

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 July 2008 (03.07.2008)

PCT

(10) International Publication Number
WO 2008/077958 A3

(51) International Patent Classification:

G01N 33/68 (2006.01) **G06F 19/00** (2006.01)
G01N 33/574 (2006.01)

(21) International Application Number:

PCT/EP2007/064497

(22) International Filing Date:

21 December 2007 (21.12.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PA 2006 01709	22 December 2006 (22.12.2006)	DK
60/876,838	22 December 2006 (22.12.2006)	US
60/947,074	29 June 2007 (29.06.2007)	US
PA 2007 00956	29 June 2007 (29.06.2007)	DK

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

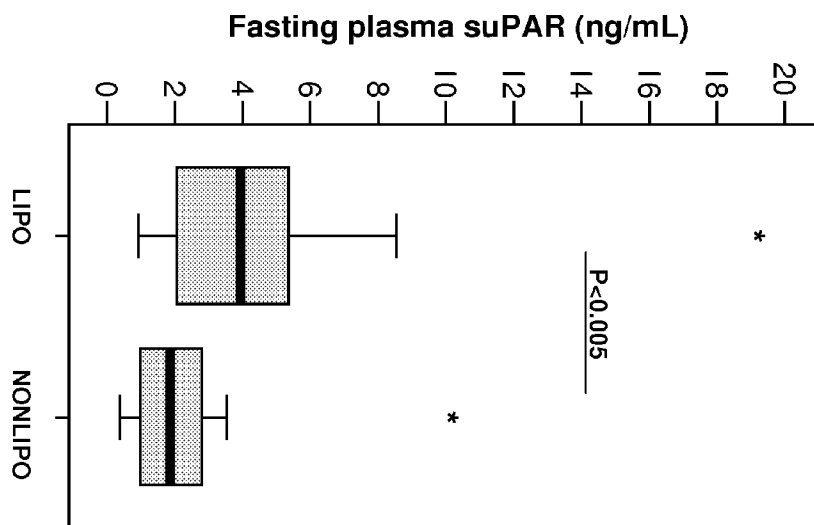
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

[Continued on next page]

(54) Title: SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR (SUPAR) AS MARKER FOR DISEASES



(57) Abstract: The invention concerns a marker for low-grade inflammation and metabolic syndrome (MS) and MS-related diseases and/or low-grade inflammation-related diseases such as cardiovascular disease, ischemic heart disease and type 2 diabetes. More particularly it concerns the measurement of the concentration of soluble urokinase plasminogen activator receptor (suPAR) in human biological fluids (sputum, cystic fluid, ascites, serum, plasma, urine) as a tool of diagnosing and/or prognosticating low-grade inflammation and metabolic syndrome and the risk of development of the related diseases such as cancer, cardiovascular disease, ischemic heart disease and type 2 diabetes.

WO 2008/077958 A3



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) **Date of publication of the international search report:**

2 April 2009

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/064497

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/68 G01N33/574 G06F19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

G01N G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SVENDSEN M N ET AL: "Preoperative concentrations of suPAR and MBL proteins are associated with the development of pneumonia after elective surgery for colorectal cancer." SURGICAL INFECTIONS, vol. 7, no. 5, October 2006 (2006-10), pages 463-471, XP002446703 the whole document in particular: abstract; p. 464, col. 1, last line to col. 2, l. 5. ----- -/--	1,4,6,7, 10-17, 29,30

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

8 January 2009

Date of mailing of the international search report

02/02/2009

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/064497

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MIZUKAMI I F ET AL: "Enzyme-linked immunoabsorbent assay detection of a soluble form of urokinase plasminogen activator receptor in vivo." BLOOD, vol. 86, no. 1, 1 July 1995 (1995-07-01), pages 203-211, XP002446706 the whole document in particular: abstract; p. 209, sentence spanning col.1+2.	1,4,6,7, 10-17, 29,30
X	OSTROWSKI S R ET AL: "Soluble Urokinase Receptor Levels in Plasma during 5 Years of Highly Active Antiretroviral Therapy in HIV-1-Infected Patients" J ACQUIR IMMUNE DEFIC SYNDR, vol. 35, no. 4, 1 April 2004 (2004-04-01), pages 337-342, XP002446705 the whole document in particular: abstract; p. 337, col. 2, l. 6-9; p. 338, par. spanning col. 1 and 2; p. 341, col. 2, par. 4 to p. 342, col. 1, par. 1; fig. 1.	1,4,5,7, 10-17, 29,30
X	OSTROWSKI S R ET AL: "Plasma levels of intact and cleaved urokinase receptor decrease in HIV-1-infected patients initiating highly active antiretroviral therapy" SCAND J IMMUNOL, vol. 63, no. 6, June 2006 (2006-06), pages 478-486, XP002446704 the whole document in particular: abstract; p. 483, col. 1, l. 37-45; p. 483, col. 2, l. 12-30; fig. 1. -& OSTROWSKI S R ET AL: "High plasma levels of intact and cleaved soluble urokinase receptor reflect immune activation and are independent predictors of mortality in HIV-1-infected patients." J ACQUIR IMMUNE DEFIC SYNDR, vol. 39, no. 1, 1 May 2005 (2005-05-01), pages 23-31, XP002488617 the whole document	1,4,5,7, 10-17, 29,30
X	WO 2005/116077 A (ATTENUON LLC; PERRY G C) 8 December 2005 (2005-12-08)	36,37
A	the whole document in particular: p. 43, last 2 par.; p. 49, par. 1; claims 1, 5, 7, 17, 25, 41, 49.	31-33
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/064497

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 248 712 B1 (DANOE K ET AL) 19 June 2001 (2001-06-19)	36, 37
A	the whole document in particular: col. 1, l. 23-28; par. spanning col. 12+13; par. spanning col. 16+17; col. 23, l. 21-24; claims 8, 9.	31, 34
X	WO 02/058714 A (SAN RAFFAELE CENTRO FOND; BLASI F; SIDENIUS N) 1 August 2002 (2002-08-01)	36, 37
A	the whole document in particular: claims 1, 6.	35
A	FLORDELLIS C S ET AL: "New therapeutic options for the metabolic syndrome: what's next?" TRENDS ENDOCRINOL METABOL, vol. 16, no. 6, August 2005 (2005-08), pages 254-260, XP004996563 the whole document	31-37, 69-71
A	KOH ET AL: "Inflammatory Markers and the Metabolic Syndrome" J AM COLLEGE CARDIOL, vol. 46, no. 11, 6 December 2005 (2005-12-06), pages 1978-1985, XP005191479 the whole document	31-37, 69-71
P, X	ANDERSEN O ET AL: "Soluble urokinase plasminogen activator receptor is a marker of dysmetabolism in HIV-infected patients receiving highly active antiretroviral therapy." J MED VIROL, vol. 80, no. 2, February 2008 (2008-02), pages 209-216, XP008094314 the whole document	1, 4-7, 10-17, 29-37, 69-71
X	WO 03/031650 A (BAYER AG; MUNNES M; GEHRMANN M; WICK M) 17 April 2003 (2003-04-17) the whole document in particular claim 3; sequence 114; table 2; p. 11, par. 3; p. 59, l. 26 to p. 65, l. 18; p. 83, par. 4.	2-4, 6-11, 38, 39, 42, 43, 48-50, 53, 54, 58, 59, 62, 63, 68-71

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/064497

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SLOAND E M ET AL: "A role for plasma urokinase plasminogen activator receptor (uPAR) in thrombosis in paroxysmal nocturnal hemoglobinuria (PNH)" BLOOD, vol. 104, no. 11, Part 1, November 2004 (2004-11), page 84A, XP008099893 & 46TH ANN MEETING AM SOC HEMATOL; SAN DIEGO, CA, USA; DEC 04 -07, 2004 abstract	2-4, 6-11,18, 19,22, 23,38, 39,42, 43, 48-50, 53,54, 58,59, 62,63, 68-71

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 7,13-19,22,23,29,30,69 comprise a step which is possibly surgical and therefore have to be considered as methods of treatment of the human/animal body by surgery, the search has been carried out in as far as no surgical step is involved.

Although claims 31-35,70,71 are directed to a method of treatment of the human/animal body by therapy, the search has been carried out and based on the alleged effects of the substance.

Continuation of Box II.2

Claims Nos.: 31-37 (incompletely)

Present claims 31-37 relate to substances defined by reference to two desirable properties, namely a) being able to modulate the level of suPAR in a mammalian subject and b) being useful for treatment or prevention of low-grade inflammation and/or metabolic syndrome. The claims cover all substances having these properties, whereas the application provides no disclosure within the meaning of Article 5 PCT for any of these substances. In the present case, the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the substances by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, namely claims 31-37 in as far as relating to substances as mentioned in claims 32-35 - independent of their ability to modulate the level of suPAR in a mammalian subject and independent of their usefulness for the treatment or prevention of low-grade inflammation and/or metabolic syndrome.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/064497

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7, 13-19, 22, 23, 29, 30-35, 69-71 (incompletely)
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 31-37 (incompletely)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
1, 5, 12-17, 22, 23, 29-37, 42, 43, 53, 54, 62, 63 (fully) 2-4, 6-11, 18, 19, 38, 39, 48-50
58, 59, 68-71 (partially)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,5,12-17,29-37 (fully) 4,6,7,10,11,69-71 (partially)

Methods for diagnosing, detecting the level or monitoring the treatment of low-grade inflammation and/or metabolic syndrome using suPAR as a marker; corresponding method of treatment of low-grade inflammation and/or metabolic syndrome; methods of reducing the risk of developing metabolic syndrome; medical uses of substances and/or pharmaceutical compositions.

2. claims: 22,23,42,43,53,54,62,63 (fully)
2-4,6-11,18,19,38,39,48-50,58,59,68-71
(partially)

Methods for predicting the risk of developing a cardiovascular disease using suPAR and/or D2D3 cleavage products of suPAR as a marker. Corresponding computer-based method, computer program product, computer readable medium, and computers.

3. claims: 2-4,6-11,18,19,38,39,48-50,58,59,68-71 (partially)

Methods for predicting the risk of developing chronic obstructive lung disease using suPAR and/or D2D3 cleavage products of suPAR as a marker. Corresponding computer-based method, computer program product, computer readable medium, and computers.

4. claims: 2-4,6-11,18,19,38,39,48-50,58,59,68-71 (partially)

Methods for predicting the risk of developing eczema using suPAR and/or D2D3 cleavage products of suPAR as a marker. Corresponding computer-based method, computer program product, computer readable medium, and computers.

5. claims: 2-4,6-11,18,19,38,39,48-50,58,59,68-71 (partially)

Methods for predicting the risk of developing obesity using suPAR and/or D2D3 cleavage products of suPAR as a marker. Corresponding computer-based method, computer program product, computer readable medium, and computers.

6. claims: 2-4,6-11,18,19,38,39,48-50,58,59,68-71 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Methods for predicting the risk of developing autoimmune disease using suPAR and/or D2D3 cleavage products of suPAR as a marker. Corresponding computer-based method, computer program product, computer readable medium, and computers.

7. claims: 24-26,44,45,55,64,65 (fully)
2-4,6-11,18,19,38,39,48-50,58,59,68-71
(partially)

Methods for predicting the risk of developing cancer using suPAR and/or D2D3 cleavage products of suPAR as a marker. Corresponding computer-based method, computer program product, computer readable medium, and computers.

8. claims: 20,21,40,41,51,52,60,61 (fully)
2-4,6-11,18,19,38,39,48-50,58,59,68-71
(partially)

Methods for predicting the risk of developing diabetes using suPAR and/or D2D3 cleavage products of suPAR as a marker. Corresponding computer-based method, computer program product, computer readable medium, and computers.

9. claims: 27,28,46,47,56,57,66,67 (fully)
2-4,6-11,18,19,38,39,48-50,58,59,68
(partially)

Methods for predicting the risk of mortality using suPAR and/or D2D3 cleavage products of suPAR as a marker. Corresponding computer-based method, computer program product, computer readable medium, and computers.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/064497

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			CN 101022830 A	22-08-2007
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			EP 1436425 A2	14-07-2004