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- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
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- Published:**
- with international search report (Art. 21(3))
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
 - with sequence listing part of description (Rule 5.2(a))
- (88) **Date of publication of the international search report:**
15 November 2012

(54) **Title:** A POLYPEPTIDE COMPRISING N-TERMINAL FRAGMENT OF A CYSTATIN FOR USE IN DIAGNOSING AND/OR TREATING STERILITY

(57) **Abstract:** The present invention concerns a polypeptide comprising the N-terminal fragment of a cystatin, and/or a cystatin expression inducer for use for the treatment of sterility and/or infertility, and a method of diagnosing and/or predicting sterility and/or infertility of a subject and/or of a couple of subjects, which method comprises measuring the level of at least one cystatin in a biological sample of a male subject and/or measuring the level of at least one cystatin in a biological sample of a female subject, and optionally measuring further the level of at least one cathepsin in a biological sample of said male of female subject.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER INV. A61K38/57 A61P15/08 G01N33/50 ADD.		
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) A61K G01N		
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 practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, Sequence Search, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 235 708 B1 (HOLLOWAY JAMES L [US] ET AL) 22 May 2001 (2001-05-22) the whole document	1-11
X	US 2003/100096 A1 (HOLLOWAY JAMES L [US]) 29 May 2003 (2003-05-29) paragraphs [0009] - [0013], [0196] ----- -/--	1-11
☒ 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 application or patent 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 4 June 2012		Date of mailing of the international search report 04/10/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Greif, Gabriela

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International application No

PCT/EP2012/053902

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHAU KIM M ET AL: "Reduced fertility in vitro in mice lacking the cystatin CRES (cystatin-related epididymal spermatogenic): rescue by exposure of spermatozoa to dibutyryl cAMP and isobutylmethylxanthine.", BIOLOGY OF REPRODUCTION JAN 2011 LNKD-PUBMED:20811015, vol. 84, no. 1, January 2011 (2011-01), pages 140-152, XP002655469, ISSN: 1529-7268 the whole document -----	1-11
Y	ABRAHAMSON M ET AL: "Identification of the probable inhibitory reactive sites of the cysteine proteinase inhibitors human cystatin C and chicken cystatin.", THE JOURNAL OF BIOLOGICAL CHEMISTRY 15 JUL 1987 LNKD- PUBMED:3496337, vol. 262, no. 20, 15 July 1987 (1987-07-15), pages 9688-9694, XP002655470, ISSN: 0021-9258 page 9693, left-hand column, paragraph 3-4 -----	1-11
Y	JIBORN THOMAS ET AL: "Cystatin C is highly expressed in the human male reproductive system", JOURNAL OF ANDROLOGY, vol. 25, no. 4, July 2004 (2004-07), pages 564-572, XP002655471, ISSN: 0196-3635 the whole document -----	1-11
Y	AFONSO S ET AL: "The expression and function of cystatin C and cathepsin B and cathepsin L during mouse embryo implantation and placentation", DEVELOPMENT, COMPANY OF BIOLOGISTS, CAMBRIDGE, GB, vol. 124, no. 17, 1 January 1997 (1997-01-01), pages 3415-3425, XP002217891, ISSN: 0950-1991 the whole document ----- -/--	1-11

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/053902

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HASEGAWA K ET AL: "Testatin transgenic and knockout mice exhibit normal sex-differentiation", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 341, no. 2, 10 March 2006 (2006-03-10), pages 369-375, XP024923883, ISSN: 0006-291X, DOI: 10.1016/J.BBRC.2005.12.183 [retrieved on 2006-03-10] the whole document -----	1-11
Y	BILODEAU MÉLANIE ET AL: "Analysis of blood stem cell activity and cystatin gene expression in a mouse model presenting a chromosomal deletion encompassing Csta and Stfa211.", PLOS ONE 2009 LNKD- PUBMED:19838297, vol. 4, no. 10, 2009, page E7500, XP002655472, ISSN: 1932-6203 the whole document -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/053902

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.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
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:
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 all searchable 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 report covers only those claims for which fees were paid, specifically claims Nos.:
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.:

1-11

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: 1-11

A polypeptide comprising N-terminal fragment of a cystatin, and/or a cystatin expression inducer for use in the treatment of sterility and/or infertility, and a method of in-vitro fertilization and/or artificial insemination comprising the steps of contacting an ovum obtained from a female mammal and a spermatozoon obtained from a male mammal in a fluid medium comprising a polypeptide comprising N-terminal fragment of a cystatin.

2. claims: 12-16

An in vitro method of diagnosing or predicting sterility and/or infertility of a subject and/or of a couple, and a kit intended for diagnosing and/or predicting sterility or infertility of a subject and/or of a couple, and a method of determining whether a subject and/or a couple suffering from sterility and/or infertility is likely to benefit from a treatment regimen that includes treatment with a polypeptide comprising N-terminal fragment of a cystatin and/or with a cystatin expression inducer.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/053902

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6235708	B1	22-05-2001	NONE

US 2003100096	A1	29-05-2003	US 2002006656 A1 17-01-2002
			US 2002164740 A1 07-11-2002
			US 2003100096 A1 29-05-2003
