

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00034117 00000005

Fecha (AMD): 2003-05-26 16:38:58

Tramite : 002 PATENTES D 1 REGISTRO/

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 55

329 CUMPLEMEN

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 34,517
FECHA : MAYO 19 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	15534322	19/05/2003	33,381,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LEMAS COMERCIALES	82,000.00
		TOTAL :	\$ 82,000.00

SON: OCHENTA Y DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Qdo 13736-005-073-3

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375
2005-05-19.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Emilio Ferrero
Apoderado

Oficio N°
00-34117-002-001-430-015

REFERENCIA	Radicación	00 34117
	Trámite	002
	Evento	001
	Actuación	430
	Folios	015

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 34117, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 2-39
- . Ejemplos: folios 39-59
- . Capítulo reivindicatorio estudiado: folios 160-174
- . Se reivindica prioridad, presentada en Estados Unidos el 01.05.99, bajo el número 60/134136

Objeto de la invención

Según las reivindicaciones 1 a 31 de la presente solicitud, se refiere a compuestos de fórmula (I), cuyos sustituyentes se revelan en la descripción. Dichos compuestos tienen un sitio de escisión que es reconocido por FAP-alfa.

Clasificación internacional de patentes A 61 K 38/04

Claridad de la solicitud

El art. 30 de la decisión 486 contempla que *“Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción”*

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Teniendo en cuenta lo anterior, el término “Derivados de antraciclina” usado en las reivindicaciones 1, 5, 6, 11, 27 y 31 hace que el ámbito de protección de dicha reivindicación no sea claro.

Favor hacer las aclaraciones y correcciones del caso

Excepciones a la patentabilidad

El art. 20 d de la decisión 486 contempla que *“No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*

El contenido de las reivindicaciones 28 y 29 que trata de “Un método para el tratamiento del cáncer...”, no es patentable.

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*

De acuerdo a lo anterior, el contenido de las reivindicaciones 20 y 30 no es patentable, debido a que la legislación vigente contempla únicamente los productos y procedimientos como objetos de patente.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 14.05.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	WO 9712624	“Péptidos novedosos”	10.04.97
2	WO 9734927	“Proteína alfa de activación de los fibroblastos dimérica aislada”	25.09.97

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 establece que *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”*

WO 9712624 provee una prodroga para el tratamiento del cáncer de próstata. El péptido es diseñado para llevar el conjugado específicamente al antígeno prostático específico. En la página 47 se revelan dos compuestos excluidos dentro del alcance de la presente solicitud, se puede esperar que dichos compuestos sean también sustratos para FAP-alfa.

WO 9734327 se relaciona con el aislamiento y uso de la FAP-alfa. Se revelan que los dipéptidos Ala-Pro, Gly-Pro y Lys-Pro como sustratos para FAP-alfa. También se publican métodos para determinar la actividad de la FAP-alfa usando el conjugado Ala-Pro-AFC.

Teniendo en cuenta el objeto de la solicitud, el cual es proveer compuestos conjugados de péptidos y agentes citotóxicos o citostáticos, es una derivación evidente del estado de la técnica ya que la combinación de las enseñanzas de los documentos citados enseñarían a una persona versada en la materia a sintetizar los compuestos de la presente solicitud.

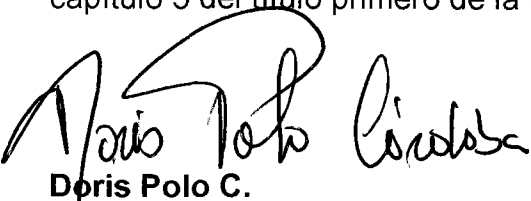
Finalmente no se demuestran propiedades sorprendentes o inesperadas de los compuestos de la presente solicitud en comparación con los del estado de la técnica.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9712624	1-19, 21-27, 31	Nivel Inventivo
2	WO 9734927	1-19, 21-27, 31	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001



Doris Polo C.
Jefe de la División de Nuevas Creaciones (e)

El anterior requerimiento fue notificado por fijación en lista, de fecha 19 MAYO 2005

CONCEPTO TÉCNICO Número 0626	EXAMINADOR TÉCNICO Código 202024
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19 May 2008

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 38/00, C07K 5/10, 7/06, 14/00	A1	(11) International Publication Number: WO 97/12624 (43) International Publication Date: 10 April 1997 (10.04.97)
(21) International Application Number: PCT/US96/15713 (22) International Filing Date: 2 October 1996 (02.10.96) (30) Priority Data: 08/540,412 6 October 1995 (06.10.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/540,412 (CIP) Filed on 6 October 1995 (06.10.95) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DeFEO-JONES, Deborah [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). FENG, Dong-Mei [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GARSKY, Victor, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). JONES, Raymond, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). OLIFF, Allen, I. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).	(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: NOVEL PEPTIDES (57) Abstract Oligopeptides which comprise amino acid sequences that are recognized and proteolytically cleaved by free prostate specific antigen (PSA) are described. Also described are assays which comprise such oligopeptides useful for determining free PSA protease activity in vitro and in vivo. Therapeutic agents which comprise conjugates of such oligopeptides and known cytotoxic agents are also described.		

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Ac—AlaAsnLysIleSerTyrGlnSerSerSerThr— (SEQ.ID.NO.: 117),

Ac—AlaAsnLysIleSerTyrGlnSerSerSerThrLeu— (SEQ.ID.NO.: 70),

Ac—AlaAsnLysAlaSerTyrGlnSerAlaSerThrLeu— (SEQ.ID.NO.: 118),

Ac—AlaAsnLysAlaSerTyrGlnSerAlaSerLeu— (SEQ.ID.NO.: 119),

Ac—AlaAsnLysAlaSerTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 120),

Ac—AlaAsnLysAlaSerTyrGlnSerSerLeu— (SEQ.ID.NO.: 121).

Ac—SerTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 144),

Ac—hArgTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 145).

Ac—LysTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 124), or
(Compound 4)Ac—LysTyrGlnSerSerNle— (SEQ.ID.NO.: 146).
N-terminus

or the pharmaceutically acceptable salt thereof.

Further examples of conjugates of an oligopeptide and doxorubicin wherein the N-terminus of the oligopeptide is acylated and the C-terminus of the oligopeptide is attached to the doxorubicin at the 3'-amine are as follows:

Ac-hArgTyrGln-SerSerPro-dox(3') (SEQ.ID.NO.: 151)

Ac-hArgTyrGln-SerPro-dox(3') (SEQ.ID.NO.: 177)

Ac-hArgTyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 154)

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WHAT IS CLAIMED IS:

1. A pharmaceutically acceptable salt of an oligopeptide that comprises a sequence of amino acids that is recognized and selectively proteolytically cleaved by free prostate specific antigen.

2. The pharmaceutically acceptable salt according to Claim 1 wherein the sequence of amino acids is

- a) AsnLysIleSerTyrGlnIleSer (SEQ.ID.NO.: 13),
- b) LysIleSerTyrGlnIleSer (SEQ.ID.NO.: 14),
- c) GlyGluAsnGlyValGlnLysAspValSerGlnXaaSerIleTyrIleSerGlnThrGlu (SEQ.ID.NO.: 15),
- d) GlyLysGlyIleSerSerGlnTyrIleSerAsnThrGluGluArgLeu (SEQ.ID.NO.: 2),
- e) AsnLysIleSerTyrTyrIleSer (SEQ.ID.NO.: 127),
- f) AsnLysAlaSerTyrGlnIleSer (SEQ.ID.NO.: 128),
- g) SerTyrGlnIleSerSer (SEQ.ID.NO.: 129);
- h) LysTyrGlnIleSerSer (SEQ.ID.NO.: 140);
- i) hArgTyrGlnIleSerSer (SEQ.ID.NO.: 141);

wherein hArg is homoarginine and Xaa is any natural amino acid.

3. The pharmaceutically acceptable salt according to Claim 2 wherein the sequence of amino acids is

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- a) AsnLysIleSerTyrGlnSerSer (SEQ.ID.NO.: 16),
- b) AsnLysIleSerTyrGlnSerAla (SEQ.ID.NO.: 130),
- c) AsnLysIleSerTyrGlnSerSerSer (SEQ.ID.NO.: 17),
- d) AlaAsnLysIleSerTyrGlnSerSerSer (SEQ.ID.NO.: 18),
- e) LysIleSerTyrGlnSerSerSerThrGlu (SEQ.ID.NO.: 19),
- f) GlyGluAsnGlyValGlnLysAspValSerGlnArgSerIleTyrSerGlnThrGlu (SEQ.ID.NO.: 4),
- g) GlyGluAsnGlyValGlnLysAspValSerGlnSerSerIleTyrSerGlnThrGlu (SEQ.ID.NO.: 5),
- h) AlaAsnLysIleSerTyrTyrSer (SEQ.ID.NO.: 131),
- i) AlaAsnLysAlaSerTyrGlnSer (SEQ.ID.NO.: 132),
- j) SerTyrGlnSerSerThr (SEQ.ID.NO.: 133),
- k) SerTyrGlnSerSerSer (SEQ.ID.NO.: 134),
- l) LysTyrGlnSerSerSer (SEQ.ID.NO.: 142),
- m) hArgTyrGlnSerSerSer (SEQ.ID.NO.: 143), or
- n) SerTyrGlnSerSerLeu (SEQ.ID.NO.: 135).

4. The pharmaceutically acceptable salt according to Claim 2 wherein the amino acid sequence is

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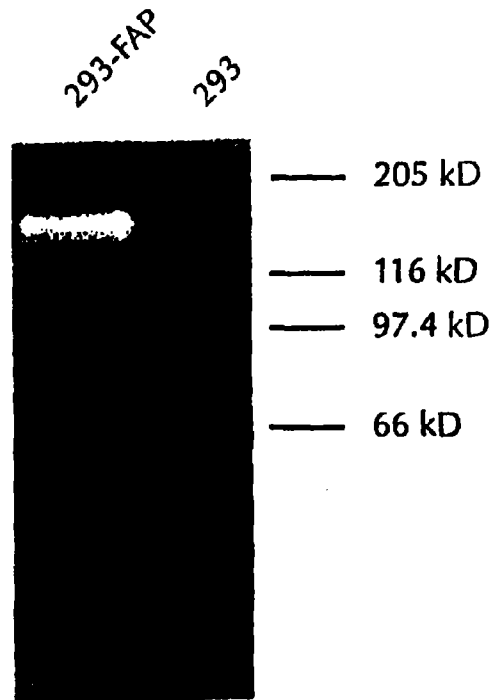
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 14/435, C12N 15/52, A61K 38/43, G01N 33/50, C12Q 1/00		A1	(11) International Publication Number: WO 97/34927 (43) International Publication Date: 25 September 1997 (25.09.97)
(21) International Application Number: PCT/US97/04215 (22) International Filing Date: 12 March 1997 (12.03.97) (30) Priority Data: 08/619,280 18 March 1996 (18.03.96) US (60) Parent Application or Grant (63) Related by Continuation US 08/619,280 (CIP) Filed on 18 March 1996 (18.03.96) (71) Applicants (for all designated States except US): LUDWIG INSTITUTE FOR CANCER RESEARCH [CH/US]; 1345 Avenue of the Americas, New York, NY 10105 (US). BOEHRINGER INGELHEIM INTERNATIONAL GMBH [DE/DE]; D-55216 Ingelheim am Rhein (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): ZIMMERMAN, Rainer [DE/DE]; Laurenbuhlstrasse 17, D-88441 Mittelbiberach (DE). PARK, John, E. [US/DE]; Widdersteinstrasse 162, D-88400 Biberach (DE). RETTIG, Wolfgang [DE/DE]; Amriswilstrasse 7, D-88400 Biberach (DE). OLD, Lloyd,		J. [US/US]; 1345 Avenue of the Americas, New York, NY 10105 (US). (74) Agent: HANSON, Norman, D.; Felfe & Lynch, 805 Third Avenue, New York, NY 10022 (US). (81) Designated States: AU, BG, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.	

(54) Title: ISOLATED DIMERIC FIBROBLAST ACTIVATION PROTEIN ALPHA, AND USES THEREOF

(57) Abstract

The invention involves dimeric forms of the pro-
tein known as fibroblast activation protein alpha, or
"FAP α " and its uses.



coumarin, and Lys-Pro-7-amino-4-trifluoromethyl coumarin.

The results of these experiments are depicted, in part, in figure 3. This figure shows zymographic detection of gelatin degrading activity, in the cell extracts. See Kleiner et al., supra. A protein species of approximately 170 kilodaltons, as determined by SDS-PAGE, was observed to have gelatin degrading activity. This species, which was found in the 293-FAP cell line, but not in untransfected 293 cells, is thus identified as FAP α . The molecular weight is consistent with a dimer, i.e., a dimeric FAP α molecule.

The proteolytic activity described herein where gelatin is the substrate, was not observed when casein was the substrate.

Example 12

Further studies were then undertaken in order to characterize the 170 kD FAP α dimer further. Specifically, the experiments described in example 11 were repeated, except that 5% of 2-mercaptoethanol or 5 μ M iodoacetamide was added to the extracts prior to SDS-PAGE, or ethylenediamine N,N,N',N'-tetraacetic acid (10 mM) was added to the incubation buffer used for gelatin zymography. None of these treatments abolished the enzymatic activity. In contrast, heating at 100°C for five minutes prior to SDS-polyacrylamide gel electrophoresis abolished the gelatin-degrading activity.

Further work, using a membrane overlay assay, described by, e.g., Smith et al., Histochem J. 24(9): 643-647 (1992), incorporated by reference, revealed that the FAP α dimers were able to cleave all of the Ala-Pro, Gly-Pro, and Lys-Pro dipeptides tested.

In further experiments, a fusion protein was produced which comprised the extracellular domains of both FAP α and murine CD8 proteins. This chimeric protein was produced in a baculovirus system in insect cells. The chimeric protein exhibited the same enzymatic activity as FAP α , using the model discussed supra.

Example 13

Two quantitative assays for FAP α enzyme activity were developed using Ala-Pro-7-amino-4-trifluoromethyl coumarin (Ala-Pro-AFC) as the substrate. In the first assay format, membrane extracts of FAP α -expressing cells were mixed with a 5-10 fold volume of reaction buffer (100mM NaCl, 100mM Tris pH 7.8), and added to an equal volume of 0.5mM Ala-Pro-AFC in reaction buffer followed by an incubation for one hour at 37°C. Release of free AFC was then measured in a fluorimeter using a 395nm excitation / 530nm emission filter set. The membrane extracts analyzed in this assay format were derived from either 293-FAP α cells (293 cells stably transfected with vector FAP.38 described supra) or HT1080-FAP α cells (HT1080 cells stably transfected with vector FAP.38). Negative control experiments assessing FAP α -specific activities were carried out with membrane extracts prepared from the respective parental 293 or HT1080 cell lines. In the second assay, FAP α was isolated from 293-FAP α or HT1080-FAP α membrane extracts via an antibody specific for FAP α . Ninety-six well ELISA plates were coated overnight at 4°C with 1 μ g/ml F19 monoclonal antibody in phosphate-buffered saline (PBS). In the case of CD8-FAP α discussed infra plates were coated with F19 antibody as above or with 1 μ g/ml rat anti-mouse CD8 overnight at 4°C. Wells were then washed with wash buffer (PBS, 0.1% Tween 20). Excess binding sites were blocked with blocking buffer (5% bovine serum albumin in PBS) for 1 hour at room temperature. Blocking buffer was removed; membrane extracts of 293-FAP α expressing cells or control cells were added and incubated for 1 hour at room temperature. The unbound material was removed, wells were washed with wash buffer, and FAP α activity was assayed using 100 μ l Ala-Pro-AFC (0.5 mM Ala-Pro-AFC in reaction buffer) for one hour at 37°C. Release of free AFC was measured as above. Binding of mab F19 to FAP α did not measurably affect its enzymatic activity.

Example 14

Using assays for FAP α enzyme activity, described supra an inhibitor of FAP α enzymatic activity has been identified. This inhibitor is (S)-Valylpyrrolidine-2(R)-boronic acid (Snow

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Exemplary are CD8 peptide sequences, such as are described supra. The fact that FAP α has particular properties, as described herein, permits the identification of the molecule on cells expressing them. In turn, because the FAP α molecule is associated with tumors and tumor stromal cells, targeting of FAP α with therapeutic agents serves as a way to treat cancerous or precancerous condition, by administering sufficient therapeutic agent to alleviate cancer load.

The experiments showing the proteolytic properties of FAP α lead to yet a further aspect of the invention. It is well known that proteases which degrade extracellular matrix, or "ECM" proteins have an important role on certain aspects of tumor growth, including their effect on tumor cell invasion, tumor blood vessel formation (i.e., neoangiogenesis), and tumor metastasis. Collagens are of special interest vis-a-vis the substrates of proteases, as the collagens are an important part of the ECM. The fact that FAP α digests ECM suggests a therapeutic role for inhibitors of the molecule. "Inhibitors", as used herein, refers to molecules which interfere with FAP α enzyme function. Specifically excluded from such inhibitors is the monoclonal antibody F19. This mAb is known to bind to but not inhibit the enzyme function of FAP α , and hence it is not an inhibitor. The art is quite well versed with respect to monoclonal antibodies which both bind to and inhibit enzymes. Further examples of such inhibitors would include, e.g., substrate derivatives, such as modified collagen molecules, which interfere with the active site or sites of the FAP α molecule. Other suitable inhibitors will be apparent to the skilled artisan, and need not be listed here. In addition, the recombinant FAP α proteins and FAP α -transfected cell lines described supra can be employed in an enzymatic screening assay, using the substrate described supra or other suitable substrates, to identify inhibitors from any compound library. The identification of substances which interact with FAP α active molecules thereby leads to therapeutic treatment of conditions where a subject exhibit abnormal FAP α activity. Specifically, an amount of an

We claim:

1. Isolated, dimeric FAP α molecule, having a molecular weight of about 170 kilodaltons as determined by SDS-PAGE, wherein said dimeric FAP α molecule is capable of degrading extracellular matrix proteins.
2. The dimeric FAP α molecule of claim 1, wherein each monomer of said dimeric FAP α molecule consists of the amino acid sequence of SEQ ID NO: 2.
3. The dimeric FAP α molecule of claim 1, produced recombinantly.
4. The dimeric FAP α molecule of claim 3, produced by a eukaryotic cell.
5. Isolated protein consisting of:
 - (i) the FAP α catalytic domain, and
 - (ii) at least one portion of a non FAP α protein.
6. Method for cleaving a terminal dipeptide of formula Xaa-Pro from a molecule, comprising contacting said molecule with a second molecule, said second molecule having FAP α enzymatic activity.

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7. The method of claim 6, wherein said second molecule is isolated, dimeric FAP α .
8. The method of claim 6, wherein said second molecule comprises an FAP α catalytic domain.
9. Method for identifying a substance which interacts with a molecule having FAP α activity, comprising combining said molecule with a sample to be tested, and determining any interaction with said molecule as an indication of a molecule which interacts with a molecule having FAP α activity.
10. The method of claim 9, wherein said FAP α molecule is dimeric.
11. The method of claim 9, wherein said molecule comprises a FAP α catalytic domain.
12. The method of claim 9, wherein said substance is an antagonist of FAP α activity.
13. The method of claim 9, wherein said substance is an agonist of FAP α activity.
14. The method of claim 9, wherein said substance is an inhibitor of FAP α activity.
15. The method of claim 9, comprising combining said substance with a cell extract which has FAP α activity.
16. The method of claim 15, wherein said cell extract is an extract of a cell which has been transformed or transfected with a nucleic acid molecule which encodes a molecule with FAP α activity.
17. The method of claim 16, wherein said cell is a

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prokaryote.

18. The method of claim 16, wherein said cell is a eukaryote.
19. Method for treating a subject with a pathological condition characterized by abnormal FAP α activity, comprising administering to a subject in need thereof an amount of a substance which interacts with molecules having FAP α activity sufficient to normalize the FAP α activity level in said subject.
20. The method of claim 19, comprising administering an inhibitor of FAP α activity.
21. The method of claim 20, wherein said inhibitor is a collagen derivative.
22. The method of claim 20, wherein said inhibitor is (S) - Valyl-pyrrolidine-2(R) -boronic acid.
23. The method of claim 19, wherein said substance is an agonist of FAP α activity.
24. The method of claim 19, wherein said substance is an antagonist of FAP α activity.
25. Method for determining if a substance interacts with a molecule having FAP α activity, comprising combining said substance and said molecule with Ala-Pro-AFC, determining interaction of said molecule with Ala-Pro-AFC, and comparing said interaction to interaction of said molecule with Ala-Pro-AFC in the absence of said substance, wherein a difference therebetween indicate that said substance interactions with said molecule.
26. Fusion protein comprising a portion of an FAP α molecule sufficient to retain FAP α activity and a non FAP α amino

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acid sequence, wherein said fusion protein is water soluble.

27. The fusion protein of claim 26, wherein said non FAP α amino acid sequence is an amino acid sequence found in a CD8 protein.
28. The fusion protein of claim 27, wherein said CD8 protein is a murine protein.
29. The fusion protein of claim 27, wherein said CD8 protein is a human protein.
30. The fusion protein of claim 27 comprising amino acid 1 to 189 of murine CD8 linked to amino acids 27 through 760 of FAP α .