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(54) Title: AGENTS IMPLICATED IN ENDOMETRIOSIS

(57) Abstract: The present invention relates to the discovery of genes and their products that are associated with the disease endometriosis. It has been discovered that cathepsin D, AEBP-1, stromelysin-3, cystatin B, protease inhibitor 1, sFRP4, gelsolin, IGFBP-3, dual specificity phosphatase 1, PAEP, immunoglobulin  $\lambda$  chain, ferritin, complement component 3, pro-alpha-1 type III collagen, proline 4-hydroxylase, alpha-2 type I collagen, claudin-4, melanoma adhesion protein, procollagen C-endopeptidase enhancer, nascent-polypeptide-associated complex alpha polypeptide, elongation factor 1 alpha (EF-1 $\alpha$ ), vitamin D3 25 hydroxylase, CSRP-1, steroidogenic acute regulatory protein, apolipoprotein E, transcobalamin II, prosaposin, early growth response 1 (EGR1), ribosomal protein S6, adenosine deaminase RNA-specific protein, RAD21, guanine nucleotide binding protein beta polypeptide 2-like 1 (RACK1) and podocalyxin are all implicated in this disease. The discovery of these associations has clear implications for the diagnosis and treatment of endometriosis and related conditions.

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 00/04228

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C12Q1/68 G01N33/543 C12N9/00 C07K14/47 A61K48/00  
A01K67/027

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)  
IPC 7 C12Q

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, PAJ, CHEM ABS Data, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BERGQVIST AGNETA ET AL: "A comparison of cathepsin D levels in endometriotic tissue and in uterine endometrium." FERTILITY AND STERILITY, vol. 65, no. 6, 1996, pages 1130-1134, XP002176154 ISSN: 0015-0282 cited in the application page 1132, right-hand column, last paragraph -page 1134 ---	1,2,4,6, 7,29-32, 45-48, 53,54
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Further documents are listed in the continuation of box C.  Patent family members are listed in 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 doubt 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 underlain 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.
  - "B" document member of the same patent family

Date of the actual completion of the international search: 30 August 2001  
Date of mailing of the international search report: 21.11.2001

Name and mailing address of the ISA: European Patent Office, P.B. 5816 Patentlaan 2, NL - 8280 HV Rijswijk, Tel. (+31-70) 340-2040, Tx. 31 851 epo nl, Fax: (+31-70) 340-3018  
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II INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04228

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS [Online]                      BIOSCIENCES INFORMATION SERVICE,                      PHILADELPHIA, PA, US; 1995                      DI BLASIO ANNA MARIA ET AL: "Basic                      fibroblast growth factor messenger                      ribonucleic acid levels in eutopic and                      ectopic human endometrial stromal cells as                      assessed by competitive polymerase chain                      reaction amplification."                      Database accession no. PREV199698647050                      XP002176155                      abstract                      &amp; MOLECULAR AND CELLULAR ENDOCRINOLOGY,                      vol. 115, no. 2, 1995, pages 169-175,                      ISSN: 0303-7207</p>	<p>1-6,19,                      29-32</p>
X	<p>---                      DATABASE BIOSIS [Online]                      BIOSCIENCES INFORMATION SERVICE,                      PHILADELPHIA, PA, US; 1994                      HUANG JAOU-CHEN ET AL: "Quantitative                      analysis of epidermal growth factor                      receptor gene expression in                      endometriosis."                      Database accession no. PREV199598004176                      XP002176156                      abstract                      &amp; JOURNAL OF CLINICAL ENDOCRINOLOGY &amp;                      METABOLISM,                      vol. 79, no. 4, 1994, pages 1097-1101,                      ISSN: 0021-972X</p>	<p>1,2,4,6,                      19,29-32</p>
X	<p>---                      DATABASE BIOSIS [Online]                      BIOSCIENCES INFORMATION SERVICE,                      PHILADELPHIA, PA, US; 1995                      MISAO R ET AL: "Levels of sex                      hormone-binding globulin (SHBG) and                      corticosteroid-binding globulin (CBG)                      messenger ribonucleic acid (mRNAs) in                      ovarian endometriosis."                      Database accession no. PREV199598288484                      XP002176157                      abstract                      &amp; REPRODUCTION NUTRITION DEVELOPMENT,                      vol. 35, no. 2, 1995, pages 155-165,                      ISSN: 0926-5287</p>	<p>1-6,19,                      29-32</p>
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INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 00/04228

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1997 KITAWAKI JO ET AL: "Expression of aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium." Database accession no. PREV199799745062 XP002176158 abstract &amp; BIOLOGY OF REPRODUCTION, vol. 57, no. 3, 1997, pages 514-519, ISSN: 0006-3363</p> <p>---</p>	1-6,18, 19,29-32
X	<p>WO 97 46664 A (UNIV WASHINGTON) 11 December 1997 (1997-12-11) page 100, last paragraph</p> <p>---</p>	55-57
X	<p>US 5 776 759 A (COLEMAN ROGER ET AL) 7 July 1998 (1998-07-07) column 3, line 13 - line 38</p> <p>---</p>	55-57
P,X	<p>SUZUMORI NOBUHIRO ET AL: "Expression of secretory leukocyte protease inhibitor in women with endometriosis." FERTILITY AND STERILITY, vol. 72, no. 5, November 1999 (1999-11), pages 857-867, XP000978987 ISSN: 0015-0282 the whole document</p> <p>---</p>	1-6,8, 19,29-32
P,X	<p>WO 99 63115 A (SCHNEIDER PATRICK ;REPROGEN INC (US); FRENCH CYNTHIA K (US); YAMAM) 9 December 1999 (1999-12-09)</p> <p>claims 1-56</p> <p>---</p>	1-12, 15-19, 29-33, 35-38, 40-54
A	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1994 TOUITOU ISABELLE ET AL: "Missense polymorphism (C/T224) in the human cathepsin D pro-fragment determined by polymerase chain reaction-single strand conformational polymorphism analysis and possible consequences in cancer cells." Database accession no. PREV199497272224 XP002176262 abstract &amp; EUROPEAN JOURNAL OF CANCER, vol. 30A, no. 3, 1994, pages 390-394, ISSN: 0959-8049</p> <p>---</p>	20-26
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04228

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>                     DATABASE BIOSIS [Online]                      BIOSCIENCES INFORMATION SERVICE,                      PHILADELPHIA, PA, US;                      1 October 1999 (1999-10-01)                      MCILROY STEPHEN P ET AL: "Cathepsin D gene                      exon 2 polymorphism and sporadic                      Alzheimer's disease."                      Database accession no. PREV199900520057                      XP002176263                      abstract                      &amp; NEUROSCIENCE LETTERS,                      vol. 273, no. 2,                      1 October 1999 (1999-10-01), pages                      140-141,                      ISSN: 0304-3940                      -----                 </p>	20-26

# INTERNATIONAL SEARCH REPORT

international application No.  
PCT/GB 00/04228

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 34  
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.: -  
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 II Observations where unity of invention is lacking (Continuation of item 2 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 fee, this Authority did not invite payment of any additional fee.
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.:  
1-33, 35-58 (all partially)

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- 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: 1-33,35-58 (all partially)

Invention 1:

Gene coding for cathepsin D, its gene product, immunospecific antibodies thereto, arrays and kits containing said sequences, modified non-human animals derived thereof, and their use in methods relating to the management (susceptibility screening, diagnosis, screening for related genes) and treatment (identification of modulating compounds, monitoring efficacy) of endometriosis.

2. Claims: 1-33,35-58 (all partially)

Invention 2:

Gene coding for AEBP-1, its gene product, immunospecific antibodies thereto, arrays and kits containing said sequences, modified non-human animals derived thereof, and their use in methods relating to the management (susceptibility screening, diagnosis, screening for related genes) and treatment (identification of modulating compounds, monitoring efficacy) of endometriosis.

Idem for the 31 other genes listed in claim 7.  
(stromelysin-3 is invention number 3, ..., podocalyxin is invention number 33)

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 35 to 44 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Claims Nos.: 34

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Present claims 4-6,18,19,24-26,29-33,35-38,40-43,45,47,49-53,55,56,58 relate to methods involving the use of compounds (genes) defined by reference to a desirable characteristic or property, namely genes which encode gene products identified according to the screening method proposed in this application (claims 1-3), e.g. comparing the pattern of gene expression in a diseased endometrium tissue from a patient suffering from endometriosis to the pattern of gene expression in healthy endometrium tissue from the same patient.

The claims cover all compounds (genes) having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a limited number of such compounds (genes), i.e. the ones listed in claim 7. In the present case, the claims so lack support, and 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 compounds (genes) 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, supported and disclosed, namely those parts relating to the 34 differentially expressed genes on pages 44 to 83 of the description (See the list of genes in claim7).

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The applicant's attention is drawn to the fact that claims, or parts of 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

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/04228

Patent document cited in search report	A	Publication date		Patent family member(s)	Publication date
WO 9746664	A	11-12-1997		AU 3640297 A	05-01-1998
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				US 5965129 A	12-10-1999
				WO 9813484 A1	02-04-1998
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				EP 1076723 A2	21-02-2001
				WO 9963115 A2	09-12-1999
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