leu Lys Lys
    1535                 1540                 1545

Cys Gly  Ser Lys Gln Gly Glu  Glu Asp Tyr Arg Pro  Leu Phe Glu
    1550                 1555                 1560

Asn Phe  Val Gln Asp Leu Leu  Ser Thr Val Asn Lys  Pro Glu Trp
    1565                 1570                 1575
```

```
Pro Ala  Ala Glu Leu Leu Leu  Ser Leu Leu Gly Arg  Leu Leu Val
    1580                 1585                 1590

His Gln  Phe Ser Asn Lys Ser  Thr Glu Met Ala Leu  Arg Val Ala
    1595                 1600                 1605

Ser Leu  Asp Tyr Leu Gly Thr  Val Ala Ala Arg Leu  Arg Lys Asp
    1610                 1615                 1620

Ala Val  Thr Ser Lys Met Asp  Gln Gly Ser Ile Glu  Arg Ile Leu
    1625                 1630                 1635

Lys Gln  Val Ser Gly Gly Glu  Asp Glu Ile Gln Gln  Leu Gln Lys
    1640                 1645                 1650

Ala Leu  Leu Asp Tyr Leu Asp  Glu Asn Thr Glu Thr  Asp Pro Ser
    1655                 1660                 1665

Leu Val  Phe Ser Arg Lys Phe  Tyr Ile Ala Gln Trp  Phe Arg Asp
    1670                 1675                 1680

Thr Thr  Leu Glu Thr Glu Lys  Ala Met Lys Ser Gln  Lys Asp Glu
    1685                 1690                 1695

Glu Ser  Ser Glu Gly Thr His  His Ala Lys Glu Ile  Glu Thr Thr
    1700                 1705                 1710

Gly Gln  Ile Met His Arg Ala  Glu Asn Arg Lys Lys  Phe Leu Arg
    1715                 1720                 1725

Ser Ile  Ile Lys Thr Thr Pro  Ser Gln Phe Ser Thr  Leu Lys Met
    1730                 1735                 1740

Asn Ser  Asp Thr Val Asp Tyr  Asp Asp Ala Cys Leu  Ile Val Arg
    1745                 1750                 1755

Tyr Leu  Ala Ser Met Arg Pro  Phe Ala Gln Ser Phe  Asp Ile Tyr
    1760                 1765                 1770

Leu Thr  Gln Ile Leu Arg Val  Leu Gly Glu Asn Ala  Ile Ala Val
    1775                 1780                 1785

Arg Thr  Lys Ala Met Lys Cys  Leu Ser Glu Val Val  Ala Val Asp
    1790                 1795                 1800
```

```
Pro Ser  Ile Leu Ala Arg Leu  Asp Met Gln Arg Gly  Val His Gly
    1805                 1810                 1815

Arg Leu  Met Asp Asn Ser Thr  Ser Val Arg Glu Ala  Ala Val Glu
    1820                 1825                 1830

Leu Leu  Gly Arg Phe Val Leu  Cys Arg Pro Gln Leu  Ala Glu Gln
    1835                 1840                 1845

Tyr Tyr  Asp Met Leu Ile Glu  Arg Ile Leu Asp Thr  Gly Ile Ser
    1850                 1855                 1860

Val Arg  Lys Arg Val Ile Lys  Ile Leu Arg Asp Ile  Cys Ile Glu
    1865                 1870                 1875

Gln Pro  Thr Phe Pro Lys Ile  Thr Glu Met Cys Val  Lys Met Ile
    1880                 1885                 1890

Arg Arg  Val Asn Asp Glu Glu  Gly Ile Lys Lys Leu  Val Asn Glu
    1895                 1900                 1905

Thr Phe  Gln Lys Leu Trp Phe  Thr Pro Thr Pro His  Asn Asp Lys
    1910                 1915                 1920

Glu Ala  Met Thr Arg Lys Ile  Leu Asn Ile Thr Asp  Val Val Ala
    1925                 1930                 1935

Ala Cys  Arg Asp Thr Gly Tyr  Asp Trp Phe Glu Gln  Leu Leu Gln
    1940                 1945                 1950

Asn Leu  Leu Lys Ser Glu Glu  Asp Ser Ser Tyr Lys  Pro Val Lys
    1955                 1960                 1965

Lys Ala  Cys Thr Gln Leu Val  Asp Asn Leu Val Glu  His Ile Leu
    1970                 1975                 1980

Lys Tyr  Glu Glu Ser Leu Ala  Asp Ser Asp Asn Lys  Gly Val Asn
    1985                 1990                 1995

Ser Gly  Arg Leu Val Ala Cys  Ile Thr Thr Leu Phe  Leu Phe Ser
    2000                 2005                 2010

Lys Ile  Arg Pro Gln Leu Met  Val Lys His Ala Met  Thr Met Gln
    2015                 2020                 2025
```

Pro Tyr Leu Thr Thr Lys Cys Ser Thr Gln Asn Asp Phe Met Val
2030 2035 2040

Ile Cys Asn Val Ala Lys Ile Leu Glu Leu Val Val Pro Leu Met
2045 2050 2055

Glu His Pro Ser Glu Thr Phe Leu Ala Thr Ile Glu Glu Asp Leu
2060 2065 2070

Met Lys Leu Ile Ile Lys Tyr Gly Met Thr Val Val Gln His Cys
2075 2080 2085

Val Ser Cys Leu Gly Ala Val Val Asn Lys Val Thr Gln Asn Phe
2090 2095 2100

Lys Phe Val Trp Ala Cys Phe Asn Arg Tyr Tyr Gly Ala Ile Ser
2105 2110 2115

Lys Leu Lys Ser Gln His Gln Glu Asp Pro Asn Asn Thr Ser Leu
2120 2125 2130

Leu Thr Asn Lys Pro Ala Leu Leu Arg Ser Leu Phe Thr Val Gly
2135 2140 2145

Ala Leu Cys Arg His Phe Asp Phe Asp Leu Glu Asp Phe Lys Gly
2150 2155 2160

Asn Ser Lys Val Asn Ile Lys Asp Lys Val Leu Glu Leu Leu Met
2165 2170 2175

Tyr Phe Thr Lys His Ser Asp Glu Glu Val Gln Thr Lys Ala Ile
2180 2185 2190

Ile Gly Leu Gly Phe Ala Phe Ile Gln His Pro Ser Leu Met Phe
2195 2200 2205

Glu Gln Glu Val Lys Asn Leu Tyr Asn Asn Ile Leu Ser Asp Lys
2210 2215 2220

Asn Ser Ser Val Asn Leu Lys Ile Gln Val Leu Lys Asn Leu Gln
2225 2230 2235

Thr Tyr Leu Gln Glu Glu Asp Thr Arg Met Gln Gln Ala Asp Arg
2240 2245 2250

```
Asp Trp  Lys Lys Val Ala Lys  Gln Glu Asp Leu Lys  Glu Met Gly
    2255                 2260                 2265


Asp Val  Ser Ser Gly Met Ser  Ser Ser Ile Met Gln  Leu Tyr Leu
    2270                 2275                 2280


Lys Gln  Val Leu Glu Ala Phe  Phe His Thr Gln Ser  Ser Val Arg
    2285                 2290                 2295


His Phe  Ala Leu Asn Val Ile  Ala Leu Thr Leu Asn  Gln Gly Leu
    2300                 2305                 2310


Ile His  Pro Val Gln Cys Val  Pro Tyr Leu Ile Ala  Met Gly Thr
    2315                 2320                 2325


Asp Pro  Glu Pro Ala Met Arg  Asn Lys Ala Asp Gln  Gln Leu Val
    2330                 2335                 2340


Glu Ile  Asp Lys Lys Tyr Ala  Gly Phe Ile His Met  Lys Ala Val
    2345                 2350                 2355


Ala Gly  Met Lys Met Ser Tyr  Gln Val Gln Gln Ala  Ile Asn Thr
    2360                 2365                 2370


Cys Leu  Lys Asp Pro Val Arg  Gly Phe Arg Gln Asp  Glu Ser Ser
    2375                 2380                 2385


Ser Ala  Leu Cys Ser His Leu  Tyr Ser Met Ile Arg  Gly Asn Arg
    2390                 2395                 2400


Gln His  Arg Arg Ala Phe Leu  Ile Ser Leu Leu Asn  Leu Phe Asp
    2405                 2410                 2415


Asp Thr  Ala Lys Thr Asp Val  Thr Met Leu Leu Tyr  Ile Ala Asp
    2420                 2425                 2430


Asn Leu  Ala Cys Phe Pro Tyr  Gln Thr Gln Glu Glu  Pro Leu Phe
    2435                 2440                 2445


Ile Met  His His Ile Asp Ile  Thr Leu Ser Val Ser  Gly Ser Asn
    2450                 2455                 2460


Leu Leu  Gln Ser Phe Lys Glu  Ser Met Val Lys Asp  Lys Arg Lys
    2465                 2470                 2475
```

```
Glu Arg  Lys Ser Ser Pro Ser  Lys Glu Asn Glu Ser  Ser Asp Ser
    2480                 2485                 2490

Glu Glu  Glu Val Ser Arg Pro  Arg Lys Ser Arg Lys  Arg Val Asp
    2495                 2500                 2505

Ser Asp  Ser Asp Ser Asp Ser  Glu Asp Asp Ile Asn  Ser Val Met
    2510                 2515                 2520

Lys Cys  Leu Pro Glu Asn Ser  Ala Pro Leu Ile Glu  Phe Ala Asn
    2525                 2530                 2535

Val Ser  Gln Gly Ile Leu Leu  Leu Leu Met Leu Lys  Gln His Leu
    2540                 2545                 2550

Lys Asn  Leu Cys Gly Phe Ser  Asp Ser Lys Ile Gln  Lys Tyr Ser
    2555                 2560                 2565

Pro Ser  Glu Ser Ala Lys Val  Tyr Asp Lys Ala Ile  Asn Arg Lys
    2570                 2575                 2580

Thr Gly  Val His Phe His Pro  Lys Gln Thr Leu Asp  Phe Leu Arg
    2585                 2590                 2595

Ser Asp  Met Ala Asn Ser Lys  Ile Thr Glu Glu Val  Lys Arg Ser
    2600                 2605                 2610

Ile Val  Lys Gln Tyr Leu Asp  Phe Lys Leu Leu Met  Glu His Leu
    2615                 2620                 2625

Asp Pro  Asp Glu Glu Glu Glu  Glu Gly Glu Val Ser  Ala Ser Thr
    2630                 2635                 2640

Asn Ala  Arg Asn Lys Ala Ile  Thr Ser Leu Leu Gly  Gly Gly Ser
    2645                 2650                 2655

Pro Lys  Asn Asn Thr Ala Ala  Glu Thr Glu Asp Asp  Glu Ser Asp
    2660                 2665                 2670

Gly Glu  Asp Arg Gly Gly Gly  Thr Ser Gly Val Arg  Arg Arg Arg
    2675                 2680                 2685

Ser Gln  Arg Ile Ser Gln Arg  Ile Thr
    2690                 2695
```

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<210>  140
<211>  2804
<212>  PRT
<213>  Homo sapiens

<400>  140

Met Asn Gly Asp Met Pro His Val Pro Ile Thr Thr Leu Ala Gly Ile
1               5                   10                  15


Ala Ser Leu Thr Asp Leu Leu Asn Gln Leu Pro Leu Pro Ser Pro Leu
            20                  25                  30


Pro Ala Thr Thr Thr Lys Ser Leu Leu Phe Asn Ala Arg Ile Ala Glu
        35                  40                  45


Glu Val Asn Cys Leu Leu Ala Cys Arg Asp Asp Asn Leu Val Ser Gln
    50                  55                  60


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


Asp Asn Leu Gly Ser Asp Asp Pro Glu Gly Asp Ile Pro Val Leu Leu
                85                  90                  95


Gln Ala Val Leu Ala Arg Ser Pro Asn Val Phe Arg Glu Lys Ser Met
            100                 105                 110


Gln Asn Arg Tyr Val Gln Ser Gly Met Met Met Ser Gln Tyr Lys Leu
        115                 120                 125


Ser Gln Asn Ser Met His Ser Ser Pro Ala Ser Ser Asn Tyr Gln Gln
    130                 135                 140


Thr Thr Ile Ser His Ser Pro Ser Ser Arg Phe Val Pro Pro Gln Thr
145                 150                 155                 160


Ser Ser Gly Asn Arg Phe Met Pro Gln Gln Asn Ser Pro Val Pro Ser
                165                 170                 175


Pro Tyr Ala Pro Gln Ser Pro Ala Gly Tyr Met Pro Tyr Ser His Pro
            180                 185                 190


Ser Ser Tyr Thr Thr His Pro Gln Met Gln Gln Ala Ser Val Ser Ser
        195                 200                 205
```

```
Pro Ile Val Ala Gly Gly Leu Arg Asn Ile His Asp Asn Lys Val Ser
    210                 215                 220

Gly Pro Leu Ser Gly Asn Ser Ala Asn His His Ala Asp Asn Pro Arg
225                 230                 235                 240

His Gly Ser Ser Glu Asp Tyr Leu His Met Val His Arg Leu Ser Ser
                245                 250                 255

Asp Asp Gly Asp Ser Ser Thr Met Arg Asn Ala Ala Ser Phe Pro Leu
            260                 265                 270

Arg Ser Pro Gln Pro Val Cys Ser Pro Ala Gly Ser Glu Gly Thr Pro
        275                 280                 285

Lys Gly Ser Arg Pro Pro Leu Ile Leu Gln Ser Gln Ser Leu Pro Cys
    290                 295                 300

Ser Ser Pro Arg Asp Val Pro Pro Asp Ile Leu Leu Asp Ser Pro Glu
305                 310                 315                 320

Arg Lys Gln Lys Lys Gln Lys Lys Met Lys Leu Gly Lys Asp Glu Lys
                325                 330                 335

Glu Gln Ser Glu Lys Ala Ala Met Tyr Asp Ile Ile Ser Ser Pro Ser
            340                 345                 350

Lys Asp Ser Thr Lys Leu Thr Leu Arg Leu Ser Arg Val Arg Ser Ser
        355                 360                 365

Asp Met Asp Gln Gln Glu Asp Met Ile Ser Gly Val Glu Asn Ser Asn
    370                 375                 380

Val Ser Glu Asn Asp Ile Pro Phe Asn Val Gln Tyr Pro Gly Gln Thr
385                 390                 395                 400

Ser Lys Thr Pro Ile Thr Pro Gln Asp Ile Asn Arg Pro Leu Asn Ala
                405                 410                 415

Ala Gln Cys Leu Ser Gln Gln Glu Gln Thr Ala Phe Leu Pro Ala Asn
            420                 425                 430

Gln Val Pro Val Leu Gln Gln Asn Thr Ser Val Ala Ala Lys Gln Pro
        435                 440                 445
```

```
Gln Thr Ser Val Val Gln Asn Gln Gln Gln Ile Ser Gln Gln Gly Pro
    450                 455                 460

Ile Tyr Asp Glu Val Glu Leu Asp Ala Leu Ala Glu Ile Glu Arg Ile
465                 470                 475                 480

Glu Arg Glu Ser Ala Ile Glu Arg Glu Arg Phe Ser Lys Glu Val Gln
                485                 490                 495

Asp Lys Asp Lys Pro Leu Lys Lys Arg Lys Gln Asp Ser Tyr Pro Gln
            500                 505                 510

Glu Ala Gly Gly Ala Thr Gly Gly Asn Arg Pro Ala Ser Gln Glu Thr
        515                 520                 525

Gly Ser Thr Gly Asn Gly Ser Arg Pro Ala Leu Met Val Ser Ile Asp
    530                 535                 540

Leu His Gln Ala Gly Arg Val Asp Ser Gln Ala Ser Ile Thr Gln Asp
545                 550                 555                 560

Ser Asp Ser Ile Lys Lys Pro Glu Glu Ile Lys Gln Cys Asn Asp Ala
                565                 570                 575

Pro Val Ser Val Leu Gln Glu Asp Ile Val Gly Ser Leu Lys Ser Thr
            580                 585                 590

Pro Glu Asn His Pro Glu Thr Pro Lys Lys Lys Ser Asp Pro Glu Leu
        595                 600                 605

Ser Lys Ser Glu Met Lys Gln Ser Glu Ser Arg Leu Ala Glu Ser Lys
    610                 615                 620

Pro Asn Glu Asn Arg Leu Val Glu Thr Lys Ser Ser Glu Asn Lys Leu
625                 630                 635                 640

Glu Thr Lys Val Glu Thr Gln Thr Glu Glu Leu Lys Gln Asn Glu Ser
                645                 650                 655

Arg Thr Thr Glu Cys Lys Gln Asn Glu Ser Thr Ile Val Glu Pro Lys
            660                 665                 670

Gln Asn Glu Asn Arg Leu Ser Asp Thr Lys Pro Asn Asp Asn Lys Gln
        675                 680                 685
```

```
Asn Asn Gly Arg Ser Glu Thr Thr Lys Ser Arg Pro Glu Thr Pro Lys
    690                 695                 700

Gln Lys Gly Glu Ser Arg Pro Glu Thr Pro Lys Gln Lys Ser Asp Gly
705                 710                 715                 720

His Pro Glu Thr Pro Lys Gln Lys Gly Asp Gly Arg Pro Glu Thr Pro
                725                 730                 735

Lys Gln Lys Gly Glu Ser Arg Pro Glu Thr Pro Lys Gln Lys Asn Glu
            740                 745                 750

Gly Arg Pro Glu Thr Pro Lys His Arg His Asp Asn Arg Arg Asp Ser
        755                 760                 765

Gly Lys Pro Ser Thr Glu Lys Lys Pro Glu Val Ser Lys His Lys Gln
    770                 775                 780

Asp Thr Lys Ser Asp Ser Pro Arg Leu Lys Ser Glu Arg Ala Glu Ala
785                 790                 795                 800

Leu Lys Gln Arg Pro Asp Gly Arg Ser Val Ser Glu Ser Leu Arg Arg
                805                 810                 815

Asp His Asp Asn Lys Gln Lys Ser Asp Asp Arg Gly Glu Ser Glu Arg
            820                 825                 830

His Arg Gly Asp Gln Ser Arg Val Arg Arg Pro Glu Thr Leu Arg Ser
        835                 840                 845

Ser Ser Arg Asn Glu His Gly Ile Lys Ser Asp Ser Ser Lys Thr Asp
    850                 855                 860

Lys Leu Glu Arg Lys His Arg His Glu Ser Gly Asp Ser Arg Glu Arg
865                 870                 875                 880

Pro Ser Ser Gly Glu Gln Lys Ser Arg Pro Asp Ser Pro Arg Val Lys
                885                 890                 895

Gln Gly Asp Ser Asn Lys Ser Arg Ser Asp Lys Leu Gly Phe Lys Ser
            900                 905                 910

Pro Thr Ser Lys Asp Asp Lys Arg Thr Glu Gly Asn Lys Ser Lys Val
        915                 920                 925
```

```
Asp Thr Asn Lys Ala His Pro Asp Asn Lys Ala Glu Phe Pro Ser Tyr
    930                 935                 940

Leu Leu Gly Gly Arg Ser Gly Ala Leu Lys Asn Phe Val Ile Pro Lys
945                 950                 955                 960

Ile Lys Arg Asp Lys Asp Gly Asn Val Thr Gln Glu Thr Lys Lys Met
                965                 970                 975

Glu Met Lys Gly Glu Pro Lys Asp Lys Val Glu Lys Ile Gly Leu Val
            980                 985                 990

Glu Asp Leu Asn Lys Gly Ala Lys  Pro Val Val Val Leu  Gln Lys Leu
        995                 1000                 1005

Ser Leu  Asp Asp Val Gln Lys  Leu Ile Lys Asp Arg  Glu Asp Lys
    1010                 1015                 1020

Ser Arg  Ser Ser Leu Lys Pro  Ile Lys Asn Lys Pro  Ser Lys Ser
    1025                 1030                 1035

Asn Lys  Gly Ser Ile Asp Gln  Ser Val Leu Lys Glu  Leu Pro Pro
    1040                 1045                 1050

Glu Leu  Leu Ala Glu Ile Glu  Ser Thr Met Pro Leu  Cys Glu Arg
    1055                 1060                 1065

Val Lys  Met Asn Lys Arg Lys  Arg Ser Thr Val Asn  Glu Lys Pro
    1070                 1075                 1080

Lys Tyr  Ala Glu Ile Ser Ser  Asp Glu Asp Asn Asp  Ser Asp Glu
    1085                 1090                 1095

Ala Phe  Glu Ser Ser Arg Lys  Arg His Lys Lys Asp  Asp Asp Lys
    1100                 1105                 1110

Ala Trp  Glu Tyr Glu Glu Arg  Asp Arg Arg Ser Ser  Gly Asp His
    1115                 1120                 1125

Arg Arg  Ser Gly His Ser His  Glu Gly Arg Arg Ser  Ser Gly Gly
    1130                 1135                 1140

Gly Arg  Tyr Arg Asn Arg Ser  Pro Ser Asp Ser Asp  Met Glu Asp
    1145                 1150                 1155
```

```
Tyr Ser  Pro Pro Pro Ser Leu  Ser Glu Val Ala Arg  Lys Met Lys
    1160                 1165                 1170

Lys Lys  Glu Lys Gln Lys Lys  Arg Lys Ala Tyr Glu  Pro Lys Leu
    1175                 1180                 1185

Thr Pro  Glu Glu Met Met Asp  Ser Ser Thr Phe Lys  Arg Phe Thr
    1190                 1195                 1200

Ala Ser  Ile Glu Asn Ile Leu  Asp Asn Leu Glu Asp  Met Asp Phe
    1205                 1210                 1215

Thr Ala  Phe Gly Asp Asp Asp  Glu Ile Pro Gln Glu  Leu Leu Leu
    1220                 1225                 1230

Gly Lys  His Gln Leu Asn Glu  Leu Gly Ser Glu Ser  Ala Lys Ile
    1235                 1240                 1245

Lys Ala  Met Gly Ile Met Asp  Lys Leu Ser Thr Asp  Lys Thr Val
    1250                 1255                 1260

Lys Val  Leu Asn Ile Leu Glu  Lys Asn Ile Gln Asp  Gly Ser Lys
    1265                 1270                 1275

Leu Ser  Thr Leu Leu Asn His  Asn Asn Asp Thr Glu  Glu Glu Glu
    1280                 1285                 1290

Arg Leu  Trp Arg Asp Leu Ile  Met Glu Arg Val Thr  Lys Ser Ala
    1295                 1300                 1305

Asp Ala  Cys Leu Thr Thr Ile  Asn Ile Met Thr Ser  Pro Asn Met
    1310                 1315                 1320

Pro Lys  Ala Val Tyr Ile Glu  Asp Val Ile Glu Arg  Val Ile Gln
    1325                 1330                 1335

Tyr Thr  Lys Phe His Leu Gln  Asn Thr Leu Tyr Pro  Gln Tyr Asp
    1340                 1345                 1350

Pro Val  Tyr Arg Leu Asp Pro  His Gly Gly Gly Leu  Leu Ser Ser
    1355                 1360                 1365

Lys Ala  Lys Arg Ala Lys Cys  Ser Thr His Lys Gln  Arg Val Ile
    1370                 1375                 1380
```

```
Val Met  Leu Tyr Asn Lys Val  Cys Asp Ile Val Ser  Ser Leu Ser
    1385                 1390                 1395

Glu Leu  Leu Glu Ile Gln Leu  Leu Thr Asp Thr Thr  Ile Leu Gln
    1400                 1405                 1410

Val Ser  Ser Met Gly Ile Thr  Pro Phe Phe Val Glu  Asn Val Ser
    1415                 1420                 1425

Glu Leu  Gln Leu Cys Ala Ile  Lys Leu Val Thr Ala  Val Phe Ser
    1430                 1435                 1440

Arg Tyr  Glu Lys His Arg Gln  Leu Ile Leu Glu Glu  Ile Phe Thr
    1445                 1450                 1455

Ser Leu  Ala Arg Leu Pro Thr  Ser Lys Arg Ser Leu  Arg Asn Phe
    1460                 1465                 1470

Arg Leu  Asn Ser Ser Asp Met  Asp Gly Glu Pro Met  Tyr Ile Gln
    1475                 1480                 1485

Met Val  Thr Ala Leu Val Leu  Gln Leu Ile Gln Cys  Val Val His
    1490                 1495                 1500

Leu Pro  Ser Ser Glu Lys Asp  Ser Asn Ala Glu Glu  Asp Ser Asn
    1505                 1510                 1515

Lys Lys  Ile Asp Gln Asp Val  Val Ile Thr Asn Ser  Tyr Glu Thr
    1520                 1525                 1530

Ala Met  Arg Thr Ala Gln Asn  Phe Leu Ser Ile Phe  Leu Lys Lys
    1535                 1540                 1545

Cys Gly  Ser Lys Gln Gly Glu  Glu Asp Tyr Arg Pro  Leu Phe Glu
    1550                 1555                 1560

Asn Phe  Val Gln Asp Leu Leu  Ser Thr Val Asn Lys  Pro Glu Trp
    1565                 1570                 1575

Pro Ala  Ala Glu Leu Leu Leu  Ser Leu Leu Gly Arg  Leu Leu Val
    1580                 1585                 1590

His Gln  Phe Ser Asn Lys Ser  Thr Glu Met Ala Leu  Arg Val Ala
    1595                 1600                 1605
```

```
Ser Leu  Asp Tyr Leu Gly Thr  Val Ala Ala Arg Leu  Arg Lys Asp
    1610                 1615                 1620

Ala Val  Thr Ser Lys Met Asp  Gln Gly Ser Ile Glu  Arg Ile Leu
    1625                 1630                 1635

Lys Gln  Val Ser Gly Gly Glu  Asp Glu Ile Gln Gln  Leu Gln Lys
    1640                 1645                 1650

Ala Leu  Leu Asp Tyr Leu Asp  Glu Asn Thr Glu Thr  Asp Pro Ser
    1655                 1660                 1665

Leu Val  Phe Ser Arg Lys Phe  Tyr Ile Ala Gln Trp  Phe Arg Asp
    1670                 1675                 1680

Thr Thr  Leu Glu Thr Glu Lys  Ala Met Lys Ser Gln  Lys Asp Glu
    1685                 1690                 1695

Glu Ser  Ser Glu Gly Thr His  His Ala Lys Glu Ile  Glu Thr Thr
    1700                 1705                 1710

Gly Gln  Ile Met His Arg Ala  Glu Asn Arg Lys Lys  Phe Leu Arg
    1715                 1720                 1725

Ser Ile  Ile Lys Thr Thr Pro  Ser Gln Phe Ser Thr  Leu Lys Met
    1730                 1735                 1740

Asn Ser  Asp Thr Val Asp Tyr  Asp Asp Ala Cys Leu  Ile Val Arg
    1745                 1750                 1755

Tyr Leu  Ala Ser Met Arg Pro  Phe Ala Gln Ser Phe  Asp Ile Tyr
    1760                 1765                 1770

Leu Thr  Gln Ile Leu Arg Val  Leu Gly Glu Asn Ala  Ile Ala Val
    1775                 1780                 1785

Arg Thr  Lys Ala Met Lys Cys  Leu Ser Glu Val Val  Ala Val Asp
    1790                 1795                 1800

Pro Ser  Ile Leu Ala Arg Leu  Asp Met Gln Arg Gly  Val His Gly
    1805                 1810                 1815

Arg Leu  Met Asp Asn Ser Thr  Ser Val Arg Glu Ala  Ala Val Glu
    1820                 1825                 1830
```

```
Leu Leu  Gly Arg Phe Val Leu  Cys Arg Pro Gln Leu  Ala Glu Gln
    1835                 1840                 1845


Tyr Tyr  Asp Met Leu Ile Glu  Arg Ile Leu Asp Thr  Gly Ile Ser
    1850                 1855                 1860


Val Arg  Lys Arg Val Ile Lys  Ile Leu Arg Asp Ile  Cys Ile Glu
    1865                 1870                 1875


Gln Pro  Thr Phe Pro Lys Ile  Thr Glu Met Cys Val  Lys Met Ile
    1880                 1885                 1890


Arg Arg  Val Asn Asp Glu Glu  Gly Ile Lys Lys Leu  Val Asn Glu
    1895                 1900                 1905


Thr Phe  Gln Lys Leu Trp Phe  Thr Pro Thr Pro His  Asn Asp Lys
    1910                 1915                 1920


Glu Ala  Met Thr Arg Lys Ile  Leu Asn Ile Thr Asp  Val Val Ala
    1925                 1930                 1935


Ala Cys  Arg Asp Thr Gly Tyr  Asp Trp Phe Glu Gln  Leu Leu Gln
    1940                 1945                 1950


Asn Leu  Leu Lys Ser Glu Glu  Asp Ser Ser Tyr Lys  Pro Val Lys
    1955                 1960                 1965


Lys Ala  Cys Thr Gln Leu Val  Asp Asn Leu Val Glu  His Ile Leu
    1970                 1975                 1980


Lys Tyr  Glu Glu Ser Leu Ala  Asp Ser Asp Asn Lys  Gly Val Asn
    1985                 1990                 1995


Ser Gly  Arg Leu Val Ala Cys  Ile Thr Thr Leu Phe  Leu Phe Ser
    2000                 2005                 2010


Lys Ile  Arg Pro Gln Leu Met  Val Lys His Ala Met  Thr Met Gln
    2015                 2020                 2025


Pro Tyr  Leu Thr Thr Lys Cys  Ser Thr Gln Asn Asp  Phe Met Val
    2030                 2035                 2040


Ile Cys  Asn Val Ala Lys Ile  Leu Glu Leu Val Val  Pro Leu Met
    2045                 2050                 2055
```

```
Glu His  Pro Ser Glu Thr Phe  Leu Ala Thr Ile Glu  Glu Asp Leu
    2060                 2065                 2070

Met Lys  Leu Ile Ile Lys Tyr  Gly Met Thr Val Val  Gln His Cys
    2075                 2080                 2085

Val Ser  Cys Leu Gly Ala Val  Val Asn Lys Val Thr  Gln Asn Phe
    2090                 2095                 2100

Lys Phe  Val Trp Ala Cys Phe  Asn Arg Tyr Tyr Gly  Ala Ile Ser
    2105                 2110                 2115

Lys Leu  Lys Ser Gln His Gln  Glu Asp Pro Asn Asn  Thr Ser Leu
    2120                 2125                 2130

Leu Thr  Asn Lys Pro Ala Leu  Leu Arg Ser Leu Phe  Thr Val Gly
    2135                 2140                 2145

Ala Leu  Cys Arg His Phe Asp  Phe Asp Leu Glu Asp  Phe Lys Gly
    2150                 2155                 2160

Asn Ser  Lys Val Asn Ile Lys  Asp Lys Val Leu Glu  Leu Leu Met
    2165                 2170                 2175

Tyr Phe  Thr Lys His Ser Asp  Glu Glu Val Gln Thr  Lys Ala Ile
    2180                 2185                 2190

Ile Gly  Leu Gly Phe Ala Phe  Ile Gln His Pro Ser  Leu Met Phe
    2195                 2200                 2205

Glu Gln  Glu Val Lys Asn Leu  Tyr Asn Asn Ile Leu  Ser Asp Lys
    2210                 2215                 2220

Asn Ser  Ser Val Asn Leu Lys  Ile Gln Val Leu Lys  Asn Leu Gln
    2225                 2230                 2235

Thr Tyr  Leu Gln Glu Glu Asp  Thr Arg Met Gln Gln  Ala Asp Arg
    2240                 2245                 2250

Asp Trp  Lys Lys Val Ala Lys  Gln Glu Asp Leu Lys  Glu Met Gly
    2255                 2260                 2265

Asp Val  Ser Ser Gly Met Ser  Ser Ser Ile Met Gln  Leu Tyr Leu
    2270                 2275                 2280
```

```
Lys Gln  Val Leu Glu Ala Phe  Phe His Thr Gln Ser  Ser Val Arg
    2285                 2290                 2295


His Phe  Ala Leu Asn Val Ile  Ala Leu Thr Leu Asn  Gln Gly Leu
    2300                 2305                 2310


Ile His  Pro Val Gln Cys Val  Pro Tyr Leu Ile Ala  Met Gly Thr
    2315                 2320                 2325


Asp Pro  Glu Pro Ala Met Arg  Asn Lys Ala Asp Gln  Gln Leu Val
    2330                 2335                 2340


Glu Ile  Asp Lys Lys Tyr Ala  Gly Phe Ile His Met  Lys Ala Val
    2345                 2350                 2355


Ala Gly  Met Lys Met Ser Tyr  Gln Val Gln Gln Ala  Ile Asn Thr
    2360                 2365                 2370


Cys Leu  Lys Asp Pro Val Arg  Gly Phe Arg Gln Asp  Glu Ser Ser
    2375                 2380                 2385


Ser Ala  Leu Cys Ser His Leu  Tyr Ser Met Ile Arg  Gly Asn Arg
    2390                 2395                 2400


Gln His  Arg Arg Ala Phe Leu  Ile Ser Leu Leu Asn  Leu Phe Asp
    2405                 2410                 2415


Asp Thr  Ala Lys Thr Asp Val  Thr Met Leu Leu Tyr  Ile Ala Asp
    2420                 2425                 2430


Asn Leu  Ala Cys Phe Pro Tyr  Gln Thr Gln Glu Glu  Pro Leu Phe
    2435                 2440                 2445


Ile Met  His His Ile Asp Ile  Thr Leu Ser Val Ser  Gly Ser Asn
    2450                 2455                 2460


Leu Leu  Gln Ser Phe Lys Glu  Ser Met Val Lys Asp  Lys Arg Lys
    2465                 2470                 2475


Glu Arg  Lys Ser Ser Pro Ser  Lys Glu Asn Glu Ser  Ser Asp Ser
    2480                 2485                 2490


Glu Glu  Glu Val Ser Arg Pro  Arg Lys Ser Arg Lys  Arg Val Asp
    2495                 2500                 2505
```

```
Ser Asp  Ser Asp Ser Asp Ser  Glu Asp Asp Ile Asn  Ser Val Met
    2510                 2515                 2520

Lys Cys  Leu Pro Glu Asn Ser  Ala Pro Leu Ile Glu  Phe Ala Asn
    2525                 2530                 2535

Val Ser  Gln Gly Ile Leu Leu  Leu Leu Met Leu Lys  Gln His Leu
    2540                 2545                 2550

Lys Asn  Leu Cys Gly Phe Ser  Asp Ser Lys Ile Gln  Lys Tyr Ser
    2555                 2560                 2565

Pro Ser  Glu Ser Ala Lys Val  Tyr Asp Lys Ala Ile  Asn Arg Lys
    2570                 2575                 2580

Thr Gly  Val His Phe His Pro  Lys Gln Thr Leu Asp  Phe Leu Arg
    2585                 2590                 2595

Ser Asp  Met Ala Asn Ser Lys  Ile Thr Glu Glu Val  Lys Arg Ser
    2600                 2605                 2610

Ile Val  Lys Gln Tyr Leu Asp  Phe Lys Leu Leu Met  Glu His Leu
    2615                 2620                 2625

Asp Pro  Asp Glu Glu Glu Glu  Glu Gly Glu Val Ser  Ala Ser Thr
    2630                 2635                 2640

Asn Ala  Arg Asn Lys Ala Ile  Thr Ser Leu Leu Gly  Gly Gly Ser
    2645                 2650                 2655

Pro Lys  Asn Asn Thr Ala Ala  Glu Thr Glu Asp Asp  Glu Ser Asp
    2660                 2665                 2670

Gly Glu  Asp Arg Gly Gly Gly  Thr Ser Gly Ser Leu  Arg Arg Ser
    2675                 2680                 2685

Lys Arg  Asn Ser Asp Ser Thr  Glu Leu Ala Ala Gln  Met Asn Glu
    2690                 2695                 2700

Ser Val  Asp Val Met Asp Val  Ile Ala Ile Cys Cys  Pro Lys Tyr
    2705                 2710                 2715

Lys Asp  Arg Pro Gln Ile Ala  Arg Val Val Gln Lys  Thr Ser Ser
    2720                 2725                 2730
```

```
Gly Phe  Ser Val Gln Trp Met  Ala Gly Ser Tyr Ser  Gly Ser Trp
    2735                2740                2745


Thr Glu  Ala Lys Arg Arg Asp  Gly Arg Lys Leu Val  Pro Trp Val
    2750                2755                2760


Asp Thr  Ile Lys Glu Ser Asp  Ile Ile Tyr Lys Lys  Ile Ala Leu
    2765                2770                2775


Thr Ser  Ala Asn Lys Leu Thr  Asn Lys Val Val Gln  Thr Leu Arg
    2780                2785                2790


Ser Leu  Tyr Ala Ala Lys Asp  Gly Thr Ser Ser
    2795                2800


<210>  141
<211>  379
<212>  PRT
<213>  Homo sapiens

<400>  141

Met Glu Met Ala Glu Ala Glu Leu His Lys Glu Arg Leu Gln Ala Ile
1               5                   10                  15


Ala Glu Lys Arg Lys Arg Gln Thr Glu Ile Glu Gly Lys Arg Gln Gln
            20                  25                  30


Leu Asp Glu Gln Ile Leu Leu Leu Gln His Ser Lys Ser Lys Val Leu
        35                  40                  45


Arg Glu Lys Trp Leu Leu Gln Gly Ile Pro Ala Gly Thr Ala Glu Glu
    50                  55                  60


Glu Glu Ala Arg Arg Arg Gln Ser Glu Glu Asp Glu Phe Arg Val Lys
65                  70                  75                  80


Gln Leu Glu Asp Asn Ile Gln Arg Leu Glu Gln Glu Ile Gln Thr Leu
                85                  90                  95


Glu Ser Glu Glu Ser Gln Ile Ser Ala Lys Glu Gln Ile Ile Leu Glu
            100                 105                 110


Lys Leu Lys Glu Thr Glu Lys Ser Phe Lys Asp Phe Gln Lys Gly Phe
        115                 120                 125
```

```
Ser Ser Thr Asp Gly Ala Val Tyr Ala Met Glu Ile Asn Val Glu Lys
    130                 135                 140


Asp Lys Gln Thr Gly Glu Thr Lys Ile Leu Ser Thr Ser Thr Ile Gly
145                 150                 155                 160


Pro Glu Gly Val His Gln Lys Gly Val Lys Val Tyr Asp Asp Gly Thr
                165                 170                 175


Lys Val Val Tyr Glu Val Arg Ser Gly Gly Thr Val Val Glu Asn Gly
            180                 185                 190


Val His Lys Leu Ser Thr Lys Asp Val Glu Glu Leu Ile Gln Lys Ala
        195                 200                 205


Gly Gln Ser Ser Leu Gly Gly Gly His Val Ser Glu Arg Thr Val Ile
    210                 215                 220


Ala Asp Gly Ser Leu Ser His Pro Lys Glu His Met Leu Cys Lys Glu
225                 230                 235                 240


Ala Lys Leu Glu Met Val His Lys Ser Arg Lys Asp His Ser Ser Gly
                245                 250                 255


Asn Pro Gly Gln Gln Ala Gln Ala Pro Ser Ala Ala Gly Pro Glu Ala
            260                 265                 270


Asn Leu Asp Gln Pro Val Thr Met Ile Phe Met Gly Tyr Gln Asn Ile
        275                 280                 285


Glu Asp Glu Glu Glu Thr Lys Lys Val Leu Gly Tyr Asp Glu Thr Ile
    290                 295                 300


Lys Ala Glu Leu Val Leu Ile Asp Glu Asp Asp Glu Lys Ser Leu Arg
305                 310                 315                 320


Glu Lys Thr Val Thr Asp Val Ser Thr Ile Asp Gly Asn Ala Ala Glu
                325                 330                 335


Leu Val Ser Gly Arg Pro Val Ser Asp Thr Thr Glu Pro Ser Ser Pro
            340                 345                 350


Glu Gly Lys Glu Glu Ser Leu Ala Thr Glu Pro Ala Pro Gly Thr Gln
        355                 360                 365
```

```
Lys Lys Lys Arg Cys Gln Cys Cys Val Val Met
    370                 375


<210>  142
<211>  411
<212>  PRT
<213>  Homo sapiens

<400>  142

Met Ala Glu Ala Glu Leu His Lys Glu Arg Leu Gln Ala Ile Ala Glu
1               5                   10                  15


Lys Arg Lys Arg Gln Thr Glu Ile Glu Gly Lys Arg Gln Gln Leu Asp
            20                  25                  30


Glu Gln Ile Leu Leu Leu Gln His Ser Lys Ser Lys Val Leu Arg Glu
        35                  40                  45


Lys Trp Leu Leu Gln Gly Ile Pro Ala Gly Thr Ala Glu Glu Glu Glu
    50                  55                  60


Ala Arg Arg Arg Gln Ser Glu Glu Asp Glu Phe Arg Val Lys Gln Leu
65                  70                  75                  80


Glu Asp Asn Ile Gln Arg Leu Glu Gln Glu Ile Gln Thr Leu Glu Ser
                85                  90                  95


Glu Glu Ser Gln Ile Ser Ala Lys Glu Gln Ile Ile Leu Glu Lys Leu
            100                 105                 110


Lys Glu Thr Glu Lys Ser Phe Lys Asp Phe Gln Lys Gly Phe Ser Ser
        115                 120                 125


Thr Asp Gly Asp Ala Val Asn Tyr Ile Ser Ser Gln Leu Pro Asp Leu
    130                 135                 140


Pro Ile Leu Cys Ser Arg Thr Ala Glu Pro Ser Pro Gly Gln Asp Gly
145                 150                 155                 160


Thr Ser Arg Ala Ala Ala Val Tyr Ala Met Glu Ile Asn Val Glu Lys
                165                 170                 175


Asp Lys Gln Thr Gly Glu Thr Lys Ile Leu Ser Thr Ser Thr Ile Gly
            180                 185                 190
```

```
Pro Glu Gly Val His Gln Lys Gly Val Lys Val Tyr Asp Asp Gly Thr
        195                 200                 205

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

Val His Lys Leu Ser Thr Lys Asp Val Glu Glu Leu Ile Gln Lys Ala
225                 230                 235                 240

Gly Gln Ser Ser Leu Gly Gly Gly His Val Ser Glu Arg Thr Val Ile
                245                 250                 255

Ala Asp Gly Ser Leu Ser His Pro Lys Glu His Met Leu Cys Lys Glu
            260                 265                 270

Ala Lys Leu Glu Met Val His Lys Ser Arg Lys Asp His Ser Ser Gly
        275                 280                 285

Asn Pro Gly Gln Gln Ala Gln Ala Pro Ser Ala Ala Gly Pro Glu Ala
    290                 295                 300

Asn Leu Asp Gln Pro Val Thr Met Ile Phe Met Gly Tyr Gln Asn Ile
305                 310                 315                 320

Glu Asp Glu Glu Glu Thr Lys Lys Val Leu Gly Tyr Asp Glu Thr Ile
                325                 330                 335

Lys Ala Glu Leu Val Leu Ile Asp Glu Asp Asp Glu Lys Ser Leu Arg
            340                 345                 350

Glu Lys Thr Val Thr Asp Val Ser Thr Ile Asp Gly Asn Ala Ala Glu
        355                 360                 365

Leu Val Ser Gly Arg Pro Val Ser Asp Thr Thr Glu Pro Ser Ser Pro
    370                 375                 380

Glu Gly Lys Glu Glu Ser Leu Ala Thr Glu Pro Ala Pro Gly Thr Gln
385                 390                 395                 400

Lys Lys Lys Arg Cys Gln Cys Cys Val Val Met
                405                 410

<210>  143
<211>  191
```

```
<212>  PRT
<213>  Homo sapiens

<400>  143

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


Val Lys Ser Thr Glu Phe Asn Glu His Glu Leu Lys Gln Trp Tyr Lys
            20                  25                  30


Gly Phe Leu Lys Asp Cys Pro Ser Gly Arg Leu Asn Leu Glu Glu Phe
        35                  40                  45


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


Ala Gln His Ala Phe Arg Thr Phe Asp Lys Asn Gly Asp Gly Thr Ile
65                  70                  75                  80


Asp Phe Arg Glu Phe Ile Cys Ala Leu Ser Ile Thr Ser Arg Gly Ser
                85                  90                  95


Phe Glu Gln Lys Leu Asn Trp Ala Phe Asn Met Tyr Asp Leu Asp Gly
            100                 105                 110


Asp Gly Lys Ile Thr Arg Val Glu Met Leu Glu Ile Ile Glu Ala Ile
        115                 120                 125


Tyr Lys Met Val Gly Thr Val Ile Met Met Lys Met Asn Glu Asp Gly
    130                 135                 140


Leu Thr Pro Glu Gln Arg Val Asp Lys Ile Phe Ser Lys Met Asp Lys
145                 150                 155                 160


Asn Lys Asp Asp Gln Ile Thr Leu Asp Glu Phe Lys Glu Ala Ala Lys
                165                 170                 175


Ser Asp Pro Ser Ile Val Leu Leu Leu Gln Cys Asp Ile Gln Lys
            180                 185                 190


<210>  144
<211>  1192
<212>  PRT
<213>  Homo sapiens
```

```
<400>  144

Met Pro Arg Arg Ala Gly Ser Gly Gln Leu Pro Leu Pro Arg Gly Trp
1               5                   10                  15


Glu Glu Ala Arg Asp Tyr Asp Gly Lys Val Phe Tyr Ile Asp His Asn
            20                  25                  30


Thr Arg Arg Thr Ser Trp Ile Asp Pro Arg Asp Arg Leu Thr Lys Pro
        35                  40                  45


Leu Ser Phe Ala Asp Cys Val Gly Asp Glu Leu Pro Trp Gly Trp Glu
    50                  55                  60


Ala Gly Phe Asp Pro Gln Ile Gly Val Tyr Tyr Ile Asp His Ile Asn
65                  70                  75                  80


Lys Thr Thr Gln Ile Glu Asp Pro Arg Lys Gln Trp Arg Gly Glu Gln
                85                  90                  95


Glu Lys Met Leu Lys Asp Tyr Leu Ser Val Ala Gln Asp Ala Leu Arg
            100                 105                 110


Thr Gln Lys Glu Leu Tyr His Val Lys Glu Gln Arg Leu Ala Leu Ala
        115                 120                 125


Leu Asp Glu Tyr Val Arg Leu Asn Asp Ala Tyr Lys Glu Lys Ser Ser
    130                 135                 140


Ser His Thr Ser Leu Phe Ser Gly Ser Ser Ser Ser Thr Lys Tyr Asp
145                 150                 155                 160


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


Lys Leu Lys Arg Glu Leu Ser Gln Met Lys Gln Glu Leu Leu Tyr Lys
            180                 185                 190


Glu Gln Gly Phe Glu Thr Leu Gln Gln Ile Asp Lys Lys Met Ser Gly
        195                 200                 205


Gly Gln Ser Gly Tyr Glu Leu Ser Glu Ala Lys Ala Ile Leu Thr Glu
    210                 215                 220
```

```
Leu Lys Ser Ile Arg Lys Ala Ile Ser Ser Gly Glu Lys Glu Lys Gln
225                 230                 235                 240

Asp Leu Met Gln Ser Leu Ala Lys Leu Gln Glu Arg Phe His Leu Asp
                245                 250                 255

Gln Asn Ile Gly Arg Ser Glu Pro Asp Leu Arg Cys Ser Pro Val Asn
            260                 265                 270

Ser His Leu Cys Leu Ser Arg Gln Thr Leu Asp Ala Gly Ser Gln Thr
        275                 280                 285

Ser Ile Ser Gly Asp Ile Gly Val Arg Ser Arg Ser Asn Leu Ala Glu
    290                 295                 300

Lys Val Arg Leu Ser Leu Gln Tyr Glu Glu Ala Lys Arg Ser Met Ala
305                 310                 315                 320

Asn Leu Lys Ile Glu Leu Ser Lys Leu Asp Ser Glu Ala Trp Pro Gly
                325                 330                 335

Ala Leu Asp Ile Glu Lys Glu Lys Leu Met Leu Ile Asn Glu Lys Glu
            340                 345                 350

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

Asp Glu Leu Glu Arg Leu Glu Ala Glu Arg Gln Arg Leu Glu Glu Glu
    370                 375                 380

Leu Leu Ser Val Arg Gly Thr Pro Ser Arg Ala Leu Ala Glu Arg Leu
385                 390                 395                 400

Arg Leu Glu Glu Arg Arg Lys Glu Leu Leu Gln Lys Leu Glu Glu Thr
                405                 410                 415

Thr Lys Leu Thr Thr Tyr Leu His Ser Gln Leu Lys Ser Leu Ser Ala
            420                 425                 430

Ser Thr Leu Ser Met Ser Ser Gly Ser Ser Leu Gly Ser Leu Ala Ser
        435                 440                 445

Ser Arg Gly Ser Leu Asn Thr Ser Ser Arg Gly Ser Leu Asn Ser Leu
    450                 455                 460
```

```
Ser Ser Thr Glu Leu Tyr Tyr Ser Ser Gln Ser Asp Gln Ile Asp Val
465                 470                 475                 480


Asp Tyr Gln Tyr Lys Leu Asp Phe Leu Leu Gln Glu Lys Ser Gly Tyr
                485                 490                 495


Ile Pro Ser Gly Pro Ile Thr Thr Ile His Glu Asn Glu Val Val Lys
            500                 505                 510


Ser Pro Ser Gln Pro Gly Gln Ser Gly Leu Cys Gly Val Ala Ala Ala
        515                 520                 525


Ala Thr Gly His Thr Pro Pro Leu Ala Glu Ala Pro Lys Ser Val Ala
    530                 535                 540


Ser Leu Ser Ser Arg Ser Ser Leu Ser Ser Leu Ser Pro Pro Gly Ser
545                 550                 555                 560


Pro Leu Val Leu Glu Gly Thr Phe Pro Met Ser Ser Ser His Asp Ala
                565                 570                 575


Ser Leu His Gln Phe Thr Ala Asp Phe Glu Asp Cys Glu Leu Ser Ser
            580                 585                 590


His Phe Ala Asp Ile Ser Leu Ile Glu Asn Gln Ile Leu Leu Asp Ser
        595                 600                 605


Asp Ser Gly Gly Ala Ser Gln Ser Leu Ser Glu Asp Lys Asp Leu Asn
    610                 615                 620


Glu Cys Ala Arg Glu Pro Leu Tyr Glu Gly Thr Ala Asp Val Glu Lys
625                 630                 635                 640


Ser Leu Pro Lys Arg Arg Val Ile His Leu Leu Gly Glu Lys Thr Thr
                645                 650                 655


Cys Val Ser Ala Ala Val Ser Asp Glu Ser Val Ala Gly Asp Ser Gly
            660                 665                 670


Val Tyr Glu Ala Phe Val Lys Gln Pro Ser Glu Met Glu Asp Val Thr
        675                 680                 685


Tyr Ser Glu Glu Asp Val Ala Ile Val Glu Thr Ala Gln Val Gln Ile
    690                 695                 700
```

```
Gly Leu Arg Tyr Asn Ala Lys Ser Ser Ser Phe Met Val Ile Ile Ala
705                 710                 715                 720

Gln Leu Arg Asn Leu His Ala Phe Leu Ile Pro His Thr Ser Lys Val
                725                 730                 735

Tyr Phe Arg Val Ala Val Leu Pro Ser Ser Thr Asp Val Ser Cys Leu
            740                 745                 750

Phe Arg Thr Lys Val His Pro Pro Thr Glu Ser Ile Leu Phe Asn Asp
        755                 760                 765

Val Phe Arg Val Ala Ile Ser Gln Thr Ala Leu Gln Gln Lys Thr Leu
    770                 775                 780

Arg Val Asp Leu Cys Ser Val Ser Lys His Arg Arg Glu Glu Cys Leu
785                 790                 795                 800

Ala Gly Thr Gln Ile Ser Leu Ala Asp Leu Pro Phe Ser Ser Glu Val
                805                 810                 815

Phe Thr Leu Trp Tyr Asn Leu Leu Pro Ser Lys Gln Met Pro Cys Lys
            820                 825                 830

Lys Asn Glu Glu Asn Glu Asp Ser Val Phe Gln Pro Asn Gln Pro Leu
        835                 840                 845

Val Asp Ser Ile Asp Leu Asp Ala Val Ser Ala Leu Leu Ala Arg Thr
    850                 855                 860

Ser Ala Glu Leu Leu Ala Val Glu Gln Glu Leu Ala Gln Glu Glu Glu
865                 870                 875                 880

Glu Glu Ser Gly Gln Glu Glu Pro Arg Gly Pro Asp Gly Asp Trp Leu
                885                 890                 895

Thr Met Leu Arg Glu Ala Ser Asp Glu Ile Val Ala Glu Lys Glu Ala
            900                 905                 910

Glu Val Lys Leu Pro Glu Asp Ser Ser Cys Thr Glu Asp Leu Ser Ser
        915                 920                 925
```

```
Cys Thr Ser Val Pro Glu Met Asn Glu Asp Gly Asn Arg Lys Glu Ser
    930                 935                 940


Asn Cys Ala Lys Asp Leu Arg Ser Gln Pro Pro Thr Arg Ile Pro Thr
945                 950                 955                 960


Leu Val Asp Lys Glu Thr Asn Thr Asp Glu Ala Ala Asn Asp Asn Met
                965                 970                 975


Ala Val Arg Pro Lys Glu Arg Ser Ser Leu Ser Ser Arg Gln His Pro
            980                 985                 990


Phe Val Arg Ser Ser Val Ile Val  Arg Ser Gln Thr Phe  Ser Pro Gly
        995                 1000                 1005


Glu Arg  Asn Gln Tyr Ile Cys  Arg Leu Asn Arg Ser  Asp Ser Asp
    1010                 1015                 1020


Ser Ser  Thr Leu Ala Lys Lys  Ser Leu Phe Val Arg  Asn Ser Thr
    1025                 1030                 1035


Glu Arg  Arg Ser Leu Arg Val  Lys Arg Thr Val Cys  Gln Ser Val
    1040                 1045                 1050


Leu Arg  Arg Thr Thr Gln Glu  Cys Pro Val Arg Thr  Ser Leu Asp
    1055                 1060                 1065


Leu Glu  Leu Asp Leu Gln Ala  Ser Leu Thr Arg Gln  Ser Arg Leu
    1070                 1075                 1080


Asn Asp  Glu Leu Gln Ala Leu  Arg Asp Leu Arg Gln  Lys Leu Glu
    1085                 1090                 1095


Glu Leu  Lys Ala Gln Gly Glu  Thr Asp Leu Pro Pro  Gly Val Leu
    1100                 1105                 1110


Glu Asp  Glu Arg Phe Gln Arg  Leu Leu Lys Gln Ala  Glu Lys Gln
    1115                 1120                 1125


Ala Glu  Gln Ser Lys Glu Glu  Gln Lys Gln Gly Leu  Asn Ala Glu
    1130                 1135                 1140


Lys Leu  Met Arg Gln Val Ser  Lys Asp Val Cys Arg  Leu Arg Glu
    1145                 1150                 1155
```

```
Gln Ser  Gln Lys Val Pro Arg  Gln Val Gln Ser Phe  Arg Glu Lys
    1160                 1165                 1170


Ile Ala  Tyr Phe Thr Arg Ala  Lys Ile Ser Ile Pro  Ser Leu Pro
    1175                 1180                 1185


Ala Asp  Asp Val
    1190


<210>  145
<211>  650
<212>  PRT
<213>  Homo sapiens

<400>  145

Met Ala Ser Asn Met Asp Arg Glu Met Ile Leu Ala Asp Phe Gln Ala
1               5                   10                  15


Cys Thr Gly Ile Glu Asn Ile Asp Glu Ala Ile Thr Leu Leu Glu Gln
            20                  25                  30


Asn Asn Trp Asp Leu Val Ala Ala Ile Asn Gly Val Ile Pro Gln Glu
        35                  40                  45


Asn Gly Ile Leu Gln Ser Glu Tyr Gly Gly Glu Thr Ile Pro Gly Pro
    50                  55                  60


Ala Phe Asn Pro Ala Ser His Pro Ala Ser Ala Pro Thr Ser Ser Ser
65                  70                  75                  80


Ser Ser Ala Phe Arg Pro Val Met Pro Ser Arg Gln Ile Val Glu Arg
                85                  90                  95


Gln Pro Arg Met Leu Asp Phe Arg Val Glu Tyr Arg Asp Arg Asn Val
            100                 105                 110


Asp Val Val Leu Glu Asp Thr Cys Thr Val Gly Glu Ile Lys Gln Ile
        115                 120                 125


Leu Glu Asn Glu Leu Gln Ile Pro Val Ser Lys Met Leu Leu Lys Gly
    130                 135                 140


Trp Lys Thr Gly Asp Val Glu Asp Ser Thr Val Leu Lys Ser Leu His
145                 150                 155                 160
```

```
Leu Pro Lys Asn Asn Ser Leu Tyr Val Leu Thr Pro Asp Leu Pro Pro
                165                 170                 175

Pro Ser Ser Ser Ser His Ala Gly Ala Leu Gln Glu Ser Leu Asn Gln
            180                 185                 190

Asn Phe Met Leu Ile Ile Thr His Arg Glu Val Gln Arg Glu Tyr Asn
        195                 200                 205

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

Tyr Asp Leu Thr Ser Ile Pro Val Arg His Gln Leu Trp Glu Gly Trp
225                 230                 235                 240

Pro Thr Ser Ala Thr Asp Asp Ser Met Cys Leu Ala Glu Ser Gly Leu
                245                 250                 255

Ser Tyr Pro Cys His Arg Leu Thr Val Gly Arg Arg Ser Ser Pro Ala
            260                 265                 270

Gln Thr Arg Glu Gln Ser Glu Glu Gln Ile Thr Asp Val His Met Val
        275                 280                 285

Ser Asp Ser Asp Gly Asp Asp Phe Glu Asp Ala Thr Glu Phe Gly Val
    290                 295                 300

Asp Asp Gly Glu Val Phe Gly Met Ala Ser Ser Ala Leu Arg Lys Ser
305                 310                 315                 320

Pro Met Met Pro Glu Asn Ala Glu Asn Glu Gly Asp Ala Leu Leu Gln
                325                 330                 335

Phe Thr Ala Glu Phe Ser Ser Arg Tyr Gly Asp Cys His Pro Val Phe
            340                 345                 350

Phe Ile Gly Ser Leu Glu Ala Ala Phe Gln Glu Ala Phe Tyr Val Lys
        355                 360                 365

Ala Arg Asp Arg Lys Leu Leu Ala Ile Tyr Leu His His Asp Glu Ser
    370                 375                 380

Val Leu Thr Asn Val Phe Cys Ser Gln Met Leu Cys Ala Glu Ser Ile
385                 390                 395                 400
```

Val Ser Tyr Leu Ser Gln Asn Phe Ile Thr Trp Ala Trp Asp Leu Thr
405 410 415

Lys Asp Ser Asn Arg Ala Arg Phe Leu Thr Met Cys Asn Arg His Phe
420 425 430

Gly Ser Val Val Ala Gln Thr Ile Arg Thr Gln Lys Thr Asp Gln Phe
435 440 445

Pro Leu Phe Leu Ile Ile Met Gly Lys Arg Ser Ser Asn Glu Val Leu
450 455 460

Asn Val Ile Gln Gly Asn Thr Thr Val Asp Glu Leu Met Met Arg Leu
465 470 475 480

Met Ala Ala Met Glu Ile Phe Thr Ala Gln Gln Gln Glu Asp Ile Lys
485 490 495

Asp Glu Asp Glu Arg Glu Ala Arg Glu Asn Val Lys Arg Glu Gln Asp
500 505 510

Glu Ala Tyr Arg Leu Ser Leu Glu Ala Asp Arg Ala Lys Arg Glu Ala
515 520 525

His Glu Arg Glu Met Ala Glu Gln Phe Arg Leu Glu Gln Ile Arg Lys
530 535 540

Glu Gln Glu Glu Glu Arg Glu Ala Ile Arg Leu Ser Leu Glu Gln Ala
545 550 555 560

Leu Pro Pro Glu Pro Lys Glu Glu Asn Ala Glu Pro Val Ser Lys Leu
565 570 575

Arg Ile Arg Thr Pro Ser Gly Glu Phe Leu Glu Arg Arg Phe Leu Ala
580 585 590

Ser Asn Lys Leu Gln Ile Val Phe Asp Phe Val Ala Ser Lys Gly Phe
595 600 605

Pro Trp Asp Glu Tyr Lys Leu Leu Ser Thr Phe Pro Arg Arg Asp Val
610 615 620

Thr Gln Leu Asp Pro Asn Lys Ser Leu Leu Glu Val Lys Leu Phe Pro
625 630 635 640

```
Gln Glu Thr Leu Phe Leu Glu Ala Lys Glu
                645                 650


<210>  146
<211>  403
<212>  PRT
<213>  Homo sapiens

<400>  146

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


Ser Asn Leu Glu Asn Arg Pro Cys Arg Ala Ala Arg Gly Ser Leu Gln
            20                  25                  30


Lys Thr Ser Ala Asp Thr Lys Gly Lys Gln Glu Gln Ala Lys Glu Glu
        35                  40                  45


Lys Ala Arg Glu Leu Phe Leu Lys Ala Val Glu Glu Glu Gln Asn Gly
    50                  55                  60


Ala Leu Tyr Glu Ala Ile Lys Phe Tyr Arg Arg Ala Met Gln Leu Val
65                  70                  75                  80


Pro Asp Ile Glu Phe Lys Ile Thr Tyr Thr Arg Ser Pro Asp Gly Asp
                85                  90                  95


Gly Val Gly Asn Ser Tyr Ile Glu Asp Asn Asp Asp Asp Ser Lys Met
            100                 105                 110


Ala Asp Leu Leu Ser Tyr Phe Gln Gln Gln Leu Thr Phe Gln Glu Ser
        115                 120                 125


Val Leu Lys Leu Cys Gln Pro Glu Leu Glu Ser Ser Gln Ile His Ile
    130                 135                 140


Ser Val Leu Pro Met Glu Val Leu Met Tyr Ile Phe Arg Trp Val Val
145                 150                 155                 160


Ser Ser Asp Leu Asp Leu Arg Ser Leu Glu Gln Leu Ser Leu Val Cys
                165                 170                 175


Arg Gly Phe Tyr Ile Cys Ala Arg Asp Pro Glu Ile Trp Arg Leu Ala
            180                 185                 190
```

Cys Leu Lys Val Trp Gly Arg Ser Cys Ile Lys Leu Val Pro Tyr Thr
195 200 205

Ser Trp Arg Glu Met Phe Leu Glu Arg Pro Arg Val Arg Phe Asp Gly
210 215 220

Val Tyr Ile Ser Lys Thr Thr Tyr Ile Arg Gln Gly Glu Gln Ser Leu
225 230 235 240

Asp Gly Phe Tyr Arg Ala Trp His Gln Val Glu Tyr Tyr Arg Tyr Ile
245 250 255

Arg Phe Phe Pro Asp Gly His Val Met Met Leu Thr Thr Pro Glu Glu
260 265 270

Pro Gln Ser Ile Val Pro Arg Leu Arg Thr Arg Asn Thr Arg Thr Asp
275 280 285

Ala Ile Leu Leu Gly His Tyr Arg Leu Ser Gln Asp Thr Asp Asn Gln
290 295 300

Thr Lys Val Phe Ala Val Ile Thr Lys Lys Lys Glu Glu Lys Pro Leu
305 310 315 320

Asp Tyr Lys Tyr Arg Tyr Phe Arg Arg Val Pro Val Gln Glu Ala Asp
325 330 335

Gln Ser Phe His Val Gly Leu Gln Leu Cys Ser Ser Gly His Gln Arg
340 345 350

Phe Asn Lys Leu Ile Trp Ile His His Ser Cys His Ile Thr Tyr Lys
355 360 365

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

Thr Pro Leu Phe Phe Ala Arg Val Arg Ser Tyr Thr Ala Phe Ser Glu
385 390 395 400

Arg Pro Leu

<210> 147
<211> 437
<212> PRT

```
<213>  Homo sapiens

<400>  147

Met Ala Glu Ala Glu Glu Asp Cys His Ser Asp Thr Val Arg Ala Asp
1               5                   10                  15


Asp Asp Glu Glu Asn Glu Ser Pro Ala Glu Thr Asp Leu Gln Ala Gln
            20                  25                  30


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


Ser Ser Ser Asn Leu Glu Asn Arg Pro Cys Arg Ala Ala Arg Gly Ser
    50                  55                  60


Leu Gln Lys Thr Ser Ala Asp Thr Lys Gly Lys Gln Glu Gln Ala Lys
65                  70                  75                  80


Glu Glu Lys Ala Arg Glu Leu Phe Leu Lys Ala Val Glu Glu Glu Gln
                85                  90                  95


Asn Gly Ala Leu Tyr Glu Ala Ile Lys Phe Tyr Arg Arg Ala Met Gln
            100                 105                 110


Leu Val Pro Asp Ile Glu Phe Lys Ile Thr Tyr Thr Arg Ser Pro Asp
        115                 120                 125


Gly Asp Gly Val Gly Asn Ser Tyr Ile Glu Asp Asn Asp Asp Asp Ser
    130                 135                 140


Lys Met Ala Asp Leu Leu Ser Tyr Phe Gln Gln Gln Leu Thr Phe Gln
145                 150                 155                 160


Glu Ser Val Leu Lys Leu Cys Gln Pro Glu Leu Glu Ser Ser Gln Ile
                165                 170                 175


His Ile Ser Val Leu Pro Met Glu Val Leu Met Tyr Ile Phe Arg Trp
            180                 185                 190


Val Val Ser Ser Asp Leu Asp Leu Arg Ser Leu Glu Gln Leu Ser Leu
        195                 200                 205


Val Cys Arg Gly Phe Tyr Ile Cys Ala Arg Asp Pro Glu Ile Trp Arg
    210                 215                 220
```

```
Leu Ala Cys Leu Lys Val Trp Gly Arg Ser Cys Ile Lys Leu Val Pro
225                 230                 235                 240


Tyr Thr Ser Trp Arg Glu Met Phe Leu Glu Arg Pro Arg Val Arg Phe
                245                 250                 255


Asp Gly Val Tyr Ile Ser Lys Thr Thr Tyr Ile Arg Gln Gly Glu Gln
            260                 265                 270


Ser Leu Asp Gly Phe Tyr Arg Ala Trp His Gln Val Glu Tyr Tyr Arg
        275                 280                 285


Tyr Ile Arg Phe Phe Pro Asp Gly His Val Met Met Leu Thr Thr Pro
    290                 295                 300


Glu Glu Pro Gln Ser Ile Val Pro Arg Leu Arg Thr Arg Asn Thr Arg
305                 310                 315                 320


Thr Asp Ala Ile Leu Leu Gly His Tyr Arg Leu Ser Gln Asp Thr Asp
                325                 330                 335


Asn Gln Thr Lys Val Phe Ala Val Ile Thr Lys Lys Lys Glu Glu Lys
            340                 345                 350


Pro Leu Asp Tyr Lys Tyr Arg Tyr Phe Arg Arg Val Pro Val Gln Glu
        355                 360                 365


Ala Asp Gln Ser Phe His Val Gly Leu Gln Leu Cys Ser Ser Gly His
    370                 375                 380


Gln Arg Phe Asn Lys Leu Ile Trp Ile His His Ser Cys His Ile Thr
385                 390                 395                 400


Tyr Lys Ser Thr Gly Glu Thr Ala Val Ser Ala Phe Glu Ile Asp Lys
                405                 410                 415


Met Tyr Thr Pro Leu Phe Phe Ala Arg Val Arg Ser Tyr Thr Ala Phe
            420                 425                 430


Ser Glu Arg Pro Leu
        435


<210>  148
<211>  447
```

```
<212>  PRT
<213>  Homo sapiens

<400>  148

Met Pro Asp Ile Ile Trp Val Phe Pro Pro Gln Ala Glu Ala Glu Glu
1               5                   10                  15


Asp Cys His Ser Asp Thr Val Arg Ala Asp Asp Asp Glu Glu Asn Glu
            20                  25                  30


Ser Pro Ala Glu Thr Asp Leu Gln Ala Gln Leu Gln Met Phe Arg Ala
        35                  40                  45


Gln Trp Met Phe Glu Leu Ala Pro Gly Val Ser Ser Ser Asn Leu Glu
    50                  55                  60


Asn Arg Pro Cys Arg Ala Ala Arg Gly Ser Leu Gln Lys Thr Ser Ala
65                  70                  75                  80


Asp Thr Lys Gly Lys Gln Glu Gln Ala Lys Glu Glu Lys Ala Arg Glu
                85                  90                  95


Leu Phe Leu Lys Ala Val Glu Glu Glu Gln Asn Gly Ala Leu Tyr Glu
            100                 105                 110


Ala Ile Lys Phe Tyr Arg Arg Ala Met Gln Leu Val Pro Asp Ile Glu
        115                 120                 125


Phe Lys Ile Thr Tyr Thr Arg Ser Pro Asp Gly Asp Gly Val Gly Asn
    130                 135                 140


Ser Tyr Ile Glu Asp Asn Asp Asp Asp Ser Lys Met Ala Asp Leu Leu
145                 150                 155                 160


Ser Tyr Phe Gln Gln Gln Leu Thr Phe Gln Glu Ser Val Leu Lys Leu
                165                 170                 175


Cys Gln Pro Glu Leu Glu Ser Ser Gln Ile His Ile Ser Val Leu Pro
            180                 185                 190


Met Glu Val Leu Met Tyr Ile Phe Arg Trp Val Val Ser Ser Asp Leu
        195                 200                 205
```

```
Asp Leu Arg Ser Leu Glu Gln Leu Ser Leu Val Cys Arg Gly Phe Tyr
    210                 215                 220

Ile Cys Ala Arg Asp Pro Glu Ile Trp Arg Leu Ala Cys Leu Lys Val
225                 230                 235                 240

Trp Gly Arg Ser Cys Ile Lys Leu Val Pro Tyr Thr Ser Trp Arg Glu
                245                 250                 255

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

Lys Thr Thr Tyr Ile Arg Gln Gly Glu Gln Ser Leu Asp Gly Phe Tyr
        275                 280                 285

Arg Ala Trp His Gln Val Glu Tyr Tyr Arg Tyr Ile Arg Phe Phe Pro
    290                 295                 300

Asp Gly His Val Met Met Leu Thr Thr Pro Glu Glu Pro Gln Ser Ile
305                 310                 315                 320

Val Pro Arg Leu Arg Thr Arg Asn Thr Arg Thr Asp Ala Ile Leu Leu
                325                 330                 335

Gly His Tyr Arg Leu Ser Gln Asp Thr Asp Asn Gln Thr Lys Val Phe
            340                 345                 350

Ala Val Ile Thr Lys Lys Lys Glu Glu Lys Pro Leu Asp Tyr Lys Tyr
        355                 360                 365

Arg Tyr Phe Arg Arg Val Pro Val Gln Glu Ala Asp Gln Ser Phe His
    370                 375                 380

Val Gly Leu Gln Leu Cys Ser Ser Gly His Gln Arg Phe Asn Lys Leu
385                 390                 395                 400

Ile Trp Ile His His Ser Cys His Ile Thr Tyr Lys Ser Thr Gly Glu
                405                 410                 415

Thr Ala Val Ser Ala Phe Glu Ile Asp Lys Met Tyr Thr Pro Leu Phe
            420                 425                 430

Phe Ala Arg Val Arg Ser Tyr Thr Ala Phe Ser Glu Arg Pro Leu
        435                 440                 445
```

```
<210>  149
<211>  1173
<212>  PRT
<213>  Homo sapiens

<400>  149

Met Ala Val Glu Thr Leu Ser Pro Asp Trp Glu Phe Asp Arg Val Asp
1               5                   10                  15


Asp Gly Ser Gln Lys Ile His Ala Glu Val Gln Leu Lys Asn Tyr Gly
            20                  25                  30


Lys Phe Leu Glu Glu Tyr Thr Ser Gln Leu Arg Arg Ile Glu Asp Ala
        35                  40                  45


Leu Asp Asp Ser Ile Gly Asp Val Trp Asp Phe Asn Leu Asp Pro Ile
    50                  55                  60


Ala Leu Lys Leu Leu Pro Tyr Glu Gln Ser Ser Leu Leu Glu Leu Ile
65                  70                  75                  80


Lys Thr Glu Asn Lys Val Leu Asn Lys Val Ile Thr Val Tyr Ala Ala
                85                  90                  95


Leu Cys Cys Glu Ile Lys Lys Leu Lys Tyr Glu Ala Glu Thr Lys Phe
            100                 105                 110


Tyr Asn Gly Leu Leu Phe Tyr Gly Glu Gly Ala Thr Asp Ala Ser Met
        115                 120                 125


Val Glu Gly Asp Cys Gln Ile Gln Met Gly Arg Phe Ile Ser Phe Leu
    130                 135                 140


Gln Glu Leu Ser Cys Phe Val Thr Arg Cys Tyr Glu Val Val Met Asn
145                 150                 155                 160


Val Val His Gln Leu Ala Ala Leu Tyr Ile Ser Asn Lys Ile Ala Pro
                165                 170                 175


Lys Ile Ile Glu Thr Thr Gly Val His Phe Gln Thr Met Tyr Glu His
            180                 185                 190


Leu Gly Glu Leu Leu Thr Val Leu Leu Thr Leu Asp Glu Ile Ile Asp
        195                 200                 205
```

```
Asn His Ile Thr Leu Lys Asp His Trp Thr Met Tyr Lys Arg Leu Leu
    210                 215                 220


Lys Ser Val His His Asn Pro Ser Lys Phe Gly Ile Gln Glu Glu Lys
225                 230                 235                 240


Leu Lys Pro Phe Glu Lys Phe Leu Leu Lys Leu Glu Gly Gln Leu Leu
                245                 250                 255


Asp Gly Met Ile Phe Gln Ala Cys Ile Glu Gln Gln Phe Asp Ser Leu
            260                 265                 270


Asn Gly Gly Val Ser Val Ser Lys Asn Ser Thr Phe Ala Glu Glu Phe
        275                 280                 285


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


Glu Pro Ser Glu Ile Asp Gln Arg Asp Lys Tyr Val Gly Ile Cys Gly
305                 310                 315                 320


Leu Phe Val Leu His Phe Gln Ile Phe Arg Thr Ile Asp Lys Lys Phe
                325                 330                 335


Tyr Lys Ser Leu Leu Asp Ile Cys Lys Lys Val Pro Ala Ile Thr Leu
            340                 345                 350


Thr Ala Asn Ile Ile Trp Phe Pro Asp Asn Phe Leu Ile Gln Lys Ile
        355                 360                 365


Pro Ala Ala Ala Lys Leu Leu Asp Arg Lys Ser Leu Gln Ala Ile Lys
    370                 375                 380


Ile His Arg Asp Thr Phe Leu Gln Gln Lys Ala Gln Ser Leu Thr Lys
385                 390                 395                 400


Asp Val Gln Ser Tyr Tyr Val Phe Val Ser Ser Trp Met Met Lys Met
                405                 410                 415


Glu Ser Ile Leu Ser Lys Glu Gln Arg Met Asp Lys Phe Ala Glu Asp
            420                 425                 430


Leu Thr Asn Arg Cys Asn Val Phe Ile Gln Gly Phe Leu Tyr Ala Tyr
        435                 440                 445
```

```
Ser Ile Ser Thr Ile Ile Lys Thr Thr Met Asn Leu Tyr Met Ser Met
    450                 455                 460


Gln Lys Pro Met Thr Lys Thr Ser Val Lys Ala Leu Cys Arg Leu Val
465                 470                 475                 480


Glu Leu Leu Lys Ala Ile Glu His Met Phe Tyr Arg Arg Ser Met Val
                485                 490                 495


Val Ala Asp Ser Val Ser His Ile Thr Gln His Leu Gln His Gln Ala
            500                 505                 510


Leu His Ser Ile Ser Val Ala Lys Lys Arg Val Ile Ser Asp Lys Lys
        515                 520                 525


Tyr Ser Glu Gln Arg Leu Asp Val Leu Ser Ala Leu Val Leu Ala Glu
    530                 535                 540


Asn Thr Leu Asn Gly Pro Ser Thr Lys Gln Arg Arg Leu Ile Val Ser
545                 550                 555                 560


Leu Ala Leu Ser Val Gly Thr Gln Met Lys Thr Phe Lys Asp Glu Glu
                565                 570                 575


Leu Phe Pro Leu Gln Val Val Met Lys Lys Leu Asp Leu Ile Ser Glu
            580                 585                 590


Leu Arg Glu Arg Val Gln Thr Gln Cys Asp Cys Cys Phe Leu Tyr Trp
        595                 600                 605


His Arg Ala Val Phe Pro Ile Tyr Leu Asp Asp Val Tyr Glu Asn Ala
    610                 615                 620


Val Asp Ala Ala Arg Leu His Tyr Met Phe Ser Ala Leu Arg Asp Cys
625                 630                 635                 640


Val Pro Ala Met Met His Ala Arg His Leu Glu Ser Tyr Glu Ile Leu
                645                 650                 655


Leu Asp Cys Tyr Asp Lys Glu Ile Met Glu Ile Leu Asn Glu His Leu
            660                 665                 670


Leu Asp Lys Leu Cys Lys Glu Ile Glu Lys Asp Leu Arg Leu Ser Val
        675                 680                 685
```

```
His Thr His Leu Lys Leu Asp Asp Arg Asn Pro Phe Lys Val Gly Met
    690                 695                 700

Lys Asp Leu Ala Leu Phe Phe Ser Leu Asn Pro Ile Arg Phe Phe Asn
705                 710                 715                 720

Arg Phe Ile Asp Ile Arg Ala Tyr Val Thr His Tyr Leu Asp Lys Thr
                725                 730                 735

Phe Tyr Asn Leu Thr Thr Val Ala Leu His Asp Trp Ala Thr Tyr Ser
            740                 745                 750

Glu Met Arg Asn Leu Ala Thr Gln Arg Tyr Gly Leu Val Met Thr Glu
        755                 760                 765

Ala His Leu Pro Ser Gln Thr Leu Glu Gln Gly Leu Asp Val Leu Glu
    770                 775                 780

Ile Met Arg Asn Ile His Ile Phe Val Ser Arg Tyr Leu Tyr Asn Leu
785                 790                 795                 800

Asn Asn Gln Ile Phe Ile Glu Arg Thr Ser Asn Asn Lys His Leu Asn
                805                 810                 815

Thr Ile Asn Ile Arg His Ile Ala Asn Ser Ile Arg Thr His Gly Thr
            820                 825                 830

Gly Ile Met Asn Thr Thr Val Asn Phe Thr Tyr Gln Phe Leu Lys Lys
        835                 840                 845

Lys Phe Tyr Ile Phe Ser Gln Phe Met Tyr Asp Glu His Ile Lys Ser
    850                 855                 860

Arg Leu Ile Lys Asp Ile Arg Phe Phe Arg Glu Ile Lys Asp Gln Asn
865                 870                 875                 880

Asp His Lys Tyr Pro Phe Asp Arg Ala Glu Lys Phe Asn Arg Gly Ile
                885                 890                 895

Arg Lys Leu Gly Val Thr Pro Glu Gly Gln Ser Tyr Leu Asp Gln Phe
            900                 905                 910

Arg Gln Leu Ile Ser Gln Ile Gly Asn Ala Met Gly Tyr Val Arg Met
        915                 920                 925
```

```
Ile Arg Ser Gly Gly Leu His Cys Ser Ser Asn Ala Ile Arg Phe Val
    930                 935                 940


Pro Asp Leu Glu Asp Ile Val Asn Phe Glu Glu Leu Val Lys Glu Glu
945                 950                 955                 960


Gly Leu Ala Glu Glu Thr Leu Lys Ala Ala Arg His Leu Asp Ser Val
                965                 970                 975


Leu Ser Asp His Thr Arg Asn Ser Ala Glu Gly Thr Glu Tyr Phe Lys
            980                 985                 990


Met Leu Val Asp Val Phe Ala Pro  Glu Phe Arg Arg Pro  Lys Asn Ile
        995                 1000                 1005


His Leu  Arg Asn Phe Tyr Ile  Ile Val Pro Pro Leu  Thr Leu Asn
    1010                 1015                 1020


Phe Val  Glu His Ser Ile Ser  Cys Lys Glu Lys Leu  Asn Lys Lys
    1025                 1030                 1035


Asn Lys  Ile Gly Ala Ala Phe  Thr Asp Asp Gly Phe  Ala Met Gly
    1040                 1045                 1050


Val Ala  Tyr Ile Leu Lys Leu  Leu Asp Gln Tyr Arg  Glu Phe Asp
    1055                 1060                 1065


Ser Leu  His Trp Phe Gln Ser  Val Arg Glu Lys Tyr  Leu Lys Glu
    1070                 1075                 1080


Ile Arg  Ala Val Ala Lys Gln  Gln Asn Val Gln Ser  Ala Ser Gln
    1085                 1090                 1095


Asp Glu  Lys Leu Leu Gln Thr  Met Asn Leu Thr Gln  Lys Arg Leu
    1100                 1105                 1110


Asp Val  Tyr Leu Gln Glu Phe  Glu Leu Leu Tyr Phe  Ser Leu Ser
    1115                 1120                 1125


Ser Ala  Arg Ile Phe Phe Arg  Ala Asp Lys Thr Ala  Ala Glu Glu
    1130                 1135                 1140


Asn Gln  Glu Lys Lys Glu Lys  Glu Glu Glu Thr Lys  Thr Ser Asn
    1145                 1150                 1155
```

Gly Asp Leu Ser Asp Ser Thr Val Ser Ala Asp Pro Val Val Lys
1160 1165 1170

<210> 150
<211> 173
<212> PRT
<213> Homo sapiens

<400> 150

Met Glu Asp Ser Phe Leu Gln Ser Phe Gly Arg Leu Ser Leu Gln Pro
1 5 10 15

Gln Gln Gln Gln Gln Arg Gln Arg Pro Pro Arg Pro Pro Pro Arg Gly
20 25 30

Thr Pro Pro Arg Arg His Ser Phe Arg Lys His Leu Tyr Leu Leu Arg
35 40 45

Gly Leu Pro Gly Ser Gly Lys Thr Thr Leu Ala Arg Gln Leu Gln His
50 55 60

Asp Phe Pro Arg Ala Leu Ile Phe Ser Thr Asp Asp Phe Phe Phe Arg
65 70 75 80

Glu Asp Gly Ala Tyr Glu Phe Asn Pro Asp Phe Leu Glu Glu Ala His
85 90 95

Glu Trp Asn Gln Lys Arg Ala Arg Lys Ala Met Arg Asn Gly Ile Ser
100 105 110

Pro Ile Ile Ile Asp Asn Thr Asn Leu His Ala Trp Glu Met Lys Pro
115 120 125

Tyr Ala Val Met Val Phe Gln Thr Glu Gln Lys Asn Leu Phe Arg Leu
130 135 140

Glu Met Asp Met Val Val Phe Arg Pro Glu Met Lys Lys His Ser Trp
145 150 155 160

Cys Leu Lys Arg Lys Asn Pro Pro Asn Glu Arg Thr Val
165 170

<210> 151
<211> 243
<212> PRT

```
<213>  Homo sapiens

<400>  151

Met Glu Asp Ser Phe Leu Gln Ser Phe Gly Arg Leu Ser Leu Gln Pro
1               5                   10                  15


Gln Gln Gln Gln Gln Arg Gln Arg Pro Pro Arg Pro Pro Pro Arg Gly
            20                  25                  30


Thr Pro Pro Arg Arg His Ser Phe Arg Lys His Leu Tyr Leu Leu Arg
        35                  40                  45


Gly Leu Pro Gly Ser Gly Lys Thr Thr Leu Ala Arg Gln Leu Gln His
    50                  55                  60


Asp Phe Pro Arg Ala Leu Ile Phe Ser Thr Asp Asp Phe Phe Phe Arg
65                  70                  75                  80


Glu Asp Gly Ala Tyr Glu Phe Asn Pro Asp Phe Leu Glu Glu Ala His
                85                  90                  95


Glu Trp Asn Gln Lys Arg Ala Arg Lys Ala Met Arg Asn Gly Ile Ser
            100                 105                 110


Pro Ile Ile Ile Asp Asn Thr Asn Leu His Ala Trp Glu Met Lys Pro
        115                 120                 125


Tyr Ala Val Met Ala Leu Glu Asn Asn Tyr Glu Val Ile Phe Arg Glu
    130                 135                 140


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


Ile His Gly Val Ser Arg Glu Lys Ile His Arg Met Lys Glu Arg Tyr
                165                 170                 175


Glu His Asp Val Thr Phe His Ser Val Leu His Ala Glu Lys Pro Ser
            180                 185                 190


Arg Met Asn Arg Asn Gln Asp Arg Asn Asn Ala Leu Pro Ser Asn Asn
        195                 200                 205


Ala Arg Tyr Trp Asn Ser Tyr Thr Glu Phe Pro Asn Arg Arg Ala His
    210                 215                 220
```

```
Gly Gly Phe Thr Asn Glu Ser Ser Tyr His Arg Arg Gly Gly Cys His
225                 230                 235                 240


His Gly Tyr



<210>  152
<211>  1087
<212>  PRT
<213>  Homo sapiens

<400>  152

Met Arg Ala Gly Gly Ala Cys Arg Pro Gly Ala Ala Gly Thr Ala Ala
1               5                   10                  15


Gly Thr Ala Ala Gly Gly Trp Asp Gly Gly Cys Gly Gly Ala Glu Pro
            20                  25                  30


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


Ala Thr Met Thr Thr Ser Arg Gly Ser Val Gly Trp Thr Thr Gly Ser
    50                  55                  60


Ala Pro Ser Trp Met Thr Arg Thr Glu Glu Leu Asp Ile Arg Pro Lys
65                  70                  75                  80


Val Ser Ser Leu Leu Gly Lys Leu Val Ser Tyr Thr Asn Leu Thr Gln
                85                  90                  95


Gly Ala Lys Glu His Glu Glu Ala Glu Ser Gly Glu Gly Thr Arg Arg
            100                 105                 110


Arg Ala Ala Glu Ala Pro Ser Met Gly Thr Leu Met Gly Val Tyr Leu
        115                 120                 125


Pro Cys Leu Gln Asn Ile Phe Gly Val Ile Leu Phe Leu Arg Leu Thr
    130                 135                 140


Trp Met Val Gly Thr Ala Gly Val Leu Gln Ala Leu Leu Ile Val Leu
145                 150                 155                 160


Ile Cys Cys Cys Cys Thr Leu Leu Thr Ala Ile Ser Met Ser Ala Ile
                165                 170                 175
```

```
Ala Thr Asn Gly Val Val Pro Ala Gly Gly Ser Tyr Phe Met Ile Ser
            180                 185                 190

Arg Ser Leu Gly Pro Glu Phe Gly Gly Ala Val Gly Leu Cys Phe Tyr
        195                 200                 205

Leu Gly Thr Thr Phe Ala Ala Ala Met Tyr Ile Leu Gly Ala Ile Glu
    210                 215                 220

Ile Leu Leu Thr Tyr Ile Ala Pro Pro Ala Ala Ile Phe Tyr Pro Ser
225                 230                 235                 240

Gly Ala His Asp Thr Ser Asn Ala Thr Leu Asn Asn Met Arg Val Tyr
                245                 250                 255

Gly Thr Ile Phe Leu Thr Phe Met Thr Leu Val Val Phe Val Gly Val
            260                 265                 270

Lys Tyr Val Asn Lys Phe Ala Ser Leu Phe Leu Ala Cys Val Ile Ile
        275                 280                 285

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

Pro Val Phe Pro Val Cys Met Leu Gly Asn Arg Thr Leu Ser Arg Asp
305                 310                 315                 320

Gln Phe Asp Ile Cys Ala Lys Thr Ala Val Val Asp Asn Glu Thr Val
                325                 330                 335

Ala Thr Gln Leu Trp Ser Phe Phe Cys His Ser Pro Asn Leu Thr Thr
            340                 345                 350

Asp Ser Cys Asp Pro Tyr Phe Met Leu Asn Asn Val Thr Glu Ile Pro
        355                 360                 365

Gly Ile Pro Gly Ala Ala Ala Gly Val Leu Gln Glu Asn Leu Trp Ser
    370                 375                 380

Ala Tyr Leu Glu Lys Gly Asp Ile Val Glu Lys His Gly Leu Pro Ser
385                 390                 395                 400

Ala Asp Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu Tyr Val Val Ala
                405                 410                 415
```

```
Asp Ile Ala Thr Ser Phe Thr Val Leu Val Gly Ile Phe Phe Pro Ser
            420                 425                 430

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

Ala Gln Lys Ser Ile Pro Val Gly Thr Ile Leu Ala Ile Ile Thr Thr
    450                 455                 460

Ser Leu Val Tyr Phe Ser Ser Val Val Leu Phe Gly Ala Cys Ile Glu
465                 470                 475                 480

Gly Val Val Leu Arg Asp Lys Tyr Gly Asp Gly Val Ser Arg Asn Leu
                485                 490                 495

Val Val Gly Thr Leu Ala Trp Pro Ser Pro Trp Val Ile Val Ile Gly
            500                 505                 510

Ser Phe Phe Ser Thr Cys Gly Ala Gly Leu Gln Ser Leu Thr Gly Ala
        515                 520                 525

Pro Arg Leu Leu Gln Ala Ile Ala Lys Asp Asn Ile Ile Pro Phe Leu
    530                 535                 540

Arg Val Phe Gly His Gly Lys Val Asn Gly Glu Pro Thr Trp Ala Leu
545                 550                 555                 560

Leu Leu Thr Ala Leu Ile Ala Glu Leu Gly Ile Leu Ile Ala Ser Leu
                565                 570                 575

Asp Met Val Ala Pro Ile Leu Ser Met Phe Phe Leu Met Cys Tyr Leu
            580                 585                 590

Phe Val Asn Leu Ala Cys Ala Val Gln Thr Leu Leu Arg Thr Pro Asn
        595                 600                 605

Trp Arg Pro Arg Phe Lys Tyr Tyr His Trp Ala Leu Ser Phe Leu Gly
    610                 615                 620

Met Ser Leu Cys Leu Ala Leu Met Phe Val Ser Ser Trp Tyr Tyr Ala
625                 630                 635                 640

Leu Val Ala Met Leu Ile Ala Gly Met Ile Tyr Lys Tyr Ile Glu Tyr
                645                 650                 655
```

```
Gln Gly Ala Glu Lys Glu Trp Gly Asp Gly Ile Arg Gly Leu Ser Leu
            660                 665                 670

Ser Ala Ala Arg Tyr Ala Leu Leu Arg Leu Glu Glu Gly Pro Pro His
        675                 680                 685

Thr Lys Asn Trp Arg Pro Gln Leu Leu Val Leu Leu Lys Leu Asp Glu
    690                 695                 700

Asp Leu His Val Lys Tyr Pro Arg Leu Leu Thr Phe Ala Ser Gln Leu
705                 710                 715                 720

Lys Ala Gly Lys Gly Leu Thr Ile Val Gly Ser Val Ile Gln Gly Ser
                725                 730                 735

Phe Leu Glu Ser Tyr Gly Glu Ala Gln Ala Ala Glu Gln Thr Ile Lys
            740                 745                 750

Asn Met Met Glu Ile Glu Lys Val Lys Gly Phe Cys Gln Val Val Val
        755                 760                 765

Ala Ser Lys Val Arg Glu Gly Leu Ala His Leu Ile Gln Ser Cys Gly
    770                 775                 780

Leu Gly Gly Met Arg His Asn Ser Val Val Leu Gly Trp Pro Tyr Gly
785                 790                 795                 800

Trp Arg Gln Ser Glu Asp Pro Arg Ala Trp Lys Thr Phe Ile Asp Thr
                805                 810                 815

Val Arg Cys Thr Thr Ala Ala His Leu Ala Leu Leu Val Pro Lys Asn
            820                 825                 830

Ile Ala Phe Tyr Pro Ser Asn His Glu Arg Tyr Leu Glu Gly His Ile
        835                 840                 845

Asp Val Trp Trp Ile Val His Asp Gly Gly Met Leu Met Leu Leu Pro
    850                 855                 860

Phe Leu Leu Arg Gln His Lys Val Trp Arg Lys Cys Arg Met Arg Ile
865                 870                 875                 880

Phe Thr Val Ala Gln Met Asp Asp Asn Ser Ile Gln Met Lys Lys Asp
                885                 890                 895
```

```
Leu Ala Val Phe Leu Tyr His Leu Arg Leu Glu Ala Glu Val Glu Val
            900                 905                 910

Val Glu Met His Asn Ser Asp Ile Ser Ala Tyr Thr Tyr Glu Arg Thr
        915                 920                 925

Leu Met Met Glu Gln Arg Ser Gln Met Leu Arg Gln Met Arg Leu Thr
    930                 935                 940

Lys Thr Glu Arg Glu Arg Glu Ala Gln Leu Val Lys Asp Arg His Ser
945                 950                 955                 960

Ala Leu Arg Leu Glu Ser Leu Tyr Ser Asp Glu Glu Asp Glu Ser Ala
                965                 970                 975

Val Gly Ala Asp Lys Ile Gln Met Thr Trp Thr Arg Asp Lys Tyr Met
            980                 985                 990

Thr Glu Thr Trp Asp Pro Ser His  Ala Pro Asp Asn Phe  Arg Glu Leu
        995                 1000                 1005

Val His  Ile Lys Pro Asp Gln  Ser Asn Val Arg Arg  Met His Thr
    1010                 1015                 1020

Ala Val  Lys Leu Asn Glu Val  Ile Val Thr Arg Ser  His Asp Ala
    1025                 1030                 1035

Arg Leu  Val Leu Leu Asn Met  Pro Gly Pro Pro Arg  Asn Ser Glu
    1040                 1045                 1050

Gly Asp  Glu Asn Tyr Met Glu  Phe Leu Glu Val Leu  Thr Glu Gly
    1055                 1060                 1065

Leu Glu  Arg Val Leu Leu Val  Arg Gly Gly Gly Arg  Glu Val Ile
    1070                 1075                 1080

Thr Ile  Tyr Ser
    1085


<210>  153
<211>  1079
<212>  PRT
<213>  Homo sapiens

<400>  153
```

```
Met Pro His Phe Thr Val Val Pro Val Asp Gly Pro Arg Arg Gly Asp
1               5                   10                  15

Tyr Asp Asn Leu Glu Gly Leu Ser Trp Val Asp Tyr Gly Glu Arg Ala
            20                  25                  30

Glu Leu Asp Asp Ser Asp Gly His Gly Asn His Arg Glu Ser Ser Pro
        35                  40                  45

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

Asn Leu Ala Leu Phe Glu Glu Glu Leu Asp Ile Arg Pro Lys Val Ser
65                  70                  75                  80

Ser Leu Leu Gly Lys Leu Val Ser Tyr Thr Asn Leu Thr Gln Gly Ala
                85                  90                  95

Lys Glu His Glu Glu Ala Glu Ser Gly Glu Gly Thr Arg Arg Arg Ala
            100                 105                 110

Ala Glu Ala Pro Ser Met Gly Thr Leu Met Gly Val Tyr Leu Pro Cys
        115                 120                 125

Leu Gln Asn Ile Phe Gly Val Ile Leu Phe Leu Arg Leu Thr Trp Met
    130                 135                 140

Val Gly Thr Ala Gly Val Leu Gln Ala Leu Leu Ile Val Leu Ile Cys
145                 150                 155                 160

Cys Cys Cys Thr Leu Leu Thr Ala Ile Ser Met Ser Ala Ile Ala Thr
                165                 170                 175

Asn Gly Val Val Pro Ala Gly Gly Ser Tyr Phe Met Ile Ser Arg Ser
            180                 185                 190

Leu Gly Pro Glu Phe Gly Gly Ala Val Gly Leu Cys Phe Tyr Leu Gly
        195                 200                 205

Thr Thr Phe Ala Ala Ala Met Tyr Ile Leu Gly Ala Ile Glu Ile Leu
    210                 215                 220

Leu Thr Tyr Ile Ala Pro Pro Ala Ala Ile Phe Tyr Pro Ser Gly Ala
225                 230                 235                 240
```

```
His Asp Thr Ser Asn Ala Thr Leu Asn Asn Met Arg Val Tyr Gly Thr
                245                 250                 255

Ile Phe Leu Thr Phe Met Thr Leu Val Val Phe Val Gly Val Lys Tyr
            260                 265                 270

Val Asn Lys Phe Ala Ser Leu Phe Leu Ala Cys Val Ile Ile Ser Ile
        275                 280                 285

Leu Ser Ile Tyr Ala Gly Gly Ile Lys Ser Ile Phe Asp Pro Pro Val
    290                 295                 300

Phe Pro Val Cys Met Leu Gly Asn Arg Thr Leu Ser Arg Asp Gln Phe
305                 310                 315                 320

Asp Ile Cys Ala Lys Thr Ala Val Val Asp Asn Glu Thr Val Ala Thr
                325                 330                 335

Gln Leu Trp Ser Phe Phe Cys His Ser Pro Asn Leu Thr Thr Asp Ser
            340                 345                 350

Cys Asp Pro Tyr Phe Met Leu Asn Asn Val Thr Glu Ile Pro Gly Ile
        355                 360                 365

Pro Gly Ala Ala Ala Gly Val Leu Gln Glu Asn Leu Trp Ser Ala Tyr
    370                 375                 380

Leu Glu Lys Gly Asp Ile Val Glu Lys His Gly Leu Pro Ser Ala Asp
385                 390                 395                 400

Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu Tyr Val Val Ala Asp Ile
                405                 410                 415

Ala Thr Ser Phe Thr Val Leu Val Gly Ile Phe Phe Pro Ser Val Thr
            420                 425                 430

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

Lys Ser Ile Pro Val Gly Thr Ile Leu Ala Ile Ile Thr Thr Ser Leu
    450                 455                 460

Val Tyr Phe Ser Ser Val Val Leu Phe Gly Ala Cys Ile Glu Gly Val
465                 470                 475                 480
```

```
Val Leu Arg Asp Lys Tyr Gly Asp Gly Val Ser Arg Asn Leu Val Val
                485                 490                 495

Gly Thr Leu Ala Trp Pro Ser Pro Trp Val Ile Val Ile Gly Ser Phe
            500                 505                 510

Phe Ser Thr Cys Gly Ala Gly Leu Gln Ser Leu Thr Gly Ala Pro Arg
        515                 520                 525

Leu Leu Gln Ala Ile Ala Lys Asp Asn Ile Ile Pro Phe Leu Arg Val
    530                 535                 540

Phe Gly His Gly Lys Val Asn Gly Glu Pro Thr Trp Ala Leu Leu Leu
545                 550                 555                 560

Thr Ala Leu Ile Ala Glu Leu Gly Ile Leu Ile Ala Ser Leu Asp Met
                565                 570                 575

Val Ala Pro Ile Leu Ser Met Phe Phe Leu Met Cys Tyr Leu Phe Val
            580                 585                 590

Asn Leu Ala Cys Ala Val Gln Thr Leu Leu Arg Thr Pro Asn Trp Arg
        595                 600                 605

Pro Arg Phe Lys Tyr Tyr His Trp Ala Leu Ser Phe Leu Gly Met Ser
    610                 615                 620

Leu Cys Leu Ala Leu Met Phe Val Ser Ser Trp Tyr Tyr Ala Leu Val
625                 630                 635                 640

Ala Met Leu Ile Ala Gly Met Ile Tyr Lys Tyr Ile Glu Tyr Gln Gly
                645                 650                 655

Ala Glu Lys Glu Trp Gly Asp Gly Ile Arg Gly Leu Ser Leu Ser Ala
            660                 665                 670

Ala Arg Tyr Ala Leu Leu Arg Leu Glu Glu Gly Pro Pro His Thr Lys
        675                 680                 685

Asn Trp Arg Pro Gln Leu Leu Val Leu Leu Lys Leu Asp Glu Asp Leu
    690                 695                 700

His Val Lys Tyr Pro Arg Leu Leu Thr Phe Ala Ser Gln Leu Lys Ala
705                 710                 715                 720
```

```
Gly Lys Gly Leu Thr Ile Val Gly Ser Val Ile Gln Gly Ser Phe Leu
                725                 730                 735

Glu Ser Tyr Gly Glu Ala Gln Ala Ala Glu Gln Thr Ile Lys Asn Met
            740                 745                 750

Met Glu Ile Glu Lys Val Lys Gly Phe Cys Gln Val Val Val Ala Ser
        755                 760                 765

Lys Val Arg Glu Gly Leu Ala His Leu Ile Gln Ser Cys Gly Leu Gly
    770                 775                 780

Gly Met Arg His Asn Ser Val Val Leu Gly Trp Pro Tyr Gly Trp Arg
785                 790                 795                 800

Gln Ser Glu Asp Pro Arg Ala Trp Lys Thr Phe Ile Asp Thr Val Arg
                805                 810                 815

Cys Thr Thr Ala Ala His Leu Ala Leu Leu Val Pro Lys Asn Ile Ala
            820                 825                 830

Phe Tyr Pro Ser Asn His Glu Arg Tyr Leu Glu Gly His Ile Asp Val
        835                 840                 845

Trp Trp Ile Val His Asp Gly Gly Met Leu Met Leu Leu Pro Phe Leu
    850                 855                 860

Leu Arg Gln His Lys Val Trp Arg Lys Cys Arg Met Arg Ile Phe Thr
865                 870                 875                 880

Val Ala Gln Met Asp Asp Asn Ser Ile Gln Met Lys Lys Asp Leu Ala
                885                 890                 895

Val Phe Leu Tyr His Leu Arg Leu Glu Ala Glu His Asn Ser Asp Ile
            900                 905                 910

Ser Ala Tyr Thr Tyr Glu Arg Thr Leu Met Met Glu Gln Arg Ser Gln
        915                 920                 925

Met Leu Arg Gln Met Arg Leu Thr Lys Thr Glu Arg Glu Arg Glu Ala
    930                 935                 940

Gln Leu Val Lys Asp Arg His Ser Ala Leu Arg Leu Glu Ser Leu Tyr
945                 950                 955                 960
```

Ser Asp Glu Glu Asp Glu Ser Ala Val Gly Ala Asp Lys Ile Gln Met
965 970 975

Thr Trp Thr Arg Asp Lys Tyr Met Thr Glu Thr Trp Asp Pro Ser His
980 985 990

Ala Pro Asp Asn Phe Arg Glu Leu Val His Ile Lys Pro Asp Gln Ser
995 1000 1005

Asn Val Arg Arg Met His Thr Ala Val Lys Leu Asn Glu Val Ile
1010 1015 1020

Val Thr Arg Ser His Asp Ala Arg Leu Val Leu Leu Asn Met Pro
1025 1030 1035

Gly Pro Pro Arg Asn Ser Glu Gly Asp Glu Asn Tyr Met Glu Phe
1040 1045 1050

Leu Glu Val Leu Thr Glu Gly Leu Glu Arg Val Leu Leu Val Arg
1055 1060 1065

Gly Gly Gly Arg Glu Val Ile Thr Ile Tyr Ser
1070 1075

<210> 154
<211> 1085
<212> PRT
<213> Homo sapiens

<400> 154

Met Pro His Phe Thr Val Val Pro Val Asp Gly Pro Arg Arg Gly Asp
1 5 10 15

Tyr Asp Asn Leu Glu Gly Leu Ser Trp Val Asp Tyr Gly Glu Arg Ala
20 25 30

Glu Leu Asp Asp Ser Asp Gly His Gly Asn His Arg Glu Ser Ser Pro
35 40 45

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

Asn Leu Ala Leu Phe Glu Glu Glu Leu Asp Ile Arg Pro Lys Val Ser
65 70 75 80

```
Ser Leu Leu Gly Lys Leu Val Ser Tyr Thr Asn Leu Thr Gln Gly Ala
                85                  90                  95

Lys Glu His Glu Glu Ala Glu Ser Gly Glu Gly Thr Arg Arg Arg Ala
            100                 105                 110

Ala Glu Ala Pro Ser Met Gly Thr Leu Met Gly Val Tyr Leu Pro Cys
        115                 120                 125

Leu Gln Asn Ile Phe Gly Val Ile Leu Phe Leu Arg Leu Thr Trp Met
    130                 135                 140

Val Gly Thr Ala Gly Val Leu Gln Ala Leu Leu Ile Val Leu Ile Cys
145                 150                 155                 160

Cys Cys Cys Thr Leu Leu Thr Ala Ile Ser Met Ser Ala Ile Ala Thr
                165                 170                 175

Asn Gly Val Val Pro Ala Gly Gly Ser Tyr Phe Met Ile Ser Arg Ser
            180                 185                 190

Leu Gly Pro Glu Phe Gly Gly Ala Val Gly Leu Cys Phe Tyr Leu Gly
        195                 200                 205

Thr Thr Phe Ala Ala Ala Met Tyr Ile Leu Gly Ala Ile Glu Ile Leu
    210                 215                 220

Leu Thr Tyr Ile Ala Pro Pro Ala Ala Ile Phe Tyr Pro Ser Gly Ala
225                 230                 235                 240

His Asp Thr Ser Asn Ala Thr Leu Asn Asn Met Arg Val Tyr Gly Thr
                245                 250                 255

Ile Phe Leu Thr Phe Met Thr Leu Val Val Phe Val Gly Val Lys Tyr
            260                 265                 270

Val Asn Lys Phe Ala Ser Leu Phe Leu Ala Cys Val Ile Ile Ser Ile
        275                 280                 285

Leu Ser Ile Tyr Ala Gly Gly Ile Lys Ser Ile Phe Asp Pro Pro Val
    290                 295                 300

Phe Pro Val Cys Met Leu Gly Asn Arg Thr Leu Ser Arg Asp Gln Phe
305                 310                 315                 320
```

```
Asp Ile Cys Ala Lys Thr Ala Val Val Asp Asn Glu Thr Val Ala Thr
                325                 330                 335

Gln Leu Trp Ser Phe Phe Cys His Ser Pro Asn Leu Thr Thr Asp Ser
            340                 345                 350

Cys Asp Pro Tyr Phe Met Leu Asn Asn Val Thr Glu Ile Pro Gly Ile
        355                 360                 365

Pro Gly Ala Ala Ala Gly Val Leu Gln Glu Asn Leu Trp Ser Ala Tyr
    370                 375                 380

Leu Glu Lys Gly Asp Ile Val Glu Lys His Gly Leu Pro Ser Ala Asp
385                 390                 395                 400

Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu Tyr Val Val Ala Asp Ile
                405                 410                 415

Ala Thr Ser Phe Thr Val Leu Val Gly Ile Phe Phe Pro Ser Val Thr
            420                 425                 430

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

Lys Ser Ile Pro Val Gly Thr Ile Leu Ala Ile Ile Thr Thr Ser Leu
    450                 455                 460

Val Tyr Phe Ser Ser Val Val Leu Phe Gly Ala Cys Ile Glu Gly Val
465                 470                 475                 480

Val Leu Arg Asp Lys Tyr Gly Asp Gly Val Ser Arg Asn Leu Val Val
                485                 490                 495

Gly Thr Leu Ala Trp Pro Ser Pro Trp Val Ile Val Ile Gly Ser Phe
            500                 505                 510

Phe Ser Thr Cys Gly Ala Gly Leu Gln Ser Leu Thr Gly Ala Pro Arg
        515                 520                 525

Leu Leu Gln Ala Ile Ala Lys Asp Asn Ile Ile Pro Phe Leu Arg Val
    530                 535                 540

Phe Gly His Gly Lys Val Asn Gly Glu Pro Thr Trp Ala Leu Leu Leu
545                 550                 555                 560
```

```
Thr Ala Leu Ile Ala Glu Leu Gly Ile Leu Ile Ala Ser Leu Asp Met
                565                 570                 575

Val Ala Pro Ile Leu Ser Met Phe Phe Leu Met Cys Tyr Leu Phe Val
            580                 585                 590

Asn Leu Ala Cys Ala Val Gln Thr Leu Leu Arg Thr Pro Asn Trp Arg
        595                 600                 605

Pro Arg Phe Lys Tyr Tyr His Trp Ala Leu Ser Phe Leu Gly Met Ser
    610                 615                 620

Leu Cys Leu Ala Leu Met Phe Val Ser Ser Trp Tyr Tyr Ala Leu Val
625                 630                 635                 640

Ala Met Leu Ile Ala Gly Met Ile Tyr Lys Tyr Ile Glu Tyr Gln Gly
                645                 650                 655

Ala Glu Lys Glu Trp Gly Asp Gly Ile Arg Gly Leu Ser Leu Ser Ala
            660                 665                 670

Ala Arg Tyr Ala Leu Leu Arg Leu Glu Glu Gly Pro Pro His Thr Lys
        675                 680                 685

Asn Trp Arg Pro Gln Leu Leu Val Leu Leu Lys Leu Asp Glu Asp Leu
    690                 695                 700

His Val Lys Tyr Pro Arg Leu Leu Thr Phe Ala Ser Gln Leu Lys Ala
705                 710                 715                 720

Gly Lys Gly Leu Thr Ile Val Gly Ser Val Ile Gln Gly Ser Phe Leu
                725                 730                 735

Glu Ser Tyr Gly Glu Ala Gln Ala Ala Glu Gln Thr Ile Lys Asn Met
            740                 745                 750

Met Glu Ile Glu Lys Val Lys Gly Phe Cys Gln Val Val Val Ala Ser
        755                 760                 765

Lys Val Arg Glu Gly Leu Ala His Leu Ile Gln Ser Cys Gly Leu Gly
    770                 775                 780

Gly Met Arg His Asn Ser Val Val Leu Gly Trp Pro Tyr Gly Trp Arg
785                 790                 795                 800
```

```
Gln Ser Glu Asp Pro Arg Ala Trp Lys Thr Phe Ile Asp Thr Val Arg
                805                 810                 815

Cys Thr Thr Ala Ala His Leu Ala Leu Leu Val Pro Lys Asn Ile Ala
            820                 825                 830

Phe Tyr Pro Ser Asn His Glu Arg Tyr Leu Glu Gly His Ile Asp Val
        835                 840                 845

Trp Trp Ile Val His Asp Gly Gly Met Leu Met Leu Leu Pro Phe Leu
    850                 855                 860

Leu Arg Gln His Lys Val Trp Arg Lys Cys Arg Met Arg Ile Phe Thr
865                 870                 875                 880

Val Ala Gln Met Asp Asp Asn Ser Ile Gln Met Lys Lys Asp Leu Ala
                885                 890                 895

Val Phe Leu Tyr His Leu Arg Leu Glu Ala Glu Val Glu Val Val Glu
            900                 905                 910

Met His Asn Ser Asp Ile Ser Ala Tyr Thr Tyr Glu Arg Thr Leu Met
        915                 920                 925

Met Glu Gln Arg Ser Gln Met Leu Arg Gln Met Arg Leu Thr Lys Thr
    930                 935                 940

Glu Arg Glu Arg Glu Ala Gln Leu Val Lys Asp Arg His Ser Ala Leu
945                 950                 955                 960

Arg Leu Glu Ser Leu Tyr Ser Asp Glu Glu Asp Glu Ser Ala Val Gly
                965                 970                 975

Ala Asp Lys Ile Gln Met Thr Trp Thr Arg Asp Lys Tyr Met Thr Glu
            980                 985                 990

Thr Trp Asp Pro Ser His Ala Pro  Asp Asn Phe Arg Glu  Leu Val His
        995                 1000                 1005

Ile Lys  Pro Asp Gln Ser Asn  Val Arg Arg Met His  Thr Ala Val
    1010                 1015                 1020

Lys Leu  Asn Glu Val Ile Val  Thr Arg Ser His Asp  Ala Arg Leu
    1025                 1030                 1035
```

```
Val Leu  Leu Asn Met Pro Gly  Pro Pro Arg Asn Ser  Glu Gly Asp
    1040                 1045                 1050


Glu Asn  Tyr Met Glu Phe Leu  Glu Val Leu Thr Glu  Gly Leu Glu
    1055                 1060                 1065


Arg Val  Leu Leu Val Arg Gly  Gly Gly Arg Glu Val  Ile Thr Ile
    1070                 1075                 1080


Tyr Ser
    1085


<210>  155
<211>  1054
<212>  PRT
<213>  Homo sapiens

<400>  155

Met Gly Asp Thr Leu Ser Pro Gly His Gly Asn His Arg Glu Ser Ser
1               5                   10                  15


Pro Phe Leu Ser Pro Leu Glu Ala Ser Arg Gly Ile Asp Tyr Tyr Asp
            20                  25                  30


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


Ser Ser Leu Leu Gly Lys Leu Val Ser Tyr Thr Asn Leu Thr Gln Gly
    50                  55                  60


Ala Lys Glu His Glu Glu Ala Glu Ser Gly Glu Gly Thr Arg Arg Arg
65                  70                  75                  80


Ala Ala Glu Ala Pro Ser Met Gly Thr Leu Met Gly Val Tyr Leu Pro
                85                  90                  95


Cys Leu Gln Asn Ile Phe Gly Val Ile Leu Phe Leu Arg Leu Thr Trp
            100                 105                 110


Met Val Gly Thr Ala Gly Val Leu Gln Ala Leu Leu Ile Val Leu Ile
        115                 120                 125


Cys Cys Cys Cys Thr Leu Leu Thr Ala Ile Ser Met Ser Ala Ile Ala
    130                 135                 140
```

```
Thr Asn Gly Val Val Pro Ala Gly Gly Ser Tyr Phe Met Ile Ser Arg
145                 150                 155                 160

Ser Leu Gly Pro Glu Phe Gly Gly Ala Val Gly Leu Cys Phe Tyr Leu
                165                 170                 175

Gly Thr Thr Phe Ala Ala Ala Met Tyr Ile Leu Gly Ala Ile Glu Ile
            180                 185                 190

Leu Leu Thr Tyr Ile Ala Pro Pro Ala Ala Ile Phe Tyr Pro Ser Gly
        195                 200                 205

Ala His Asp Thr Ser Asn Ala Thr Leu Asn Asn Met Arg Val Tyr Gly
    210                 215                 220

Thr Ile Phe Leu Thr Phe Met Thr Leu Val Val Phe Val Gly Val Lys
225                 230                 235                 240

Tyr Val Asn Lys Phe Ala Ser Leu Phe Leu Ala Cys Val Ile Ile Ser
                245                 250                 255

Ile Leu Ser Ile Tyr Ala Gly Gly Ile Lys Ser Ile Phe Asp Pro Pro
            260                 265                 270

Val Phe Pro Val Cys Met Leu Gly Asn Arg Thr Leu Ser Arg Asp Gln
        275                 280                 285

Phe Asp Ile Cys Ala Lys Thr Ala Val Val Asp Asn Glu Thr Val Ala
    290                 295                 300

Thr Gln Leu Trp Ser Phe Phe Cys His Ser Pro Asn Leu Thr Thr Asp
305                 310                 315                 320

Ser Cys Asp Pro Tyr Phe Met Leu Asn Asn Val Thr Glu Ile Pro Gly
                325                 330                 335

Ile Pro Gly Ala Ala Ala Gly Val Leu Gln Glu Asn Leu Trp Ser Ala
            340                 345                 350

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

Asp Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu Tyr Val Val Ala Asp
    370                 375                 380
```

```
Ile Ala Thr Ser Phe Thr Val Leu Val Gly Ile Phe Phe Pro Ser Val
385                 390                 395                 400

Thr Gly Ile Met Ala Gly Ser Asn Arg Ser Gly Asp Leu Arg Asp Ala
                405                 410                 415

Gln Lys Ser Ile Pro Val Gly Thr Ile Leu Ala Ile Ile Thr Thr Ser
            420                 425                 430

Leu Val Tyr Phe Ser Ser Val Val Leu Phe Gly Ala Cys Ile Glu Gly
        435                 440                 445

Val Val Leu Arg Asp Lys Tyr Gly Asp Gly Val Ser Arg Asn Leu Val
    450                 455                 460

Val Gly Thr Leu Ala Trp Pro Ser Pro Trp Val Ile Val Ile Gly Ser
465                 470                 475                 480

Phe Phe Ser Thr Cys Gly Ala Gly Leu Gln Ser Leu Thr Gly Ala Pro
                485                 490                 495

Arg Leu Leu Gln Ala Ile Ala Lys Asp Asn Ile Ile Pro Phe Leu Arg
            500                 505                 510

Val Phe Gly His Gly Lys Val Asn Gly Glu Pro Thr Trp Ala Leu Leu
        515                 520                 525

Leu Thr Ala Leu Ile Ala Glu Leu Gly Ile Leu Ile Ala Ser Leu Asp
    530                 535                 540

Met Val Ala Pro Ile Leu Ser Met Phe Phe Leu Met Cys Tyr Leu Phe
545                 550                 555                 560

Val Asn Leu Ala Cys Ala Val Gln Thr Leu Leu Arg Thr Pro Asn Trp
                565                 570                 575

Arg Pro Arg Phe Lys Tyr Tyr His Trp Ala Leu Ser Phe Leu Gly Met
            580                 585                 590

Ser Leu Cys Leu Ala Leu Met Phe Val Ser Ser Trp Tyr Tyr Ala Leu
        595                 600                 605

Val Ala Met Leu Ile Ala Gly Met Ile Tyr Lys Tyr Ile Glu Tyr Gln
    610                 615                 620
```

```
Gly Ala Glu Lys Glu Trp Gly Asp Gly Ile Arg Gly Leu Ser Leu Ser
625                 630                 635                 640

Ala Ala Arg Tyr Ala Leu Leu Arg Leu Glu Glu Gly Pro Pro His Thr
                645                 650                 655

Lys Asn Trp Arg Pro Gln Leu Leu Val Leu Leu Lys Leu Asp Glu Asp
            660                 665                 670

Leu His Val Lys Tyr Pro Arg Leu Leu Thr Phe Ala Ser Gln Leu Lys
        675                 680                 685

Ala Gly Lys Gly Leu Thr Ile Val Gly Ser Val Ile Gln Gly Ser Phe
    690                 695                 700

Leu Glu Ser Tyr Gly Glu Ala Gln Ala Ala Glu Gln Thr Ile Lys Asn
705                 710                 715                 720

Met Met Glu Ile Glu Lys Val Lys Gly Phe Cys Gln Val Val Val Ala
                725                 730                 735

Ser Lys Val Arg Glu Gly Leu Ala His Leu Ile Gln Ser Cys Gly Leu
            740                 745                 750

Gly Gly Met Arg His Asn Ser Val Val Leu Gly Trp Pro Tyr Gly Trp
        755                 760                 765

Arg Gln Ser Glu Asp Pro Arg Ala Trp Lys Thr Phe Ile Asp Thr Val
    770                 775                 780

Arg Cys Thr Thr Ala Ala His Leu Ala Leu Leu Val Pro Lys Asn Ile
785                 790                 795                 800

Ala Phe Tyr Pro Ser Asn His Glu Arg Tyr Leu Glu Gly His Ile Asp
                805                 810                 815

Val Trp Trp Ile Val His Asp Gly Gly Met Leu Met Leu Leu Pro Phe
            820                 825                 830

Leu Leu Arg Gln His Lys Val Trp Arg Lys Cys Arg Met Arg Ile Phe
        835                 840                 845

Thr Val Ala Gln Met Asp Asp Asn Ser Ile Gln Met Lys Lys Asp Leu
    850                 855                 860
```

```
Ala Val Phe Leu Tyr His Leu Arg Leu Glu Ala Glu Val Glu Val Val
865                 870                 875                 880


Glu Met His Asn Ser Asp Ile Ser Ala Tyr Thr Tyr Glu Arg Thr Leu
                885                 890                 895


Met Met Glu Gln Arg Ser Gln Met Leu Arg Gln Met Arg Leu Thr Lys
            900                 905                 910


Thr Glu Arg Glu Arg Glu Ala Gln Leu Val Lys Asp Arg His Ser Ala
        915                 920                 925


Leu Arg Leu Glu Ser Leu Tyr Ser Asp Glu Glu Asp Glu Ser Ala Val
    930                 935                 940


Gly Ala Asp Lys Ile Gln Met Thr Trp Thr Arg Asp Lys Tyr Met Thr
945                 950                 955                 960


Glu Thr Trp Asp Pro Ser His Ala Pro Asp Asn Phe Arg Glu Leu Val
                965                 970                 975


His Ile Lys Pro Asp Gln Ser Asn Val Arg Arg Met His Thr Ala Val
            980                 985                 990


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


Leu Leu  Asn Met Pro Gly Pro  Pro Arg Asn Ser Glu  Gly Asp Glu
    1010                1015                1020


Asn Tyr  Met Glu Phe Leu Glu  Val Leu Thr Glu Gly  Leu Glu Arg
    1025                1030                1035


Val Leu  Leu Val Arg Gly Gly  Gly Arg Glu Val Ile  Thr Ile Tyr
    1040                1045                1050


Ser



<210>  156
<211>  1079
<212>  PRT
<213>  Homo sapiens

<400>  156
```

```
Met Ala Ala Glu Gly Ala Val Cys Gly Phe Val Tyr Leu Glu Gly Thr
1               5                   10                  15

Ala Trp Ala Val Pro Glu Asp Thr Glu Pro Leu Ala Ser Cys Thr Leu
            20                  25                  30

Gly His Gly Asn His Arg Glu Ser Ser Pro Phe Leu Ser Pro Leu Glu
        35                  40                  45

Ala Ser Arg Gly Ile Asp Tyr Tyr Asp Arg Asn Leu Ala Leu Phe Glu
    50                  55                  60

Glu Glu Leu Asp Ile Arg Pro Lys Val Ser Ser Leu Leu Gly Lys Leu
65                  70                  75                  80

Val Ser Tyr Thr Asn Leu Thr Gln Gly Ala Lys Glu His Glu Glu Ala
                85                  90                  95

Glu Ser Gly Glu Gly Thr Arg Arg Arg Ala Ala Glu Ala Pro Ser Met
            100                 105                 110

Gly Thr Leu Met Gly Val Tyr Leu Pro Cys Leu Gln Asn Ile Phe Gly
        115                 120                 125

Val Ile Leu Phe Leu Arg Leu Thr Trp Met Val Gly Thr Ala Gly Val
    130                 135                 140

Leu Gln Ala Leu Leu Ile Val Leu Ile Cys Cys Cys Cys Thr Leu Leu
145                 150                 155                 160

Thr Ala Ile Ser Met Ser Ala Ile Ala Thr Asn Gly Val Val Pro Ala
                165                 170                 175

Gly Gly Ser Tyr Phe Met Ile Ser Arg Ser Leu Gly Pro Glu Phe Gly
            180                 185                 190

Gly Ala Val Gly Leu Cys Phe Tyr Leu Gly Thr Thr Phe Ala Ala Ala
        195                 200                 205

Met Tyr Ile Leu Gly Ala Ile Glu Ile Leu Leu Thr Tyr Ile Ala Pro
    210                 215                 220

Pro Ala Ala Ile Phe Tyr Pro Ser Gly Ala His Asp Thr Ser Asn Ala
225                 230                 235                 240
```

```
Thr Leu Asn Asn Met Arg Val Tyr Gly Thr Ile Phe Leu Thr Phe Met
                245                 250                 255

Thr Leu Val Val Phe Val Gly Val Lys Tyr Val Asn Lys Phe Ala Ser
            260                 265                 270

Leu Phe Leu Ala Cys Val Ile Ile Ser Ile Leu Ser Ile Tyr Ala Gly
        275                 280                 285

Gly Ile Lys Ser Ile Phe Asp Pro Pro Val Phe Pro Val Cys Met Leu
    290                 295                 300

Gly Asn Arg Thr Leu Ser Arg Asp Gln Phe Asp Ile Cys Ala Lys Thr
305                 310                 315                 320

Ala Val Val Asp Asn Glu Thr Val Ala Thr Gln Leu Trp Ser Phe Phe
                325                 330                 335

Cys His Ser Pro Asn Leu Thr Thr Asp Ser Cys Asp Pro Tyr Phe Met
            340                 345                 350

Leu Asn Asn Val Thr Glu Ile Pro Gly Ile Pro Gly Ala Ala Ala Gly
        355                 360                 365

Val Leu Gln Glu Asn Leu Trp Ser Ala Tyr Leu Glu Lys Gly Asp Ile
    370                 375                 380

Val Glu Lys His Gly Leu Pro Ser Ala Asp Ala Pro Ser Leu Lys Glu
385                 390                 395                 400

Ser Leu Pro Leu Tyr Val Val Ala Asp Ile Ala Thr Ser Phe Thr Val
                405                 410                 415

Leu Val Gly Ile Phe Phe Pro Ser Val Thr Gly Ile Met Ala Gly Ser
            420                 425                 430

Asn Arg Ser Gly Asp Leu Arg Asp Ala Gln Lys Ser Ile Pro Val Gly
        435                 440                 445

Thr Ile Leu Ala Ile Ile Thr Thr Ser Leu Val Tyr Phe Ser Ser Val
    450                 455                 460

Val Leu Phe Gly Ala Cys Ile Glu Gly Val Val Leu Arg Asp Lys Tyr
465                 470                 475                 480
```

```
Gly Asp Gly Val Ser Arg Asn Leu Val Val Gly Thr Leu Ala Trp Pro
                485                 490                 495

Ser Pro Trp Val Ile Val Ile Gly Ser Phe Phe Ser Thr Cys Gly Ala
            500                 505                 510

Gly Leu Gln Ser Leu Thr Gly Ala Pro Arg Leu Leu Gln Ala Ile Ala
        515                 520                 525

Lys Asp Asn Ile Ile Pro Phe Leu Arg Val Phe Gly His Gly Lys Val
    530                 535                 540

Asn Gly Glu Pro Thr Trp Ala Leu Leu Leu Thr Ala Leu Ile Ala Glu
545                 550                 555                 560

Leu Gly Ile Leu Ile Ala Ser Leu Asp Met Val Ala Pro Ile Leu Ser
                565                 570                 575

Met Phe Phe Leu Met Cys Tyr Leu Phe Val Asn Leu Ala Cys Ala Val
            580                 585                 590

Gln Thr Leu Leu Arg Thr Pro Asn Trp Arg Pro Arg Phe Lys Tyr Tyr
        595                 600                 605

His Trp Ala Leu Ser Phe Leu Gly Met Ser Leu Cys Leu Ala Leu Met
    610                 615                 620

Phe Val Ser Ser Trp Tyr Tyr Ala Leu Val Ala Met Leu Ile Ala Gly
625                 630                 635                 640

Met Ile Tyr Lys Tyr Ile Glu Tyr Gln Gly Ala Glu Lys Glu Trp Gly
                645                 650                 655

Asp Gly Ile Arg Gly Leu Ser Leu Ser Ala Ala Arg Tyr Ala Leu Leu
            660                 665                 670

Arg Leu Glu Glu Gly Pro Pro His Thr Lys Asn Trp Arg Pro Gln Leu
        675                 680                 685

Leu Val Leu Leu Lys Leu Asp Glu Asp Leu His Val Lys Tyr Pro Arg
    690                 695                 700

Leu Leu Thr Phe Ala Ser Gln Leu Lys Ala Gly Lys Gly Leu Thr Ile
705                 710                 715                 720
```

```
Val Gly Ser Val Ile Gln Gly Ser Phe Leu Glu Ser Tyr Gly Glu Ala
                725                 730                 735

Gln Ala Ala Glu Gln Thr Ile Lys Asn Met Met Glu Ile Glu Lys Val
            740                 745                 750

Lys Gly Phe Cys Gln Val Val Val Ala Ser Lys Val Arg Glu Gly Leu
        755                 760                 765

Ala His Leu Ile Gln Ser Cys Gly Leu Gly Gly Met Arg His Asn Ser
    770                 775                 780

Val Val Leu Gly Trp Pro Tyr Gly Trp Arg Gln Ser Glu Asp Pro Arg
785                 790                 795                 800

Ala Trp Lys Thr Phe Ile Asp Thr Val Arg Cys Thr Thr Ala Ala His
                805                 810                 815

Leu Ala Leu Leu Val Pro Lys Asn Ile Ala Phe Tyr Pro Ser Asn His
            820                 825                 830

Glu Arg Tyr Leu Glu Gly His Ile Asp Val Trp Trp Ile Val His Asp
        835                 840                 845

Gly Gly Met Leu Met Leu Leu Pro Phe Leu Leu Arg Gln His Lys Val
    850                 855                 860

Trp Arg Lys Cys Arg Met Arg Ile Phe Thr Val Ala Gln Met Asp Asp
865                 870                 875                 880

Asn Ser Ile Gln Met Lys Lys Asp Leu Ala Val Phe Leu Tyr His Leu
                885                 890                 895

Arg Leu Glu Ala Glu Val Glu Val Val Glu Met His Asn Ser Asp Ile
            900                 905                 910

Ser Ala Tyr Thr Tyr Glu Arg Thr Leu Met Met Glu Gln Arg Ser Gln
        915                 920                 925

Met Leu Arg Gln Met Arg Leu Thr Lys Thr Glu Arg Glu Arg Glu Ala
    930                 935                 940

Gln Leu Val Lys Asp Arg His Ser Ala Leu Arg Leu Glu Ser Leu Tyr
945                 950                 955                 960
```

```
Ser Asp Glu Glu Asp Glu Ser Ala Val Gly Ala Asp Lys Ile Gln Met
                965                 970                 975


Thr Trp Thr Arg Asp Lys Tyr Met Thr Glu Thr Trp Asp Pro Ser His
            980                 985                 990


Ala Pro Asp Asn Phe Arg Glu Leu  Val His Ile Lys Pro  Asp Gln Ser
        995                 1000                 1005


Asn Val  Arg Arg Met His Thr  Ala Val Lys Leu Asn  Glu Val Ile
    1010                 1015                 1020


Val Thr  Arg Ser His Asp Ala  Arg Leu Val Leu Leu  Asn Met Pro
    1025                 1030                 1035


Gly Pro  Pro Arg Asn Ser Glu  Gly Asp Glu Asn Tyr  Met Glu Phe
    1040                 1045                 1050


Leu Glu  Val Leu Thr Glu Gly  Leu Glu Arg Val Leu  Leu Val Arg
    1055                 1060                 1065


Gly Gly  Gly Arg Glu Val Ile  Thr Ile Tyr Ser
    1070                 1075


<210>  157
<211>  1078
<212>  PRT
<213>  Homo sapiens

<400>  157

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


Pro Lys Glu Arg Val Glu Ile Glu Ala Lys Glu Ala Cys Asp Trp Leu
            20                  25                  30


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


Phe Pro Ile Asn Ile Val Ala Val Lys Asn Asp His Asp Phe Leu Glu
    50                  55                  60


Lys Asp Leu Val Glu Pro Leu Cys Arg Arg Leu Asn Thr Leu Asn Lys
65                  70                  75                  80
```

```
Cys Ala Ser Met Lys Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp
                85                  90                  95

Asp Ser Asp Glu Glu Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln
            100                 105                 110

Arg Thr Ser Arg Arg Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu
        115                 120                 125

Pro Arg Gly Asp Arg Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn
    130                 135                 140

Thr Thr Ser Ser Glu Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val
145                 150                 155                 160

Cys Ser Ile His Ser Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln
                165                 170                 175

Pro Gly Gln Cys Cys Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu
            180                 185                 190

Val Ser Ser Ser Leu Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro
        195                 200                 205

Phe His Pro Lys Asn Glu Lys Pro Thr Arg Ala Arg Ala Lys Ser Phe
    210                 215                 220

Leu Lys Arg Met Glu Thr Leu Arg Gly Lys Gly Ala His Gly Arg His
225                 230                 235                 240

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

Gln Gln Glu Pro Glu Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro
            260                 265                 270

Asn Gly Asp Leu Gln Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu
        275                 280                 285

Pro Cys Ser Gly Lys Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser
    290                 295                 300

Ser Ser Gly Val Ser Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu
305                 310                 315                 320
```

```
Ala Asn Lys Arg Gly Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala
                325                 330                 335


Gly Thr Ala Leu Pro Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe
            340                 345                 350


His Ser Gln Glu Asn Leu Val Val His Ile Pro Lys Asp His Lys Pro
        355                 360                 365


Gly Thr Phe Pro Lys Ala Leu Ser Ile Glu Ser Leu Ser Pro Thr Asp
    370                 375                 380


Ser Ser Asn Gly Val Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg
385                 390                 395                 400


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


Arg Ala Ser Arg Val Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu
            420                 425                 430


Tyr Ala Ser Thr Gly Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe
        435                 440                 445


Pro His Leu Asp Asp Ile Leu Gln His Val Asn Gly Leu Gln Glu Val
    450                 455                 460


Val Asp Asp Trp Ser Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp
465                 470                 475                 480


Thr Leu Val Gly Glu Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln
                485                 490                 495


Ile Thr Leu Asp Phe Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr
            500                 505                 510


Pro Ser Asp Val Glu Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro
        515                 520                 525


Pro Gly Val Arg Asp Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr
    530                 535                 540


Arg Pro Asn Arg Arg Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln
545                 550                 555                 560
```

```
Pro Arg Pro Ala Pro Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser
                565                 570                 575

Gln Leu Ser Leu Leu Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile
            580                 585                 590

Met Glu Lys His Ser Met Ser Asn Lys His Gly Trp Thr Trp Ser Val
        595                 600                 605

Pro Lys Phe Met Lys Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala
    610                 615                 620

Val Phe Gly Val Pro Leu Ile Val His Val Gln Arg Thr Gly Gln Pro
625                 630                 635                 640

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

Leu Asp Gln Val Gly Leu Phe Arg Lys Ser Gly Val Lys Ser Arg Ile
            660                 665                 670

His Ala Leu Arg Gln Met Asn Glu Asn Phe Pro Glu Asn Val Asn Tyr
        675                 680                 685

Glu Asp Gln Ser Ala Tyr Asp Val Ala Asp Met Val Lys Gln Phe Phe
    690                 695                 700

Arg Asp Leu Pro Glu Pro Leu Phe Thr Asn Lys Leu Ser Glu Thr Phe
705                 710                 715                 720

Leu His Ile Tyr Gln Tyr Val Ser Lys Glu Gln Arg Leu Gln Ala Val
                725                 730                 735

Gln Ala Ala Ile Leu Leu Leu Ala Asp Glu Asn Arg Glu Val Leu Gln
            740                 745                 750

Thr Leu Leu Cys Phe Leu Asn Asp Val Val Asn Leu Val Glu Glu Asn
        755                 760                 765

Gln Met Thr Pro Met Asn Leu Ala Val Cys Leu Ala Pro Ser Leu Phe
    770                 775                 780

His Leu Asn Leu Leu Lys Lys Glu Ser Ser Pro Arg Val Ile Gln Lys
785                 790                 795                 800
```

```
Lys Tyr Ala Thr Gly Lys Pro Asp Gln Lys Asp Leu Asn Glu Asn Leu
                805                 810                 815


Ala Ala Ala Gln Gly Leu Ala His Met Ile Met Glu Cys Asp Arg Leu
            820                 825                 830


Phe Glu Val Pro His Glu Leu Val Ala Gln Ser Arg Asn Ser Tyr Val
        835                 840                 845


Glu Ala Glu Ile His Val Pro Thr Leu Glu Glu Leu Gly Thr Gln Leu
    850                 855                 860


Glu Glu Ser Gly Ala Thr Phe His Thr Tyr Leu Asn His Leu Ile Gln
865                 870                 875                 880


Gly Leu Gln Lys Glu Ala Lys Glu Lys Phe Lys Gly Trp Val Thr Cys
                885                 890                 895


Ser Ser Thr Asp Asn Thr Asp Leu Ala Phe Lys Lys Val Gly Asp Gly
            900                 905                 910


Asn Pro Leu Lys Leu Trp Lys Ala Ser Val Glu Val Glu Ala Pro Pro
        915                 920                 925


Ser Val Val Leu Asn Arg Val Leu Arg Glu Arg His Leu Trp Asp Glu
    930                 935                 940


Asp Phe Val Gln Trp Lys Val Val Glu Thr Leu Asp Arg Gln Thr Glu
945                 950                 955                 960


Ile Tyr Gln Tyr Val Leu Asn Ser Met Ala Pro His Pro Ser Arg Asp
                965                 970                 975


Phe Val Val Leu Arg Thr Trp Lys Thr Asp Leu Pro Lys Gly Met Cys
            980                 985                 990


Thr Leu Val Ser Leu Ser Val Glu  His Glu Glu Ala Gln  Leu Leu Gly
        995                 1000                 1005


Gly Val  Arg Ala Val Val Met  Asp Ser Gln Tyr Leu  Ile Glu Pro
    1010                 1015                 1020


Cys Gly  Ser Gly Lys Ser Arg  Leu Thr His Ile Cys  Arg Ile Asp
    1025                 1030                 1035
```

```
Leu Lys  Gly His Ser Pro Glu  Trp Tyr Ser Lys Gly  Phe Gly His
    1040                 1045                 1050


Leu Cys  Ala Ala Glu Val Ala  Arg Ile Arg Asn Ser  Phe Gln Pro
    1055                 1060                 1065


Leu Ile  Ala Glu Gly Pro Glu  Thr Lys Ile
    1070                 1075


<210>  158
<211>  1113
<212>  PRT
<213>  Homo sapiens

<400>  158

Met Phe Ser Gln Val Pro Arg Thr Pro Ala Ser Gly Cys Tyr Tyr Leu
1               5                   10                  15


Asn Ser Met Thr Pro Glu Gly Gln Glu Met Tyr Leu Arg Phe Asp Gln
            20                  25                  30


Thr Thr Arg Arg Ser Pro Tyr Arg Met Ser Arg Ile Leu Ala Arg His
        35                  40                  45


Gln Leu Val Thr Lys Ile Gln Gln Glu Ile Glu Ala Lys Glu Ala Cys
    50                  55                  60


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


Asp Ser Gln Phe Pro Ile Asn Ile Val Ala Val Lys Asn Asp His Asp
                85                  90                  95


Phe Leu Glu Lys Asp Leu Val Glu Pro Leu Cys Arg Arg Leu Asn Thr
            100                 105                 110


Leu Asn Lys Cys Ala Ser Met Lys Leu Asp Val Asn Phe Gln Arg Lys
        115                 120                 125


Lys Gly Asp Asp Ser Asp Glu Glu Asp Leu Cys Ile Ser Asn Lys Trp
    130                 135                 140


Thr Phe Gln Arg Thr Ser Arg Arg Trp Ser Arg Val Asp Asp Leu Tyr
145                 150                 155                 160
```

```
Thr Leu Leu Pro Arg Gly Asp Arg Asn Gly Ser Pro Gly Gly Thr Gly
                165                 170                 175

Met Arg Asn Thr Thr Ser Ser Glu Ser Val Leu Thr Asp Leu Ser Glu
            180                 185                 190

Pro Glu Val Cys Ser Ile His Ser Glu Ser Ser Gly Gly Ser Asp Ser
        195                 200                 205

Arg Ser Gln Pro Gly Gln Cys Cys Thr Asp Asn Pro Val Met Leu Asp
    210                 215                 220

Ala Pro Leu Val Ser Ser Ser Leu Pro Gln Pro Pro Arg Asp Val Leu
225                 230                 235                 240

Asn His Pro Phe His Pro Lys Asn Glu Lys Pro Thr Arg Ala Arg Ala
                245                 250                 255

Lys Ser Phe Leu Lys Arg Met Glu Thr Leu Arg Gly Lys Gly Ala His
            260                 265                 270

Gly Arg His Lys Gly Ser Gly Arg Thr Gly Gly Leu Val Ile Ser Gly
        275                 280                 285

Pro Met Leu Gln Gln Glu Pro Glu Ser Phe Lys Ala Met Gln Cys Ile
    290                 295                 300

Gln Ile Pro Asn Gly Asp Leu Gln Asn Ser Pro Pro Pro Ala Cys Arg
305                 310                 315                 320

Lys Gly Leu Pro Cys Ser Gly Lys Ser Ser Gly Glu Ser Ser Pro Ser
                325                 330                 335

Glu His Ser Ser Ser Gly Val Ser Thr Pro Cys Leu Lys Glu Arg Lys
            340                 345                 350

Cys His Glu Ala Asn Lys Arg Gly Gly Met Tyr Leu Glu Asp Leu Asp
        355                 360                 365

Val Leu Ala Gly Thr Ala Leu Pro Asp Ala Gly Asp Gln Ser Arg Met
    370                 375                 380

His Glu Phe His Ser Gln Glu Asn Leu Val Val His Ile Pro Lys Asp
385                 390                 395                 400
```

```
His Lys Pro Gly Thr Phe Pro Lys Ala Leu Ser Ile Glu Ser Leu Ser
                405                 410                 415

Pro Thr Asp Ser Ser Asn Gly Val Asn Trp Arg Thr Gly Ser Ile Ser
            420                 425                 430

Leu Gly Arg Glu Gln Val Pro Gly Ala Arg Glu Pro Arg Leu Met Ala
        435                 440                 445

Ser Cys His Arg Ala Ser Arg Val Ser Ile Tyr Asp Asn Val Pro Gly
    450                 455                 460

Ser His Leu Tyr Ala Ser Thr Gly Asp Leu Leu Asp Leu Glu Lys Asp
465                 470                 475                 480

Asp Leu Phe Pro His Leu Asp Asp Ile Leu Gln His Val Asn Gly Leu
                485                 490                 495

Gln Glu Val Val Asp Asp Trp Ser Lys Asp Val Leu Pro Glu Leu Gln
            500                 505                 510

Thr His Asp Thr Leu Val Gly Glu Pro Gly Leu Ser Thr Phe Pro Ser
        515                 520                 525

Pro Asn Gln Ile Thr Leu Asp Phe Glu Gly Asn Ser Val Ser Glu Gly
    530                 535                 540

Arg Thr Thr Pro Ser Asp Val Glu Arg Asp Val Thr Ser Leu Asn Glu
545                 550                 555                 560

Ser Glu Pro Pro Gly Val Arg Asp Arg Arg Asp Ser Gly Val Gly Ala
                565                 570                 575

Ser Leu Thr Arg Pro Asn Arg Arg Leu Arg Trp Asn Ser Phe Gln Leu
            580                 585                 590

Ser His Gln Pro Arg Pro Ala Pro Ala Ser Pro His Ile Ser Ser Gln
        595                 600                 605

Thr Ala Ser Gln Leu Ser Leu Leu Gln Arg Phe Ser Leu Leu Arg Leu
    610                 615                 620

Thr Ala Ile Met Glu Lys His Ser Met Ser Asn Lys His Gly Trp Thr
625                 630                 635                 640
```

```
Trp Ser Val Pro Lys Phe Met Lys Arg Met Lys Val Pro Asp Tyr Lys
                645                 650                 655

Asp Lys Ala Val Phe Gly Val Pro Leu Ile Val His Val Gln Arg Thr
            660                 665                 670

Gly Gln Pro Leu Pro Gln Ser Ile Gln Gln Ala Leu Arg Tyr Leu Arg
        675                 680                 685

Ser Asn Cys Leu Asp Gln Val Gly Leu Phe Arg Lys Ser Gly Val Lys
    690                 695                 700

Ser Arg Ile His Ala Leu Arg Gln Met Asn Glu Asn Phe Pro Glu Asn
705                 710                 715                 720

Val Asn Tyr Glu Asp Gln Ser Ala Tyr Asp Val Ala Asp Met Val Lys
                725                 730                 735

Gln Phe Phe Arg Asp Leu Pro Glu Pro Leu Phe Thr Asn Lys Leu Ser
            740                 745                 750

Glu Thr Phe Leu His Ile Tyr Gln Tyr Val Ser Lys Glu Gln Arg Leu
        755                 760                 765

Gln Ala Val Gln Ala Ala Ile Leu Leu Leu Ala Asp Glu Asn Arg Glu
    770                 775                 780

Val Leu Gln Thr Leu Leu Cys Phe Leu Asn Asp Val Val Asn Leu Val
785                 790                 795                 800

Glu Glu Asn Gln Met Thr Pro Met Asn Leu Ala Val Cys Leu Ala Pro
                805                 810                 815

Ser Leu Phe His Leu Asn Leu Leu Lys Lys Glu Ser Ser Pro Arg Val
            820                 825                 830

Ile Gln Lys Lys Tyr Ala Thr Gly Lys Pro Asp Gln Lys Asp Leu Asn
        835                 840                 845

Glu Asn Leu Ala Ala Ala Gln Gly Leu Ala His Met Ile Met Glu Cys
    850                 855                 860

Asp Arg Leu Phe Glu Val Pro His Glu Leu Val Ala Gln Ser Arg Asn
865                 870                 875                 880
```

```
Ser Tyr Val Glu Ala Glu Ile His Val Pro Thr Leu Glu Glu Leu Gly
                885                 890                 895

Thr Gln Leu Glu Glu Ser Gly Ala Thr Phe His Thr Tyr Leu Asn His
            900                 905                 910

Leu Ile Gln Gly Leu Gln Lys Glu Ala Lys Glu Lys Phe Lys Gly Trp
        915                 920                 925

Val Thr Cys Ser Ser Thr Asp Asn Thr Asp Leu Ala Phe Lys Lys Val
    930                 935                 940

Gly Asp Gly Asn Pro Leu Lys Leu Trp Lys Ala Ser Val Glu Val Glu
945                 950                 955                 960

Ala Pro Pro Ser Val Val Leu Asn Arg Val Leu Arg Glu Arg His Leu
                965                 970                 975

Trp Asp Glu Asp Phe Val Gln Trp Lys Val Val Glu Thr Leu Asp Arg
            980                 985                 990

Gln Thr Glu Ile Tyr Gln Tyr Val  Leu Asn Ser Met Ala  Pro His Pro
        995                 1000                 1005

Ser Arg  Asp Phe Val Val Leu  Arg Thr Trp Lys Thr  Asp Leu Pro
    1010                 1015                 1020

Lys Gly  Met Cys Thr Leu Val  Ser Leu Ser Val Glu  His Glu Glu
    1025                 1030                 1035

Ala Gln  Leu Leu Gly Gly Val  Arg Ala Val Val Met  Asp Ser Gln
    1040                 1045                 1050

Tyr Leu  Ile Glu Pro Cys Gly  Ser Gly Lys Ser Arg  Leu Thr His
    1055                 1060                 1065

Ile Cys  Arg Ile Asp Leu Lys  Gly His Ser Pro Glu  Trp Tyr Ser
    1070                 1075                 1080

Lys Gly  Phe Gly His Leu Cys  Ala Ala Glu Val Ala  Arg Ile Arg
    1085                 1090                 1095

Asn Ser  Phe Gln Pro Leu Ile  Ala Glu Gly Pro Glu  Thr Lys Ile
    1100                 1105                 1110
```

```
<210>  159
<211>  995
<212>  PRT
<213>  Homo sapiens

<400>  159

Met Lys Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp Asp Ser Asp
1               5                   10                  15


Glu Glu Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln Arg Thr Ser
            20                  25                  30


Arg Arg Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu Pro Arg Gly
        35                  40                  45


Asp Arg Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn Thr Thr Ser
    50                  55                  60


Ser Glu Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val Cys Ser Ile
65                  70                  75                  80


His Ser Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln Pro Gly Gln
                85                  90                  95


Cys Cys Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu Val Ser Ser
            100                 105                 110


Ser Leu Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro Phe His Pro
        115                 120                 125


Lys Asn Glu Lys Pro Thr Arg Ala Arg Ala Lys Ser Phe Leu Lys Arg
    130                 135                 140


Met Glu Thr Leu Arg Gly Lys Gly Ala His Gly Arg His Lys Gly Ser
145                 150                 155                 160


Gly Arg Thr Gly Gly Leu Val Ile Ser Gly Pro Met Leu Gln Gln Glu
                165                 170                 175


Pro Glu Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro Asn Gly Asp
            180                 185                 190


Leu Gln Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu Pro Cys Ser
        195                 200                 205
```

```
Gly Lys Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser Ser Ser Gly
    210                 215                 220


Val Ser Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu Ala Asn Lys
225                 230                 235                 240


Arg Gly Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala Gly Thr Ala
                245                 250                 255


Leu Pro Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe His Ser Gln
            260                 265                 270


Glu Asn Leu Val Val His Ile Pro Lys Asp His Lys Pro Gly Thr Phe
        275                 280                 285


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


Gly Val Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg Glu Gln Val
305                 310                 315                 320


Pro Gly Ala Arg Glu Pro Arg Leu Met Ala Ser Cys His Arg Ala Ser
                325                 330                 335


Arg Val Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu Tyr Ala Ser
            340                 345                 350


Thr Gly Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe Pro His Leu
        355                 360                 365


Asp Asp Ile Leu Gln His Val Asn Gly Leu Gln Glu Val Val Asp Asp
    370                 375                 380


Trp Ser Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp Thr Leu Val
385                 390                 395                 400


Gly Glu Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln Ile Thr Leu
                405                 410                 415


Asp Phe Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr Pro Ser Asp
            420                 425                 430


Val Glu Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro Pro Gly Val
        435                 440                 445
```

```
Arg Asp Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr Arg Pro Asn
    450                 455                 460

Arg Arg Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln Pro Arg Pro
465                 470                 475                 480

Ala Pro Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser Gln Leu Ser
                485                 490                 495

Leu Leu Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile Met Glu Lys
            500                 505                 510

His Ser Met Ser Asn Lys His Gly Trp Thr Trp Ser Val Pro Lys Phe
        515                 520                 525

Met Lys Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala Val Phe Gly
    530                 535                 540

Val Pro Leu Ile Val His Val Gln Arg Thr Gly Gln Pro Leu Pro Gln
545                 550                 555                 560

Ser Ile Gln Gln Ala Leu Arg Tyr Leu Arg Ser Asn Cys Leu Asp Gln
                565                 570                 575

Val Gly Leu Phe Arg Lys Ser Gly Val Lys Ser Arg Ile His Ala Leu
            580                 585                 590

Arg Gln Met Asn Glu Asn Phe Pro Glu Asn Val Asn Tyr Glu Asp Gln
        595                 600                 605

Ser Ala Tyr Asp Val Ala Asp Met Val Lys Gln Phe Phe Arg Asp Leu
    610                 615                 620

Pro Glu Pro Leu Phe Thr Asn Lys Leu Ser Glu Thr Phe Leu His Ile
625                 630                 635                 640

Tyr Gln Tyr Val Ser Lys Glu Gln Arg Leu Gln Ala Val Gln Ala Ala
                645                 650                 655

Ile Leu Leu Leu Ala Asp Glu Asn Arg Glu Val Leu Gln Thr Leu Leu
            660                 665                 670

Cys Phe Leu Asn Asp Val Val Asn Leu Val Glu Glu Asn Gln Met Thr
        675                 680                 685
```

```
Pro Met Asn Leu Ala Val Cys Leu Ala Pro Ser Leu Phe His Leu Asn
    690                 695                 700


Leu Leu Lys Lys Glu Ser Ser Pro Arg Val Ile Gln Lys Lys Tyr Ala
705                 710                 715                 720


Thr Gly Lys Pro Asp Gln Lys Asp Leu Asn Glu Asn Leu Ala Ala Ala
                725                 730                 735


Gln Gly Leu Ala His Met Ile Met Glu Cys Asp Arg Leu Phe Glu Val
            740                 745                 750


Pro His Glu Leu Val Ala Gln Ser Arg Asn Ser Tyr Val Glu Ala Glu
        755                 760                 765


Ile His Val Pro Thr Leu Glu Glu Leu Gly Thr Gln Leu Glu Glu Ser
    770                 775                 780


Gly Ala Thr Phe His Thr Tyr Leu Asn His Leu Ile Gln Gly Leu Gln
785                 790                 795                 800


Lys Glu Ala Lys Glu Lys Phe Lys Gly Trp Val Thr Cys Ser Ser Thr
                805                 810                 815


Asp Asn Thr Asp Leu Ala Phe Lys Lys Val Gly Asp Gly Asn Pro Leu
            820                 825                 830


Lys Leu Trp Lys Ala Ser Val Glu Val Glu Ala Pro Pro Ser Val Val
        835                 840                 845


Leu Asn Arg Val Leu Arg Glu Arg His Leu Trp Asp Glu Asp Phe Val
    850                 855                 860


Gln Trp Lys Val Val Glu Thr Leu Asp Arg Gln Thr Glu Ile Tyr Gln
865                 870                 875                 880


Tyr Val Leu Asn Ser Met Ala Pro His Pro Ser Arg Asp Phe Val Val
                885                 890                 895


Leu Arg Thr Trp Lys Thr Asp Leu Pro Lys Gly Met Cys Thr Leu Val
            900                 905                 910


Ser Leu Ser Val Glu His Glu Glu Ala Gln Leu Leu Gly Gly Val Arg
        915                 920                 925
```

```
Ala Val Val Met Asp Ser Gln Tyr Leu Ile Glu Pro Cys Gly Ser Gly
    930                 935                 940


Lys Ser Arg Leu Thr His Ile Cys Arg Ile Asp Leu Lys Gly His Ser
945                 950                 955                 960


Pro Glu Trp Tyr Ser Lys Gly Phe Gly His Leu Cys Ala Ala Glu Val
                965                 970                 975


Ala Arg Ile Arg Asn Ser Phe Gln Pro Leu Ile Ala Glu Gly Pro Glu
            980                 985                 990


Thr Lys Ile
        995


<210>  160
<211>  1105
<212>  PRT
<213>  Homo sapiens

<400>  160

Met Leu Glu Pro Ser Ser Val Leu His Ala Asn Val Asn Gln Ala Pro
1               5                   10                  15


Leu Trp Cys Leu Val Leu Arg Trp Cys Arg Glu Cys Lys Asp Thr Val
            20                  25                  30


Cys Gly Gly Lys Gln Lys Ser Arg Val Asn His Thr Phe Gln Arg Arg
        35                  40                  45


Glu Ile Glu Ala Lys Glu Ala Cys Asp Trp Leu Arg Ala Ala Gly Phe
    50                  55                  60


Pro Gln Tyr Ala Gln Leu Tyr Glu Asp Ser Gln Phe Pro Ile Asn Ile
65                  70                  75                  80


Val Ala Val Lys Asn Asp His Asp Phe Leu Glu Lys Asp Leu Val Glu
                85                  90                  95


Pro Leu Cys Arg Arg Leu Asn Thr Leu Asn Lys Cys Ala Ser Met Lys
            100                 105                 110


Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp Asp Ser Asp Glu Glu
        115                 120                 125
```

```
Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln Arg Thr Ser Arg Arg
    130                 135                 140

Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu Pro Arg Gly Asp Arg
145                 150                 155                 160

Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn Thr Thr Ser Ser Glu
                165                 170                 175

Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val Cys Ser Ile His Ser
            180                 185                 190

Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln Pro Gly Gln Cys Cys
        195                 200                 205

Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu Val Ser Ser Ser Leu
    210                 215                 220

Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro Phe His Pro Lys Asn
225                 230                 235                 240

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

Thr Leu Arg Gly Lys Gly Ala His Gly Arg His Lys Gly Ser Gly Arg
            260                 265                 270

Thr Gly Gly Leu Val Ile Ser Gly Pro Met Leu Gln Gln Glu Pro Glu
        275                 280                 285

Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro Asn Gly Asp Leu Gln
    290                 295                 300

Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu Pro Cys Ser Gly Lys
305                 310                 315                 320

Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser Ser Ser Gly Val Ser
                325                 330                 335

Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu Ala Asn Lys Arg Gly
            340                 345                 350

Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala Gly Thr Ala Leu Pro
        355                 360                 365
```

```
Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe His Ser Gln Glu Asn
    370                 375                 380


Leu Val Val His Ile Pro Lys Asp His Lys Pro Gly Thr Phe Pro Lys
385                 390                 395                 400


Ala Leu Ser Ile Glu Ser Leu Ser Pro Thr Asp Ser Ser Asn Gly Val
                405                 410                 415


Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg Glu Gln Val Pro Gly
            420                 425                 430


Ala Arg Glu Pro Arg Leu Met Ala Ser Cys His Arg Ala Ser Arg Val
        435                 440                 445


Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu Tyr Ala Ser Thr Gly
    450                 455                 460


Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe Pro His Leu Asp Asp
465                 470                 475                 480


Ile Leu Gln His Val Asn Gly Leu Gln Glu Val Val Asp Asp Trp Ser
                485                 490                 495


Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp Thr Leu Val Gly Glu
            500                 505                 510


Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln Ile Thr Leu Asp Phe
        515                 520                 525


Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr Pro Ser Asp Val Glu
    530                 535                 540


Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro Pro Gly Val Arg Asp
545                 550                 555                 560


Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr Arg Pro Asn Arg Arg
                565                 570                 575


Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln Pro Arg Pro Ala Pro
            580                 585                 590


Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser Gln Leu Ser Leu Leu
        595                 600                 605
```

```
Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile Met Glu Lys His Ser
    610                 615                 620


Met Ser Asn Lys His Gly Trp Thr Trp Ser Val Pro Lys Phe Met Lys
625                 630                 635                 640


Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala Val Phe Gly Val Pro
                645                 650                 655


Leu Ile Val His Val Gln Arg Thr Gly Gln Pro Leu Pro Gln Ser Ile
            660                 665                 670


Gln Gln Ala Leu Arg Tyr Leu Arg Ser Asn Cys Leu Asp Gln Val Gly
        675                 680                 685


Leu Phe Arg Lys Ser Gly Val Lys Ser Arg Ile His Ala Leu Arg Gln
    690                 695                 700


Met Asn Glu Asn Phe Pro Glu Asn Val Asn Tyr Glu Asp Gln Ser Ala
705                 710                 715                 720


Tyr Asp Val Ala Asp Met Val Lys Gln Phe Phe Arg Asp Leu Pro Glu
                725                 730                 735


Pro Leu Phe Thr Asn Lys Leu Ser Glu Thr Phe Leu His Ile Tyr Gln
            740                 745                 750


Tyr Val Ser Lys Glu Gln Arg Leu Gln Ala Val Gln Ala Ala Ile Leu
        755                 760                 765


Leu Leu Ala Asp Glu Asn Arg Glu Val Leu Gln Thr Leu Leu Cys Phe
    770                 775                 780


Leu Asn Asp Val Val Asn Leu Val Glu Glu Asn Gln Met Thr Pro Met
785                 790                 795                 800


Asn Leu Ala Val Cys Leu Ala Pro Ser Leu Phe His Leu Asn Leu Leu
                805                 810                 815


Lys Lys Glu Ser Ser Pro Arg Val Ile Gln Lys Lys Tyr Ala Thr Gly
            820                 825                 830


Lys Pro Asp Gln Lys Asp Leu Asn Glu Asn Leu Ala Ala Ala Gln Gly
        835                 840                 845
```

```
Leu Ala His Met Ile Met Glu Cys Asp Arg Leu Phe Glu Val Pro His
    850                 855                 860


Glu Leu Val Ala Gln Ser Arg Asn Ser Tyr Val Glu Ala Glu Ile His
865                 870                 875                 880


Val Pro Thr Leu Glu Glu Leu Gly Thr Gln Leu Glu Glu Ser Gly Ala
                885                 890                 895


Thr Phe His Thr Tyr Leu Asn His Leu Ile Gln Gly Leu Gln Lys Glu
            900                 905                 910


Ala Lys Glu Lys Phe Lys Gly Trp Val Thr Cys Ser Ser Thr Asp Asn
        915                 920                 925


Thr Asp Leu Ala Phe Lys Lys Val Gly Asp Gly Asn Pro Leu Lys Leu
    930                 935                 940


Trp Lys Ala Ser Val Glu Val Glu Ala Pro Pro Ser Val Val Leu Asn
945                 950                 955                 960


Arg Val Leu Arg Glu Arg His Leu Trp Asp Glu Asp Phe Val Gln Trp
                965                 970                 975


Lys Val Val Glu Thr Leu Asp Arg Gln Thr Glu Ile Tyr Gln Tyr Val
            980                 985                 990


Leu Asn Ser Met Ala Pro His Pro  Ser Arg Asp Phe Val  Val Leu Arg
        995                 1000                 1005


Thr Trp  Lys Thr Asp Leu Pro  Lys Gly Met Cys Thr  Leu Val Ser
    1010                 1015                 1020


Leu Ser  Val Glu His Glu Glu  Ala Gln Leu Leu Gly  Gly Val Arg
    1025                 1030                 1035


Ala Val  Val Met Asp Ser Gln  Tyr Leu Ile Glu Pro  Cys Gly Ser
    1040                 1045                 1050


Gly Lys  Ser Arg Leu Thr His  Ile Cys Arg Ile Asp  Leu Lys Gly
    1055                 1060                 1065


His Ser  Pro Glu Trp Tyr Ser  Lys Gly Phe Gly His  Leu Cys Ala
    1070                 1075                 1080
```

```
Ala Glu  Val Ala Arg Ile Arg  Asn Ser Phe Gln Pro  Leu Ile Ala
    1085                 1090                 1095


Glu Gly  Pro Glu Thr Lys Ile
    1100                 1105


<210>  161
<211>  646
<212>  PRT
<213>  Homo sapiens

<400>  161

Met Lys Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp Asp Ser Asp
1               5                   10                  15


Glu Glu Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln Arg Thr Ser
            20                  25                  30


Arg Arg Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu Pro Arg Gly
        35                  40                  45


Asp Arg Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn Thr Thr Ser
    50                  55                  60


Ser Glu Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val Cys Ser Ile
65                  70                  75                  80


His Ser Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln Pro Gly Gln
                85                  90                  95


Cys Cys Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu Val Ser Ser
            100                 105                 110


Ser Leu Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro Phe His Pro
        115                 120                 125


Lys Asn Glu Lys Pro Thr Arg Ala Arg Ala Lys Ser Phe Leu Lys Arg
    130                 135                 140


Met Glu Thr Leu Arg Gly Lys Gly Ala His Gly Arg His Lys Gly Ser
145                 150                 155                 160


Gly Arg Thr Gly Gly Leu Val Ile Ser Gly Pro Met Leu Gln Gln Glu
                165                 170                 175
```

```
Pro Glu Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro Asn Gly Asp
            180                 185                 190

Leu Gln Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu Pro Cys Ser
        195                 200                 205

Gly Lys Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser Ser Ser Gly
    210                 215                 220

Val Ser Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu Ala Asn Lys
225                 230                 235                 240

Arg Gly Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala Gly Thr Ala
                245                 250                 255

Leu Pro Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe His Ser Gln
            260                 265                 270

Glu Asn Leu Val Val His Ile Pro Lys Asp His Lys Pro Gly Thr Phe
        275                 280                 285

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

Gly Val Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg Glu Gln Val
305                 310                 315                 320

Pro Gly Ala Arg Glu Pro Arg Leu Met Ala Ser Cys His Arg Ala Ser
                325                 330                 335

Arg Val Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu Tyr Ala Ser
            340                 345                 350

Thr Gly Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe Pro His Leu
        355                 360                 365

Asp Asp Ile Leu Gln His Val Asn Gly Leu Gln Glu Val Val Asp Asp
    370                 375                 380

Trp Ser Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp Thr Leu Val
385                 390                 395                 400

Gly Glu Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln Ile Thr Leu
                405                 410                 415
```

```
Asp Phe Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr Pro Ser Asp
            420                 425                 430

Val Glu Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro Pro Gly Val
        435                 440                 445

Arg Asp Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr Arg Pro Asn
    450                 455                 460

Arg Arg Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln Pro Arg Pro
465                 470                 475                 480

Ala Pro Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser Gln Leu Ser
                485                 490                 495

Leu Leu Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile Met Glu Lys
            500                 505                 510

His Ser Met Ser Asn Lys His Gly Trp Thr Trp Ser Val Pro Lys Phe
        515                 520                 525

Met Lys Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala Val Phe Gly
    530                 535                 540

Val Pro Leu Ile Val His Val Gln Arg Thr Gly Gln Pro Leu Pro Gln
545                 550                 555                 560

Ser Ile Gln Gln Ala Leu Arg Tyr Leu Arg Ser Asn Cys Leu Asp Gln
                565                 570                 575

Val Gly Leu Phe Arg Lys Ser Gly Val Lys Ser Arg Ile His Ala Leu
            580                 585                 590

Arg Gln Met Asn Glu Asn Phe Pro Glu Asn Val Asn Tyr Glu Asp Gln
        595                 600                 605

Ser Ala Tyr Asp Val Ala Asp Met Val Lys Gln Phe Phe Arg Asp Leu
    610                 615                 620

Pro Glu Pro Leu Phe Thr Asn Lys Leu Ser Glu Thr Phe Leu His Ile
625                 630                 635                 640

Tyr Gln Cys Lys Trp Lys
                645
```

```
<210>  162
<211>  687
<212>  PRT
<213>  Homo sapiens

<400>  162

Met Leu Glu Pro Ser Ser Val Leu His Ala Asn Val Asn Gln Ala Pro
1               5                   10                  15


Leu Trp Cys Leu Val Leu Arg Trp Cys Arg Glu Cys Lys Asp Thr Val
            20                  25                  30


Cys Gly Gly Lys Gln Lys Ser Arg Val Asn His Thr Phe Gln Arg Arg
        35                  40                  45


Glu Ile Glu Ala Lys Glu Ala Cys Asp Trp Leu Arg Ala Ala Gly Phe
    50                  55                  60


Pro Gln Tyr Ala Gln Leu Tyr Glu Asp Ser Gln Phe Pro Ile Asn Ile
65                  70                  75                  80


Val Ala Val Lys Asn Asp His Asp Phe Leu Glu Lys Asp Leu Val Glu
                85                  90                  95


Pro Leu Cys Arg Arg Leu Asn Thr Leu Asn Lys Cys Ala Ser Met Lys
            100                 105                 110


Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp Asp Ser Asp Glu Glu
        115                 120                 125


Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln Arg Thr Ser Arg Arg
    130                 135                 140


Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu Pro Arg Gly Asp Arg
145                 150                 155                 160


Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn Thr Thr Ser Ser Glu
                165                 170                 175


Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val Cys Ser Ile His Ser
            180                 185                 190


Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln Pro Gly Gln Cys Cys
        195                 200                 205
```

```
Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu Val Ser Ser Ser Leu
    210                 215                 220


Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro Phe His Pro Lys Asn
225                 230                 235                 240


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


Thr Leu Arg Gly Lys Gly Ala His Gly Arg His Lys Gly Ser Gly Arg
            260                 265                 270


Thr Gly Gly Leu Val Ile Ser Gly Pro Met Leu Gln Gln Glu Pro Glu
        275                 280                 285


Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro Asn Gly Asp Leu Gln
    290                 295                 300


Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu Pro Cys Ser Gly Lys
305                 310                 315                 320


Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser Ser Ser Gly Val Ser
                325                 330                 335


Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu Ala Asn Lys Arg Gly
            340                 345                 350


Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala Gly Thr Ala Leu Pro
        355                 360                 365


Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe His Ser Gln Glu Asn
    370                 375                 380


Leu Val Val His Ile Pro Lys Asp His Lys Pro Gly Thr Phe Pro Lys
385                 390                 395                 400


Ala Leu Ser Ile Glu Ser Leu Ser Pro Thr Asp Ser Ser Asn Gly Val
                405                 410                 415


Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg Glu Gln Val Pro Gly
            420                 425                 430


Ala Arg Glu Pro Arg Leu Met Ala Ser Cys His Arg Ala Ser Arg Val
        435                 440                 445
```

```
Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu Tyr Ala Ser Thr Gly
    450                 455                 460

Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe Pro His Leu Asp Asp
465                 470                 475                 480

Ile Leu Gln His Val Asn Gly Leu Gln Glu Val Val Asp Asp Trp Ser
                485                 490                 495

Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp Thr Leu Val Gly Glu
            500                 505                 510

Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln Ile Thr Leu Asp Phe
        515                 520                 525

Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr Pro Ser Asp Val Glu
    530                 535                 540

Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro Pro Gly Val Arg Asp
545                 550                 555                 560

Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr Arg Pro Asn Arg Arg
                565                 570                 575

Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln Pro Arg Pro Ala Pro
            580                 585                 590

Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser Gln Leu Ser Leu Leu
        595                 600                 605

Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile Met Glu Lys His Ser
    610                 615                 620

Met Ser Asn Lys His Gly Trp Thr Trp Ser Val Pro Lys Phe Met Lys
625                 630                 635                 640

Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala Val Phe Gly Val Pro
                645                 650                 655

Leu Ile Val His Val Gln Arg Thr Gly Gln Pro Leu Pro Gln Ser Ile
            660                 665                 670

Gln Gln Ala Leu Arg Tyr Leu Arg Ser Asn Cys Leu Asp Gln Glu
        675                 680                 685
```

```
<210>  163
<211>  1591
<212>  PRT
<213>  Homo sapiens

<400>  163

Met Lys Leu Tyr Val Phe Leu Val Asn Thr Gly Thr Thr Leu Thr Phe
1               5                   10                  15


Asp Thr Glu Leu Thr Val Gln Thr Val Ala Asp Leu Lys His Ala Ile
            20                  25                  30


Gln Ser Lys Tyr Lys Ile Ala Ile Gln His Gln Val Leu Val Val Asn
        35                  40                  45


Gly Gly Glu Cys Met Ala Ala Asp Arg Arg Val Cys Thr Tyr Ser Ala
    50                  55                  60


Gly Thr Asp Thr Asn Pro Ile Phe Leu Phe Asn Lys Glu Met Ile Leu
65                  70                  75                  80


Cys Asp Arg Pro Pro Ala Ile Pro Lys Thr Thr Phe Ser Thr Glu Asn
                85                  90                  95


Asp Met Glu Ile Lys Val Glu Glu Ser Leu Met Met Pro Ala Val Phe
            100                 105                 110


His Thr Val Ala Ser Arg Thr Gln Leu Ala Leu Glu Met Tyr Glu Val
        115                 120                 125


Ala Lys Lys Leu Cys Ser Phe Cys Glu Gly Leu Val His Asp Glu His
    130                 135                 140


Leu Gln His Gln Gly Trp Ala Ala Ile Met Ala Asn Leu Glu Asp Cys
145                 150                 155                 160


Ser Asn Ser Tyr Gln Lys Leu Leu Phe Lys Phe Glu Ser Ile Tyr Ser
                165                 170                 175


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


Gly Thr Ala Val Ser Val Met Ala Lys Ile Pro Leu Leu Glu Cys Leu
        195                 200                 205
```

```
Thr Arg His Ser Tyr Arg Glu Cys Leu Gly Arg Leu Asp Ser Leu Pro
    210                 215                 220


Glu His Glu Asp Ser Glu Lys Ala Glu Met Lys Arg Ser Thr Glu Leu
225                 230                 235                 240


Val Leu Ser Pro Asp Met Pro Arg Thr Thr Asn Glu Ser Leu Leu Thr
                245                 250                 255


Ser Phe Pro Lys Ser Val Glu His Val Ser Pro Asp Thr Ala Asp Ala
            260                 265                 270


Glu Ser Gly Lys Glu Ile Arg Glu Ser Cys Gln Ser Thr Val His Gln
        275                 280                 285


Gln Asp Glu Thr Thr Ile Asp Thr Lys Asp Gly Asp Leu Pro Phe Phe
    290                 295                 300


Asn Val Ser Leu Leu Asp Trp Ile Asn Val Gln Asp Arg Pro Asn Asp
305                 310                 315                 320


Val Glu Ser Leu Val Arg Lys Cys Phe Asp Ser Met Ser Arg Leu Asp
                325                 330                 335


Pro Arg Ile Ile Arg Pro Phe Ile Ala Glu Cys Arg Gln Thr Ile Ala
            340                 345                 350


Lys Leu Asp Asn Gln Asn Met Lys Ala Ile Lys Gly Leu Glu Asp Arg
        355                 360                 365


Leu Tyr Ala Leu Asp Gln Met Ile Ala Ser Cys Gly Arg Leu Val Asn
    370                 375                 380


Glu Gln Lys Glu Leu Ala Gln Gly Phe Leu Ala Asn Gln Lys Arg Ala
385                 390                 395                 400


Glu Asn Leu Lys Asp Ala Ser Val Leu Pro Asp Leu Cys Leu Ser His
                405                 410                 415


Ala Asn Gln Leu Met Ile Met Leu Gln Asn His Arg Lys Leu Leu Asp
            420                 425                 430


Ile Lys Gln Lys Cys Thr Thr Ala Lys Gln Glu Leu Ala Asn Asn Leu
        435                 440                 445
```

```
His Val Arg Leu Lys Trp Cys Cys Phe Val Met Leu His Ala Asp Gln
    450                 455                 460

Asp Gly Glu Lys Leu Gln Ala Leu Leu Arg Leu Val Ile Glu Leu Leu
465                 470                 475                 480

Glu Arg Val Lys Ile Val Glu Ala Leu Ser Thr Val Pro Gln Met Tyr
                485                 490                 495

Cys Leu Ala Val Val Glu Val Val Arg Arg Lys Met Phe Ile Lys His
            500                 505                 510

Tyr Arg Glu Trp Ala Gly Ala Leu Val Lys Asp Gly Lys Arg Leu Tyr
        515                 520                 525

Glu Ala Glu Lys Ser Lys Arg Glu Ser Phe Gly Lys Leu Phe Arg Lys
    530                 535                 540

Ser Phe Leu Arg Asn Arg Leu Phe Arg Gly Leu Asp Ser Trp Pro Pro
545                 550                 555                 560

Ser Phe Cys Thr Gln Lys Pro Arg Lys Phe Asp Cys Glu Leu Pro Asp
                565                 570                 575

Ile Ser Leu Lys Asp Leu Gln Phe Leu Gln Ser Phe Cys Pro Ser Glu
            580                 585                 590

Val Gln Pro Phe Leu Arg Val Pro Leu Leu Cys Asp Phe Glu Pro Leu
        595                 600                 605

His Gln His Val Leu Ala Leu His Asn Leu Val Lys Ala Ala Gln Ser
    610                 615                 620

Leu Asp Glu Met Ser Gln Thr Ile Thr Asp Leu Leu Ser Glu Gln Lys
625                 630                 635                 640

Ala Ser Val Ser Gln Thr Ser Pro Gln Ser Ala Ser Ser Pro Arg Met
                645                 650                 655

Glu Ser Thr Ala Gly Ile Thr Thr Thr Thr Ser Pro Arg Thr Pro Pro
            660                 665                 670

Pro Leu Thr Val Gln Asp Pro Leu Cys Pro Ala Val Cys Pro Leu Glu
        675                 680                 685
```

```
Glu Leu Ser Pro Asp Ser Ile Asp Ala His Thr Phe Asp Phe Glu Thr
    690                 695                 700


Ile Pro His Pro Asn Ile Glu Gln Thr Ile His Gln Val Ser Leu Asp
705                 710                 715                 720


Leu Asp Ser Leu Ala Glu Ser Pro Glu Ser Asp Phe Met Ser Ala Val
                725                 730                 735


Asn Glu Phe Val Ile Glu Glu Asn Leu Ser Ser Pro Asn Pro Ile Ser
            740                 745                 750


Asp Pro Gln Ser Pro Glu Met Met Val Glu Ser Leu Tyr Ser Ser Val
        755                 760                 765


Ile Asn Ala Ile Asp Ser Arg Arg Met Gln Asp Thr Asn Val Cys Gly
    770                 775                 780


Lys Glu Asp Phe Gly Asp His Thr Ser Leu Asn Val Gln Leu Glu Arg
785                 790                 795                 800


Cys Arg Val Val Ala Gln Asp Ser His Phe Ser Ile Gln Thr Ile Lys
                805                 810                 815


Glu Asp Leu Cys His Phe Arg Thr Phe Val Gln Lys Glu Gln Cys Asp
            820                 825                 830


Phe Ser Asn Ser Leu Lys Cys Thr Ala Val Glu Ile Arg Asn Ile Ile
        835                 840                 845


Glu Lys Val Lys Cys Ser Leu Glu Ile Thr Leu Lys Glu Lys His Gln
    850                 855                 860


Lys Glu Leu Leu Ser Leu Lys Asn Glu Tyr Glu Gly Lys Leu Asp Gly
865                 870                 875                 880


Leu Ile Lys Glu Thr Glu Glu Asn Glu Asn Lys Ile Lys Lys Leu Lys
                885                 890                 895


Gly Glu Leu Val Cys Leu Glu Glu Val Leu Gln Asn Lys Asp Asn Glu
            900                 905                 910


Phe Ala Leu Val Lys His Glu Lys Glu Ala Val Ile Cys Leu Gln Asn
        915                 920                 925
```

Glu Lys Asp Gln Lys Leu Leu Glu Met Glu Asn Ile Met His Ser Gln
930 935 940

Asn Cys Glu Ile Lys Glu Leu Lys Gln Ser Arg Glu Ile Val Leu Glu
945 950 955 960

Asp Leu Lys Lys Leu His Val Glu Asn Asp Glu Lys Leu Gln Leu Leu
965 970 975

Arg Ala Glu Leu Gln Ser Leu Glu Gln Ser His Leu Lys Glu Leu Glu
980 985 990

Asp Thr Leu Gln Val Arg His Ile Gln Glu Phe Glu Lys Val Met Thr
995 1000 1005

Asp His Arg Val Ser Leu Glu Glu Leu Lys Lys Glu Asn Gln Gln
1010 1015 1020

Ile Ile Asn Gln Ile Gln Glu Ser His Ala Glu Ile Ile Gln Glu
1025 1030 1035

Lys Glu Lys Gln Leu Gln Glu Leu Lys Leu Lys Val Ser Asp Leu
1040 1045 1050

Ser Asp Thr Arg Cys Lys Leu Glu Val Glu Leu Ala Leu Lys Glu
1055 1060 1065

Ala Glu Thr Asp Glu Ile Lys Ile Leu Leu Glu Glu Ser Arg Ala
1070 1075 1080

Gln Gln Lys Glu Thr Leu Lys Ser Leu Leu Glu Gln Glu Thr Glu
1085 1090 1095

Asn Leu Arg Thr Glu Ile Ser Lys Leu Asn Gln Lys Ile Gln Asp
1100 1105 1110

Asn Asn Glu Asn Tyr Gln Val Gly Leu Ala Glu Leu Arg Thr Leu
1115 1120 1125

Met Thr Ile Glu Lys Asp Gln Cys Ile Ser Glu Leu Ile Ser Arg
1130 1135 1140

His Glu Glu Glu Ser Asn Ile Leu Lys Ala Glu Leu Asn Lys Val
1145 1150 1155

```
Thr Ser  Leu His Asn Gln Ala  Phe Glu Ile Glu Lys  Asn Leu Lys
    1160                 1165                 1170


Glu Gln  Ile Ile Glu Leu Gln  Ser Lys Leu Asp Ser  Glu Leu Ser
    1175                 1180                 1185


Ala Leu  Glu Arg Gln Lys Asp  Glu Lys Ile Thr Gln  Gln Glu Glu
    1190                 1195                 1200


Lys Tyr  Glu Ala Ile Ile Gln  Asn Leu Glu Lys Asp  Arg Gln Lys
    1205                 1210                 1215


Leu Val  Ser Ser Gln Glu Gln  Asp Arg Glu Gln Leu  Ile Gln Lys
    1220                 1225                 1230


Leu Asn  Cys Glu Lys Asp Glu  Ala Ile Gln Thr Ala  Leu Lys Glu
    1235                 1240                 1245


Phe Lys  Leu Glu Arg Glu Val  Val Glu Lys Glu Leu  Leu Glu Lys
    1250                 1255                 1260


Val Lys  His Leu Glu Asn Gln  Ile Ala Lys Ser Pro  Ala Ile Asp
    1265                 1270                 1275


Ser Thr  Arg Gly Asp Ser Ser  Ser Leu Val Ala Glu  Leu Gln Glu
    1280                 1285                 1290


Lys Leu  Gln Glu Glu Lys Ala  Lys Phe Leu Glu Gln  Leu Glu Glu
    1295                 1300                 1305


Gln Glu  Lys Arg Lys Asn Glu  Glu Met Gln Asn Val  Arg Thr Ser
    1310                 1315                 1320


Leu Ile  Ala Glu Gln Gln Thr  Asn Phe Asn Thr Val  Leu Thr Arg
    1325                 1330                 1335


Glu Lys  Met Arg Lys Glu Asn  Ile Ile Asn Asp Leu  Ser Asp Lys
    1340                 1345                 1350


Leu Lys  Ser Thr Met Gln Gln  Gln Glu Arg Asp Lys  Asp Leu Ile
    1355                 1360                 1365


Glu Ser  Leu Ser Glu Asp Arg  Ala Arg Leu Leu Glu  Glu Lys Lys
    1370                 1375                 1380
```

```
Lys Leu  Glu Glu Glu Val Ser  Lys Leu Arg Ser Ser  Ser Phe Val
    1385                 1390                 1395


Pro Ser  Pro Tyr Val Ala Thr  Ala Pro Glu Leu Tyr  Gly Ala Cys
    1400                 1405                 1410


Ala Pro  Glu Leu Pro Gly Glu  Ser Asp Arg Ser Ala  Val Glu Thr
    1415                 1420                 1425


Ala Asp  Glu Gly Arg Val Asp  Ser Ala Met Glu Thr  Ser Met Met
    1430                 1435                 1440


Ser Val  Gln Glu Asn Ile His  Met Leu Ser Glu Glu  Lys Gln Arg
    1445                 1450                 1455


Ile Met  Leu Leu Glu Arg Thr  Leu Gln Leu Lys Glu  Glu Glu Asn
    1460                 1465                 1470


Lys Arg  Leu Asn Gln Arg Leu  Met Ser Gln Ser Met  Ser Ser Val
    1475                 1480                 1485


Ser Ser  Arg His Ser Glu Lys  Ile Ala Ile Arg Asp  Phe Gln Val
    1490                 1495                 1500


Gly Asp  Leu Val Leu Ile Ile  Leu Asp Glu Arg His  Asp Asn Tyr
    1505                 1510                 1515


Val Leu  Phe Thr Val Ser Pro  Thr Leu Tyr Phe Leu  His Ser Glu
    1520                 1525                 1530


Ser Leu  Pro Ala Leu Asp Leu  Lys Pro Ala Ser Gly  Ala Ser Arg
    1535                 1540                 1545


Arg Pro  Trp Val Leu Gly Lys  Val Met Glu Lys Glu  Tyr Cys Gln
    1550                 1555                 1560


Ala Lys  Lys Ala Gln Asn Arg  Phe Lys Val Pro Leu  Gly Thr Lys
    1565                 1570                 1575


Phe Tyr  Arg Val Lys Ala Val  Ser Trp Asn Lys Lys  Val
    1580                 1585                 1590


<210>  164
<211>  1594
```

```
<212>  PRT
<213>  Homo sapiens

<400>  164

Met Lys Leu Tyr Val Phe Leu Val Asn Thr Gly Thr Thr Leu Thr Phe
1               5                   10                  15


Asp Thr Glu Leu Thr Val Gln Thr Val Ala Asp Leu Lys His Ala Ile
            20                  25                  30


Gln Ser Lys Tyr Lys Ile Ala Ile Gln His Gln Val Leu Val Val Asn
        35                  40                  45


Gly Gly Glu Cys Met Ala Ala Asp Arg Arg Val Cys Thr Tyr Ser Ala
    50                  55                  60


Gly Thr Asp Thr Asn Pro Ile Phe Leu Phe Asn Lys Glu Met Ile Leu
65                  70                  75                  80


Cys Asp Arg Pro Pro Ala Ile Pro Lys Thr Thr Phe Ser Thr Glu Asn
                85                  90                  95


Asp Met Glu Ile Lys Val Glu Glu Ser Leu Met Met Pro Ala Val Phe
            100                 105                 110


His Thr Val Ala Ser Arg Thr Gln Leu Ala Leu Glu Met Tyr Glu Val
        115                 120                 125


Ala Lys Lys Leu Cys Ser Phe Cys Glu Gly Leu Val His Asp Glu His
    130                 135                 140


Leu Gln His Gln Gly Trp Ala Ala Ile Met Ala Asn Leu Glu Asp Cys
145                 150                 155                 160


Ser Asn Ser Tyr Gln Lys Leu Leu Phe Lys Phe Glu Ser Ile Tyr Ser
                165                 170                 175


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


Gly Thr Ala Val Ser Val Met Ala Lys Ile Pro Leu Leu Glu Cys Leu
        195                 200                 205
```

```
Thr Arg His Ser Tyr Arg Glu Cys Leu Gly Arg Leu Asp Ser Leu Pro
    210                 215                 220

Glu His Glu Asp Ser Glu Lys Ala Glu Met Lys Arg Ser Thr Glu Leu
225                 230                 235                 240

Val Leu Ser Pro Asp Met Pro Arg Thr Thr Asn Glu Ser Leu Leu Thr
                245                 250                 255

Ser Phe Pro Lys Ser Val Glu His Val Ser Pro Asp Thr Ala Asp Ala
            260                 265                 270

Glu Ser Gly Lys Glu Ile Arg Glu Ser Cys Gln Ser Thr Val His Gln
        275                 280                 285

Gln Asp Glu Thr Thr Ile Asp Thr Lys Asp Gly Asp Leu Pro Phe Phe
    290                 295                 300

Asn Val Ser Leu Leu Asp Trp Ile Asn Val Gln Asp Arg Pro Asn Asp
305                 310                 315                 320

Val Glu Ser Leu Val Arg Lys Cys Phe Asp Ser Met Ser Arg Leu Asp
                325                 330                 335

Pro Arg Ile Ile Arg Pro Phe Ile Ala Glu Cys Arg Gln Thr Ile Ala
            340                 345                 350

Lys Leu Asp Asn Gln Asn Met Lys Ala Ile Lys Gly Leu Glu Asp Arg
        355                 360                 365

Leu Tyr Ala Leu Asp Gln Met Ile Ala Ser Cys Gly Arg Leu Val Asn
    370                 375                 380

Glu Gln Lys Glu Leu Ala Gln Gly Phe Leu Ala Asn Gln Lys Arg Ala
385                 390                 395                 400

Glu Asn Leu Lys Asp Ala Ser Val Leu Pro Asp Leu Cys Leu Ser His
                405                 410                 415

Ala Asn Gln Leu Met Ile Met Leu Gln Asn His Arg Lys Leu Leu Asp
            420                 425                 430

Ile Lys Gln Lys Cys Thr Thr Ala Lys Gln Glu Leu Ala Asn Asn Leu
        435                 440                 445
```

```
His Val Arg Leu Lys Trp Cys Cys Phe Val Met Leu His Ala Asp Gln
    450                 455                 460


Asp Gly Glu Lys Leu Gln Ala Leu Leu Arg Leu Val Ile Glu Leu Leu
465                 470                 475                 480


Glu Arg Val Lys Ile Val Glu Ala Leu Ser Thr Val Pro Gln Met Tyr
                485                 490                 495


Cys Leu Ala Val Val Glu Val Val Arg Arg Lys Met Phe Ile Lys His
            500                 505                 510


Tyr Arg Glu Trp Ala Gly Ala Leu Val Lys Asp Gly Lys Arg Leu Tyr
        515                 520                 525


Glu Ala Glu Lys Ser Lys Arg Glu Ser Phe Gly Lys Leu Phe Arg Lys
    530                 535                 540


Ser Phe Leu Arg Asn Arg Leu Phe Arg Gly Leu Asp Ser Trp Pro Pro
545                 550                 555                 560


Ser Phe Cys Thr Gln Lys Pro Arg Lys Phe Asp Cys Glu Leu Pro Asp
                565                 570                 575


Ile Ser Leu Lys Asp Leu Gln Phe Leu Gln Ser Phe Cys Pro Ser Glu
            580                 585                 590


Val Gln Pro Phe Leu Arg Val Pro Leu Leu Cys Asp Phe Glu Pro Leu
        595                 600                 605


His Gln His Val Leu Ala Leu His Asn Leu Val Lys Ala Ala Gln Ser
    610                 615                 620


Leu Asp Glu Met Ser Gln Thr Ile Thr Asp Leu Leu Ser Glu Gln Lys
625                 630                 635                 640


Ala Ser Val Ser Gln Thr Ser Pro Gln Ser Ala Ser Ser Pro Arg Met
                645                 650                 655


Glu Ser Thr Ala Gly Ile Thr Thr Thr Thr Ser Pro Arg Thr Pro Pro
            660                 665                 670


Pro Leu Thr Val Gln Asp Pro Leu Cys Pro Ala Val Cys Pro Leu Glu
        675                 680                 685
```

```
Glu Leu Ser Pro Asp Ser Ile Asp Ala His Thr Phe Asp Phe Glu Thr
    690                 695                 700

Ile Pro His Pro Asn Ile Glu Gln Thr Ile His Gln Val Ser Leu Asp
705                 710                 715                 720

Leu Asp Ser Leu Ala Glu Ser Pro Glu Ser Asp Phe Met Ser Ala Val
                725                 730                 735

Asn Glu Phe Val Ile Glu Glu Asn Leu Ser Ser Pro Asn Pro Ile Ser
            740                 745                 750

Asp Pro Gln Ser Pro Glu Met Met Val Glu Ser Leu Tyr Ser Ser Val
        755                 760                 765

Ile Asn Ala Ile Asp Ser Arg Arg Met Gln Asp Thr Asn Val Cys Gly
    770                 775                 780

Lys Glu Asp Phe Gly Asp His Thr Ser Leu Asn Val Gln Leu Glu Arg
785                 790                 795                 800

Cys Arg Val Val Ala Gln Asp Ser His Phe Ser Ile Gln Thr Ile Lys
                805                 810                 815

Glu Asp Leu Cys His Phe Arg Thr Phe Val Gln Lys Glu Gln Cys Asp
            820                 825                 830

Phe Ser Asn Ser Leu Lys Cys Thr Ala Val Glu Ile Arg Asn Ile Ile
        835                 840                 845

Glu Lys Val Lys Cys Ser Leu Glu Ile Thr Leu Lys Glu Lys His Gln
    850                 855                 860

Lys Glu Leu Leu Ser Leu Lys Asn Glu Tyr Glu Gly Lys Leu Asp Gly
865                 870                 875                 880

Leu Ile Lys Glu Thr Glu Glu Asn Glu Asn Lys Ile Lys Lys Leu Lys
                885                 890                 895

Gly Glu Leu Val Cys Leu Glu Glu Val Leu Gln Asn Lys Asp Asn Glu
            900                 905                 910

Phe Ala Leu Val Lys His Glu Lys Glu Ala Val Ile Cys Leu Gln Asn
        915                 920                 925
```

```
Glu Lys Asp Gln Lys Leu Leu Glu Met Glu Asn Ile Met His Ser Gln
    930                 935                 940


Asn Cys Glu Ile Lys Glu Leu Lys Gln Ser Arg Glu Ile Val Leu Glu
945                 950                 955                 960


Asp Leu Lys Lys Leu His Val Glu Asn Asp Glu Lys Leu Gln Leu Leu
                965                 970                 975


Arg Ala Glu Leu Gln Ser Leu Glu Gln Ser His Leu Lys Glu Leu Glu
            980                 985                 990


Asp Thr Leu Gln Val Arg His Ile  Gln Glu Phe Glu Lys  Val Met Thr
        995                 1000                 1005


Asp His  Arg Val Ser Leu Glu  Glu Leu Lys Lys Glu  Asn Gln Gln
    1010                 1015                 1020


Ile Ile  Asn Gln Ile Gln Glu  Ser His Ala Glu Ile  Ile Gln Glu
    1025                 1030                 1035


Lys Glu  Lys Gln Leu Gln Glu  Leu Lys Leu Lys Val  Ser Asp Leu
    1040                 1045                 1050


Ser Asp  Thr Arg Cys Lys Leu  Glu Val Glu Leu Ala  Leu Lys Glu
    1055                 1060                 1065


Ala Glu  Thr Asp Glu Ile Lys  Ile Leu Leu Glu Glu  Ser Arg Ala
    1070                 1075                 1080


Gln Gln  Lys Glu Thr Leu Lys  Ser Leu Leu Glu Gln  Glu Thr Glu
    1085                 1090                 1095


Asn Leu  Arg Thr Glu Ile Ser  Lys Leu Asn Gln Lys  Ile Gln Asp
    1100                 1105                 1110


Asn Asn  Glu Asn Tyr Gln Val  Gly Leu Ala Glu Leu  Arg Thr Leu
    1115                 1120                 1125


Met Thr  Ile Glu Lys Asp Gln  Cys Ile Ser Glu Leu  Ile Ser Arg
    1130                 1135                 1140


His Glu  Glu Glu Ser Asn Ile  Leu Lys Ala Glu Leu  Asn Lys Val
    1145                 1150                 1155
```

Thr Ser Leu His Asn Gln Ala Phe Glu Ile Glu Lys Asn Leu Lys
1160 1165 1170

Glu Gln Ile Ile Glu Leu Gln Ser Lys Leu Asp Ser Glu Leu Ser
1175 1180 1185

Ala Leu Glu Arg Gln Lys Asp Glu Lys Ile Thr Gln Gln Glu Glu
1190 1195 1200

Lys Tyr Glu Ala Ile Ile Gln Asn Leu Glu Lys Asp Arg Gln Lys
1205 1210 1215

Leu Val Ser Ser Gln Glu Gln Asp Arg Glu Gln Leu Ile Gln Lys
1220 1225 1230

Leu Asn Cys Glu Lys Asp Glu Ala Ile Gln Thr Ala Leu Lys Glu
1235 1240 1245

Phe Lys Leu Glu Arg Glu Val Val Glu Lys Glu Leu Leu Glu Lys
1250 1255 1260

Val Lys His Leu Glu Asn Gln Ile Ala Lys Ser Pro Ala Ile Asp
1265 1270 1275

Ser Thr Arg Gly Asp Ser Ser Ser Leu Val Ala Glu Leu Gln Glu
1280 1285 1290

Lys Leu Gln Glu Glu Lys Ala Lys Phe Leu Glu Gln Leu Glu Glu
1295 1300 1305

Gln Glu Lys Arg Lys Asn Glu Glu Met Gln Asn Val Arg Thr Ser
1310 1315 1320

Leu Ile Ala Glu Gln Gln Thr Asn Phe Asn Thr Val Leu Thr Arg
1325 1330 1335

Glu Lys Met Arg Lys Glu Asn Ile Ile Asn Asp Leu Ser Asp Lys
1340 1345 1350

Leu Lys Ser Thr Met Gln Gln Gln Glu Arg Asp Lys Asp Leu Ile
1355 1360 1365

Glu Ser Leu Ser Glu Asp Arg Ala Arg Leu Leu Glu Glu Lys Lys
1370 1375 1380

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Lys Leu  Glu Glu Glu Val Ser  Lys Leu Arg Ser Ser  Ser Phe Val
    1385                 1390                 1395

Pro Ser  Pro Tyr Val Ala Thr  Ala Pro Glu Leu Tyr  Gly Ala Cys
    1400                 1405                 1410

Ala Pro  Glu Leu Pro Gly Glu  Ser Asp Arg Ser Ala  Val Glu Thr
    1415                 1420                 1425

Ala Asp  Glu Gly Arg Val Asp  Ser Ala Met Glu Thr  Ser Met Met
    1430                 1435                 1440

Ser Val  Gln Glu Asn Ile His  Met Leu Ser Glu Glu  Lys Gln Arg
    1445                 1450                 1455

Ile Met  Leu Leu Glu Arg Thr  Leu Gln Leu Lys Glu  Glu Glu Asn
    1460                 1465                 1470

Lys Arg  Leu Asn Gln Arg Leu  Met Ser Gln Ser Met  Ser Ser Val
    1475                 1480                 1485

Ser Ser  Arg His Ser Glu Lys  Ile Ala Ile Arg Asp  Phe Gln Val
    1490                 1495                 1500

Gly Asp  Leu Val Leu Ile Ile  Leu Asp Glu Arg His  Asp Asn Tyr
    1505                 1510                 1515

Val Leu  Phe Thr Val Ser Pro  Thr Leu Tyr Phe Leu  His Ser Glu
    1520                 1525                 1530

Ser Leu  Pro Ala Leu Asp Leu  Lys Pro Gly Glu Gly  Ala Ser Gly
    1535                 1540                 1545

Ala Ser  Arg Arg Pro Trp Val  Leu Gly Lys Val Met  Glu Lys Glu
    1550                 1555                 1560

Tyr Cys  Gln Ala Lys Lys Ala  Gln Asn Arg Phe Lys  Val Pro Leu
    1565                 1570                 1575

Gly Thr  Lys Phe Tyr Arg Val  Lys Ala Val Ser Trp  Asn Lys Lys
    1580                 1585                 1590

Val
```