

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10902 A3

(51) International Patent Classification⁷: C12N 15/12,
C07K 14/47, C12N 15/63, A61K 38/00, 48/00

US Not furnished (CIP)
Filed on 10 August 2000 (10.08.2000)

(21) International Application Number: PCT/US00/21857

(71) Applicant (for all designated States except US): CURA-
GEN CORPORATION [US/US]; 555 Long Wharf Drive,
11th floor, New Haven, CT 06511 (US).

(22) International Filing Date: 11 August 2000 (11.08.2000)

(25) Filing Language: English

(72) Inventors; and
(75) Inventors/Applicants (for US only): SHIMKETS,
Richard, A. [US/US]; 191 Leete Street, West Haven, CT
06516 (US). FERNANDES, Elma [US/US]; 77 Florence
Road, #2B, Branford, CT 06405 (US).

(26) Publication Language: English

(30) Priority Data:
60/148,433 11 August 1999 (11.08.1999) US
09/635,949 10 August 2000 (10.08.2000) US

(74) Agent: ELRIFI, Ivor, R.; Mintz, Levin, Cohn, Ferris,
Glovsky, and Popeo, P.C., One Financial Center, Boston,
MA 02111 (US).

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier applications:
US 60/148,433 (CIP)
Filed on 11 August 1999 (11.08.1999)

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,

[Continued on next page]

(54) Title: NUCLEOC ACIDS AND SECRETED POLYPEPTIDES ENCODED THEREBY

cura_58_17931354.0.35.1 (SEQ ID NO: 14)
cura_58_17931354.0.35.2 (SEQ ID NO: 16)
cura_58_179313540351 MRPVALLLLPSLLALLAHGLSLEAPTVMKQAPGIEETDGLTAAPTPEQPERGVHVFVT
cura_58_179313540352 MRPVALLLLPSLLALLAHGLSLEAPTVMKQAPGIEETDGLTAAPTPEQPERGVHVFVT
cura_58_179313540351 APTLKLINHHPLLEEFQEGLEKGEDEELRPAFPQDPAPPTPSPLRANQDSRPVFT
cura_58_179313540352 APTLKLINHHPLLEEFQEGLEKGEDEELRPAFPQDPAPPTPSPLRANQDSRPVFT
cura_58_179313540351 SPTPAMA AVPTQPQSKGEPWSESEPMILRITAPLPPGSPMAVPTLPGGEIASTTTPSRA
cura_58_179313540352 SPTPAMA AVPTQPQSKGEPWSESEPMILRITAPLPPGSPMAVPTLPGGEIASTTTPSRA
cura_58_179313540351 WPTPQEGPDMGRPWVAEVVSGAGIGIQGITITSSTASGDDEETTTTTIIITTIITVQT
cura_58_179313540352 WPTPQEGPDMGRPWVAEVVSGAGIGIQGITITSSTASGDDEETTTTTIIITTIITVQT
cura_58_179313540351 PGPCSWNFGSPGEGSLDPTDLSPTDVLGDCFFYISVYVPGYGVKIQNISLRGETVTV
cura_58_179313540352 PGPCSWNFGSPGEGSLDPTDLSPTDVLGDCFFYISVYVPGYGVKIQNISLRGETVTV
cura_58_179313540351 EGLGGPDPPLANQSFLLRQVIRSPTRQAALRFQSLPPAGPTPHFYQAYLLSCHFP
cura_58_179313540352 EGLGGPDPPLANQSFLLRQVIRSPTRQAALRFQSLPPAGPTPHFYQAYLLSCHFP
cura_58_179313540351 RRQAYEDVTVTSHPGGARFHCATGYQLKARHLTCLNATQPWDSKEPVCIAACGGVI
cura_58_179313540352 RRQAYEDVTVTSHPGGARFHCATGYQLKARHLTCLNATQPWDSKEPVCIAACGGVI
cura_58_179313540351 RNATTGRIVSPGFPGNYSNLTCEWLLRAPEQRHLHFEKVSIAEDDDRLIIRNGDNVE
cura_58_179313540352 RNATTGRIVSPGFPGNYSNLTCEWLLRAPEQRHLHFEKVSIAEDDDRLIIRNGDNVE
cura_58_179313540351 APPVYDSYEVEYLPLEGLSSGKHFVVELSDSSGAAAGMALRYEAFQGGHCYEPFVYK
cura_58_179313540352 APPVYDSYEVEYLPLEGLSSGKHFVVELSDSSGAAAGMALRYEAFQGGHCYEPFVYK
cura_58_179313540351 NFSSTPTYPVGTTFVFSQDPTGTEQSSIIIECVDPHDPQWNETEPACRAVCSGEIIDS
cura_58_179313540352 NFSSTPTYPVGTTFVFSQDPTGTEQSSIIIECVDPHDPQWNETEPACRAVCSGEIIDS
cura_58_179313540351 AGVVLSPNWPPEYSRGQDCINGVHVEDKRIIMLDIRVLRIGPQDVLTFYDGDLLTARVLG
cura_58_179313540352 AGVVLSPNWPPEYSRGQDCINGVHVEDKRIIMLDIRVLRIGPQDVLTFYDGDLLTARVLG
cura_58_179313540351 QVSGPRSHKFLTSMADVTIQFQSDPGTSLVGYQQGFVHFFEVPRNDTCPELPEIPNGW
cura_58_179313540352 QVSGPRSHKFLTSMADVTIQFQSDPGTSLVGYQQGFVHFFEVPRNDTCPELPEIPNGW
cura_58_179313540351 KSPSQPELVHGTVVYQCTYQYVVGSSVLMQWDLTWSDELPSQRTVTSCHDPGDVHES
cura_58_179313540352 KSPSQPELVHGTVVYQCTYQYVVGSSVLMQWDLTWSDELPSQRTVTSCHDPGDVHES
cura_58_179313540351 RRLISSPKFPVGTATVQYICDQGFVLTGSSILTCHDRQAGSPKNSDRAPKCLLEQLKPCHEG
cura_58_179313540352 RRLISSPKFPVGTATVQYICDQGFVLTGSSILTCHDRQAGSPKNSDRAPKCLLEQLKPCHEG
cura_58_179313540351 LSAPENGARSPERQLHPAGATIHFSAPGVYLVKQASIKCVPHGPHSEWSDPPPICRAASL
cura_58_179313540352 LSAPENGARSPERQLHPAGATIHFSAPGVYLVKQASIKCVPHGPHSEWSDPPPICRAASL
cura_58_179313540351 DGFYNSRSLDVARAPASSTLDAAHIAAIFLPLVAMVLLVGGVYFFSRILQKSSLLQP
cura_58_179313540352 DGFYNSRSLDVARAPASSTLDAAHIAAIFLPLVAMVLLVGGVYFFSRILQKSSLLQP
cura_58_179313540351 RPRPRPNRITIEAFDNPTTYETGETRETEVSI-
cura_58_179313540351 RPRPRPNRITIEAFDNPTTYETGETRETEVSI-

(57) Abstract: The invention provides polypeptides, designated herein as PROX polypeptides, as well as polynucleotides encoding PROX polypeptides, and antibodies that immunospecifically-bind to PROX polypeptides or polynucleotide, or derivatives, variants, mutants, or fragments thereof. The invention additionally provides methods in which the PROX polypeptide, polynucleotide, and antibody are used in the detection, prevention, and treatment of a broad range of pathological states.

WO 01/10902 A3



HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, 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, GW, ML, MR, NE, SN, TD, TG).

Published:

— *With international search report.*

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

7 June 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/21857

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12N15/12 C07K14/47 C12N15/63 A61K38/00 A61K48/00

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)
 IPC 7 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)
 EPO-Internal, EMBL, PAJ, WPI Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 07198 A (GENETICS INST) 27 February 1997 (1997-02-27) page 1 -page 11 ---	1-41
Y	WO 98 25959 A (CHIRON CORP) 18 June 1998 (1998-06-18) page 21, line 23 -page 25, line 22 ---	1-41
Y	WO 99 05256 A (HARVARD COLLEGE) 4 February 1999 (1999-02-04) page 2, line 17 -page 4, line 4 ---	1-41
Y	WO 98 45712 A (HUMAN GENOME SCIENCES INC) 15 October 1998 (1998-10-15) page 2 -page 5; claims 1-23 ---	1-41
	-/--	

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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.</p> <p>"&" document member of the same patent family</p>
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Date of the actual completion of the international search 8 March 2001	Date of mailing of the international search report 09.03.01
--------------------------------------------------------------------------------------	---------------------------------------------------------------------------

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Nichogiannopoulou, A
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/21857

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JACOBS K A ET AL: "A genetic selection for isolating cDNAs encoding secreted proteins" GENE, vol. 198, no. 1-2, 1 October 1997 (1997-10-01), pages 289-296, XP004116069 ISSN: 0378-1119 the whole document	1-14
Y	SHIROZU M ET AL: "CHARACTERIZATION OF NOVEL SECRETED AND MEMBRANE PROTEINS ISOLATED BY THE SIGNAL SEQUENCE TRAP METHOD" GENOMICS, vol. 37, no. 3, 1 November 1996 (1996-11-01), pages 273-280, XP002054773 ISSN: 0888-7543 the whole document	1-14
X	WO 99 06550 A (GENSET (FR)) 11 February 1999 (1999-02-11) the whole document & DATABASE EMBL [Online] Y11743, 18 June 1999 (1999-06-18) DUCLERT A ET AL: "Human 5' EST secreted protein SEQ ID No: 343" Protein with 97% identity with SEQ ID No: 2 over 103 aa abstract	1-14
P,X	WO 99 63088 A (GENENTECH INC (US)) 9 December 1999 (1999-12-09) cited in the application PRO1344 has 99.5% identity with SEQ ID No 2 over 565 aa and 99.7% identity with SEQ ID No:1 over 1766 nt the whole document	1-41
X	DATABASE EMBL [Online] HSM013345, 13 March 1999 (1999-03-13) DUESTERHOEFT A. ET AL.: "Homo sapiens mRNA; EST" XP002155624 EST with 96% identity with SEQ ID No: 1 over 702 nt abstract	5-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/21857

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:

Although claim(s) 23-28 and 36-41 are directed to a diagnostic method practised on the human/animal body, or 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.
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.:

1-41 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: claims 1-41 all partially

Polypeptides and variants thereof, nucleic acids and variants thereof, vectors and host cells comprising the same, antibodies, diagnostic and therapeutic methods, pharmaceutical compositions and kits relating to PR01 (SEQ ID NOs: 1 and 2).

2. Claims: claims 1-41 all partially

As subject 1 but relating to PR02 (SEQ ID NOs: 3 and 4).

3. Claims: claims 1-41 all partially

As subject 1 but relating to PR03 (SEQ ID NOs: 5 and 6).

4. Claims: claims 1-41 all partially

As subject 1 but relating to PR04 (SEQ ID NOs: 7 and 8).

5. Claims: claims 1-41 all partially

As subject 1 but relating to PR05 (SEQ ID NOs: 9 and 10).

6. Claims: claims 1-41 all partially

As subject 1 but relating to PR06 (SEQ ID NOs: 11 and 12).

7. Claims: claims 1-41 all partially

As subject 1 but relating to PR07 (SEQ ID NOs: 13 and 14).

8. Claims: claims 1-41 all partially

As subject 1 but relating to PR08 (SEQ ID NOs: 15 and 16).

9. Claims: claims 1-41 all partially

As subject 1 but relating to PR09 (SEQ ID NOs: 17 and 18).

10. Claims: claims 1-41 all partially

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

As subject 1 but relating to PR010 (SEQ ID NOs: 19 and 20).

11. Claims: claims 1-41 all partially

As subject 1 but relating to PR011 (SEQ ID NOs: 21 and 22).

12. Claims: claims 1-41 all partially

As subject 1 but relating to PR012 (SEQ ID NOs: 23 and 24).

13. Claims: claims 1-41 all partially

As subject 1 but relating to PR013 (SEQ ID NOs: 25 and 26).

14. Claims: claims 1-41 all partially

As subject 1 but relating to PR014 (SEQ ID NOs: 27 and 28).

15. Claims: claims 1-41 all partially

As subject 1 but relating to PR015 (SEQ ID NOs: 29 and 30).

16. Claims: claims 1-41 all partially

As subject 1 but relating to PR016 (SEQ ID NOs: 31 and 32).

17. Claims: claims 1-41 all partially

As subject 1 but relating to PR017 (SEQ ID NOs: 33 and 34).

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 00/21857

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
WO 9707198	A	27-02-1997	US 5707829 A	13-01-1998
			AU 727480 B	14-12-2000
			AU 6712396 A	18-02-1997
			AU 727489 B	14-12-2000
			AU 6768596 A	12-03-1997
			CA 2227220 A	06-02-1997
			CA 2229208 A	27-02-1997
			EP 0839196 A	06-05-1998
			EP 0851875 A	08-07-1998
			JP 11510045 T	07-09-1999
			US 6043344 A	28-03-2000
			WO 9704097 A	06-02-1997
			US 6074849 A	13-06-2000
			US 5969093 A	19-10-1999

WO 9825959	A	18-06-1998	AU 5796298 A	03-07-1998
			EP 0948531 A	13-10-1999

WO 9905256	A	04-02-1999	US 6066460 A	23-05-2000

WO 9845712	A	15-10-1998	AU 6952998 A	30-10-1998
			EP 0974058 A	26-01-2000

WO 9906550	A	11-02-1999	AU 8555198 A	22-02-1999
			EP 1000148 A	17-05-2000

WO 9963088	A	09-12-1999	AU 4328699 A	20-12-1999
			AU 2212299 A	26-07-1999
			WO 9935170 A	15-07-1999
