



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|   |                        |   |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
|---|------------------------|---|----|------------|------------------------|----|------------|------------------------|----|------------|------------------------|----|------------|------------------------|----|------------|------------------------|----|------------|------------------------|----|------------|------------------------|----|------------|------------------------|----|------------|------------------------|----|------------|------------------------|----|---|
| <b>(51) International Patent Classification <sup>6</sup> :</b><br><b>C12N 15/12, C07K 14/47, A61K 38/17</b>   | <b>A3</b>              | <b>(11) International Publication Number:</b> <b>WO 98/55614</b><br><b>(43) International Publication Date:</b> 10 December 1998 (10.12.98) |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| <b>(21) International Application Number:</b> PCT/US98/11210<br><b>(22) International Filing Date:</b> 1 June 1998 (01.06.98)<br><b>(30) Priority Data:</b> <table border="0" style="width: 100%;"> <tr><td>08/868,899</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>08/868,898</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>08/869,192</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>08/869,191</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>08/869,193</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>08/868,697</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>08/868,698</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>08/868,900</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>08/868,696</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>08/869,194</td><td>4 June 1997 (04.06.97)</td><td>US</td></tr> <tr><td>09/087,255</td><td>29 May 1998 (29.05.98)</td><td>US</td></tr> </table><br><b>(71) Applicant:</b> GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US). | 08/868,899             | 4 June 1997 (04.06.97)  | US | 08/868,898 | 4 June 1997 (04.06.97) | US | 08/869,192 | 4 June 1997 (04.06.97) | US | 08/869,191 | 4 June 1997 (04.06.97) | US | 08/869,193 | 4 June 1997 (04.06.97) | US | 08/868,697 | 4 June 1997 (04.06.97) | US | 08/868,698 | 4 June 1997 (04.06.97) | US | 08/868,900 | 4 June 1997 (04.06.97) | US | 08/868,696 | 4 June 1997 (04.06.97) | US | 08/869,194 | 4 June 1997 (04.06.97) | US | 09/087,255 | 29 May 1998 (29.05.98) | US | <b>(72) Inventors:</b> JACOBS, Kenneth; 151 Beaumont Street, Newton, MA 02160 (US). McCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVALLIE, Edward, R.; 113 Ann Lee Road, Harvard, MA 01451 (US). RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). TREACY, Maurice; 93 Walcott Road, Chestnut Hill, MA 02167 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US). AGOSTINO, Michael, J.; 26 Wolcott Avenue, Andover, MA 01810 (US). HOWES, Steven, H.; Apartment 2, 44 Chester Street, Somerville, MA 02144 (US). FECHTEL, Kim; 46 Marion Road, Arlington, MA 02174 (US).<br><b>(74) Agent:</b> SPRUNGER, Suzanne, A.; Genetics Institute, Inc., 87 CambridgePark Drive, Cambridge, MA 02140 (US).<br><b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, 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).<br><b>Published</b><br><i>With international search report.</i><br><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i><br><b>(88) Date of publication of the international search report:</b><br>1 April 1999 (01.04.99) |
| 08/868,899  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 08/868,898  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 08/869,192  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 08/869,191  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 08/869,193  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 08/868,697  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 08/868,698  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 08/868,900  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 08/868,696  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 08/869,194  | 4 June 1997 (04.06.97) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| 09/087,255  | 29 May 1998 (29.05.98) | US  |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| <b>(54) Title:</b> SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM  |                        |   |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |
| <b>(57) Abstract</b><br><p>Polynucleotides and the proteins encoded thereby are disclosed.</p>  |                        |   |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |            |                        |    |   |

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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| DK | Denmark                  | LR | Liberia                                  | SG | Singapore                                    |    |                          |
| EE | Estonia                  |    |  |    |  |    |                          |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JS 98/11210

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/47 A61K38/17

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 6 C12N C07K A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  |
|------------|---|------------------------|
| 3<br>E     | <p>WO 98 25959 A (CHIRON CORP. (US); ESCOBEDO J; HU Q; GARCIA P; WILLIAMS L; KOTHAKOTA S) 18 June 1998<br/>                     see page 3, line 21-24<br/>                     see page 9, line 26-31<br/>                     see page 10, line 24-29<br/>                     see page 18, line 18-23<br/>                     see page 19, line 30 - page 20, line 6<br/>                     see page 20, line 28 - page 21, line 17<br/>                     Seq.ID:15<br/>                     see page 42<br/>                     Seq.ID:34<br/>                     see page 66 - page 68<br/>                     see page 74 - page 77; claims<br/>                     ---<br/>                     -/--</p> | <p>1-7, 10,<br/>11</p> |



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 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

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- \*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
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Date of the actual completion of the international search

13 November 1998

Date of mailing of the international search report

15.02.1999

Name and mailing address of the ISA

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Macchia, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/11210

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
|--|--|-----------------------|
| Category   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
| E  | <p>WO 98 45435 A (GENETICS INSTITUTE INC (US); JACOBS; MCCOY; LAVALLIE; RACIE ET AL.) 15 October 1998<br/>                     see page 56, line 28 - page 57, line 6<br/>                     Seq.ID:494<br/>                     see page 259</p>  | 1-7,9-11              |
| X  | <p>---<br/>                     EP 0 679 716 A (MATSUBARA KENICHI; OKUBO KOUSAKU (JP)) 2 November 1995<br/>                     cited in the application<br/>                     see page 8, line 20-35<br/>                     see page 20, line 25-51<br/>                     Seq.ID:2648<br/>                     see page 907 - page 908</p>                    | 1,11                  |
| X  | <p>---<br/>                     Database EMBL Emest10, Entry HS673190<br/>                     Accession number R88673<br/>                     26 August 1995<br/>                     97% identity with Seq.ID:1 nt.1-338<br/>                     XP002084310<br/>                     cited in the application<br/>                     see the whole document</p> | 1,11                  |
| X  | <p>---<br/>                     Database EMBL Emest9, Entry HS37978<br/>                     Accession number R15379<br/>                     22 April 1995<br/>                     97% identity with Seq.ID:1 nt.326-725<br/>                     XP002084311<br/>                     cited in the application<br/>                     see the whole document</p>  | 1,11                  |
| X  | <p>---<br/>                     Database EMBL Emest9, Entry HS273155<br/>                     Accession number H18273<br/>                     2 July 1995<br/>                     98% identity with Seq.ID:1 nt.641-1065<br/>                     XP002084312<br/>                     see the whole document</p>  | 1,11                  |
| X  | <p>---<br/>                     Database EMBL Emest7, Entry HS1210943<br/>                     Accession number AA405257<br/>                     11 May 1997<br/>                     99% identity with Seq.ID:1 nt.831-1339<br/>                     XP002084313<br/>                     see the whole document</p>   | 1,11                  |
| X  | <p>---<br/>                     Database EMBL Emest11, Entry HS796352<br/>                     Accession number W56796<br/>                     8 June 1996<br/>                     98% identity with Seq.ID:1 nt.1319-1741<br/>                     reverse orientation<br/>                     XP002084314<br/>                     see the whole document</p>     | 1,11                  |
|  | <p>---<br/>                     -/--</p>   |                       |

INTERNATIONAL SEARCH REPORT

International Application No  
PCT, US 98/11210

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
|--|--|-----------------------|
| Category °   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
| A  | WO 97 07198 A (GENETICS INSTITUTE INC (US); JACOBS K; MCCOY JM; KELLEHER K; CARLIN M) 27 February 1997<br>---  |                       |
| A  | TASHIRO K. ET AL.: "Signal sequence trap: a cloning strategy for secreted proteins and type I membrane proteins"<br>SCIENCE,<br>vol. 261, 30 July 1993, pages 600-603,<br>XP000673204<br>--- |                       |
| A  | YOKOYAMA-KOBAYASHI M. ET AL.: "A signal sequence detection system using secreted protease activity as an indicator"<br>GENE,<br>vol. 163, 1995, pages 193-196, XP002053953<br>---            |                       |
| A  | US 5 536 637 A (JACOBS KENNETH; GENETICS INSTITUTE INC. (US)) 16 July 1996<br>cited in the application<br>-----  |                       |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 98/11210

## 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.:  
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 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.:

1-11

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**

1. Claims: 1-11

Polynucleotide comprising the nucleotide sequence of Seq.ID:1 and encoding a polypeptide of Seq.ID:2 or fragments. Polynucleotide fragments, variants, homologues, gene thereof. Host cell transformed with said polynucleotide. Protein comprising an amino acid sequence of Seq.ID:2 or fragments thereof. Process for producing said protein.

2. Claims: 12-14

Polynucleotide comprising the nucleotide sequence of Seq.ID:3 and encoding a polypeptide of Seq.ID:4 or fragments. Polynucleotide fragments, variants, homologues, gene thereof. Protein comprising an amino acid sequence of Seq.ID:4 or fragments thereof.

3. Claims: 15-17

As invention 2 but concerning Seq.ID:5 and 6.

4. Claims: 18-20

As invention 2 but concerning Seq.ID:7 and 8.

5. Claims: 21-23

As invention 2 but concerning Seq.ID:9 and 10.

6. Claims: 24-26

As invention 2 but concerning Seq.ID:11 and 12.

7. Claims: 27-29

As invention 2 but concerning Seq.ID:13 and 14.

8. Claims: 30-32

As invention 2 but concerning Seq.ID:15 and 16.

9. Claims: 33-35

As invention 2 but concerning Seq.ID:17 and 18.

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

10. Claims: 36-38

As invention 2 but concerning Seq.ID:19 and 20.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JS 98/11210

| Patent document cited in search report | Publication date | Patent family member(s)  | Publication date   |
|--|------------------|--|--|
| WO 9825959 A                           | 18-06-1998       | AU 5796298 A   | 03-07-1998   |
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| WO 9707198 A                           | 27-02-1997       | US 5707829 A<br>AU 6712396 A<br>AU 6768596 A<br>CA 2227220 A<br>CA 2229208 A<br>EP 0839196 A<br>EP 0851875 A<br>WO 9704097 A | 13-01-1998<br>18-02-1997<br>12-03-1997<br>06-02-1997<br>27-02-1997<br>06-05-1998<br>08-07-1998<br>06-02-1997 |
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