

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 February 2003 (13.02.2003)

PCT

(10) International Publication Number
WO 03/012113 A3

(51) International Patent Classification⁷: **C12N 15/85**,
C07K 14/705, C12N 15/67, C12Q 1/68

(21) International Application Number: PCT/EP02/09416

(22) International Filing Date: 1 August 2002 (01.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/309,189 2 August 2001 (02.08.2001) US
01120270.2 23 August 2001 (23.08.2001) EP

(71) Applicant (*for all designated States except US*): **GEN-CELL S.A.** [FR/FR]; 72-82 rue Léon Geffroy, 94400 Vitry sur Seine (FR).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): **DARTEIL, Raphaël** [FR/FR]; 30 Passage Thiéré, F-75011 PARIS (FR).

(74) Agent: **LECCA, Patricia**; AVENTIS PHARMA S.A., Patent Department, 20 Avenue Raymond Aron, F-92165 ANTONY CEDEX (FR).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, 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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
18 September 2003

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.

(54) Title: INDUCIBLE EXPRESSION SYSTEMS EMPLOYING PPAR TRANSCRIPTIONAL ACTIVATORS

(57) Abstract: The invention relates to gene expression systems that employ novel variants of mammalian peroxisome proliferator-activated receptor (PPAR) proteins as transcriptional activators, as well as novel PPAR polypeptides and nucleic acids that encode them.



WO 03/012113 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/09416

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/85 C07K14/705 C12N15/67 C12Q1/68				
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				
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, BIOSIS				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	WO 00 78986 A (STAELS BART; AVENTIS PHARMA SA (FR); MAHFOUDI ABDERRAHIM (FR); CRO) 28 December 2000 (2000-12-28) cited in the application * page 3, 4 and 11 * claims 6,7 ---	14-16		
X	WO 98 21349 A (STAELS BART; MAHFOUDI ABDERRAHIM (FR); AUWERX JOHAN (FR); BENOIT P) 22 May 1998 (1998-05-22) page 2 -page 6 --- -/---	14-16		
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.				
° Special categories of cited documents : <table border="0"> <tr> <td> *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 </td> <td> *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 </td> </tr> </table>			*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
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		Date of mailing of the international search report		
13 March 2003		24/03/2003		
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 Sirim, P		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/09416

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUN GUAN-CHENG ET AL: "Intermittent expression of BmFTZ-F1, a member of the nuclear hormone receptor superfamily during development of the silkworm Bombyx mori." DEVELOPMENTAL BIOLOGY, vol. 162, no. 2, 2 April 1994 (1994-04-02), pages 426-437, XP001057100 ISSN: 0012-1606 the whole document	1, 34-37
X	JUGE-AUBRY C ET AL: "DNA binding properties of peroxisome proliferator-activated receptor subtypes on various natural peroxisome proliferator response elements. Importance of the 5'-flanking region" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 40, 3 October 1997 (1997-10-03), pages 25252-25259, XP002154469 ISSN: 0021-9258 figure 2; table 1	14-16
X	BARDOT O ET AL: "PPAR-RXR HETERODIMER ACTIVATES A PEROXISOME PROLIFERATOR RESPONSE ELEMENT UPSTREAM OF THE BIFUNCTIONAL ENZYME GENE" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 192, no. 1, 15 April 1993 (1993-04-15), pages 37-45, XP000907578 ISSN: 0006-291X figure 1	14-16
X	RODRIGUEZ JOAN C ET AL: "Peroxisome proliferator-activated receptor mediates induction of the mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase gene by fatty acids." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 29, 1994, pages 18767-18772, XP001061650 ISSN: 0021-9258 page 18769 -page 18770; figure 3; table 1	14-16

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/09416

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ALDRIDGE THOMAS C ET AL: "Identification and characterization of DNA elements implicated in the regulation of CYP4A1 transcription." BIOCHEMICAL JOURNAL, vol. 306, no. 2, 1 March 1995 (1995-03-01), pages 473-479, XP001055459 ISSN: 0264-6021 the whole document	14-16
Y	EP 0 798 378 A (AKZO NOBEL NV) 1 October 1997 (1997-10-01) page 2 -page 6	8-13, 17-33
Y	EP 0 752 477 A (BAYLOR COLLEGE MEDICINE) 8 January 1997 (1997-01-08) * page 1, 5 and 6 * examples 7,10	8-13, 17-33
Y	US 5 597 693 A (EVANS RONALD M ET AL) 28 January 1997 (1997-01-28) the whole document	8-13,17, 33
Y	EP 0 325 849 A (SALK INST FOR BIOLOGICAL STUDI) 2 August 1989 (1989-08-02) the whole document	8-13, 17-33
Y	WO 98 26063 A (MAIRA MARIO ;DROUIN JACQUES (CA); MONTREAL INST RECH CLINIQUES (CA) 18 June 1998 (1998-06-18) page 6 -page 11	27-33
Y	MADER S ET AL: "THREE AMINO ACIDS OF THE ESTROGEN RECEPTOR ARE ESSENTIAL TO ITS ABILITY TO DISTINGUISH AN ESTROGEN FROM A GLUCOCORTICOID-RESPONSIVE ELEMENT" NATURE (LONDON), vol. 338, no. 6212, 1989, pages 271-274, XP001061690 ISSN: 0028-0836 the whole document	8-13,17, 33
Y	UMESONO K ET AL: "DETERMINANTS OF TARGET GENE SPECIFICITY FOR STEROID-THYROID HORMONE RECEPTORS" CELL, vol. 57, no. 7, 30 July 1989 (1989-07-30), pages 1139-1146, XP001057651 ISSN: 0092-8674 abstract	8-13, 17-33
P,X	FR 2 806 418 A (AVENTIS PHARMA SA) 21 September 2001 (2001-09-21) abstract	14-16

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 1-13, 17-37

- modified PPAR polypeptides, vectors and cells comprising said polypeptides
- inducible expression system consisting of modified PPAR polypeptides and response elements
- method for screening response elements using modified PPAR polypeptides

2. Claims: 14-16

- vectors comprising response elements

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/09416

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.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/09416

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0078986	A	28-12-2000	FR	2795425 A1	29-12-2000
			AU	6164500 A	09-01-2001
			BR	0011897 A	26-03-2002
			CN	1370240 T	18-09-2002
			CZ	20014609 A3	15-05-2002
			EP	1190084 A1	27-03-2002
			WO	0078986 A1	28-12-2000
			JP	2003503034 T	28-01-2003
			NO	20016347 A	19-02-2002
WO 9821349	A	22-05-1998	FR	2755699 A1	15-05-1998
			AU	5057898 A	03-06-1998
			BR	9713981 A	02-05-2000
			CZ	9901633 A3	11-08-1999
			EP	0946740 A1	06-10-1999
			WO	9821349 A1	22-05-1998
			HU	9904235 A2	28-04-2000
			JP	2001503279 T	13-03-2001
			KR	2000053163 A	25-08-2000
			NO	992153 A	04-05-1999
			SK	61499 A3	14-02-2000
			US	2002144302 A1	03-10-2002
			ZA	9710114 A	08-06-1998
EP 0798378	A	01-10-1997	EP	0798378 A2	01-10-1997
			EP	1162264 A2	12-12-2001
			GR	98300076 T1	30-11-1998
			AT	212055 T	15-02-2002
			AU	715812 B2	10-02-2000
			AU	1652197 A	02-10-1997
			CA	2200423 A1	26-09-1997
			DE	69709561 D1	21-02-2002
			DE	69709561 T2	29-08-2002
			DE	798378 T1	04-03-1999
			DK	798378 T3	29-04-2002
			ES	2123482 T1	16-01-1999
			HK	1001978 A1	03-05-2002
			HU	9700636 A2	28-04-1998
			JP	10004986 A	13-01-1998
EP 0752477	A	08-01-1997	EP	0752477 A2	08-01-1997
			AU	4493393 A	18-11-1993
			AU	637446 B2	27-05-1993
			AU	6935291 A	18-07-1991
			CA	2034220 A1	17-07-1991
			EP	0441483 A2	14-08-1991
			JP	6022766 A	01-02-1994
US 5597693	A	28-01-1997	AT	166360 T	15-06-1998
			AU	655912 B2	19-01-1995
			AU	5342390 A	22-10-1990
			CA	2047752 A1	18-09-1990
			DE	69032324 D1	25-06-1998
			DE	69032324 T2	08-10-1998
			EP	0463081 A1	02-01-1992
			JP	4505012 T	03-09-1992
			WO	9011273 A1	04-10-1990

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/09416

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0325849	A	02-08-1989	US 4981784 A	01-01-1991
			AT 124721 T	15-07-1995
			AT 182685 T	15-08-1999
			AU 628312 B2	17-09-1992
			AU 2818889 A	05-07-1989
			AU 665039 B2	14-12-1995
			AU 3026892 A	22-04-1993
			DE 3854120 D1	10-08-1995
			DE 3856354 D1	02-09-1999
			DE 3856354 T2	16-12-1999
			DK 136890 A	01-06-1990
			EP 0325849 A2	02-08-1989
			EP 0540065 A1	05-05-1993
			ES 2073408 T3	16-08-1995
			IE 68590 B1	26-06-1996
			JP 10295385 A	10-11-1998
			JP 10279599 A	20-10-1998
			JP 3006716 B2	07-02-2000
			JP 3503597 T	15-08-1991
			KR 9709951 B1	19-06-1997
			WO 8905355 A1	15-06-1989
			US 5571692 A	05-11-1996
			US 5548063 A	20-08-1996
			US 5171671 A	15-12-1992
			US 5599904 A	04-02-1997
			US 5274077 A	28-12-1993
WO 9826063	A	18-06-1998	CA 2192754 A1	12-06-1998
			AU 5470598 A	03-07-1998
			WO 9826063 A1	18-06-1998
FR 2806418	A	21-09-2001	FR 2806418 A1	21-09-2001
			AU 3939201 A	24-09-2001
			EP 1263978 A2	11-12-2002
			WO 0168845 A2	20-09-2001
			US 2002081719 A1	27-06-2002