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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 January 2003 (09.01.2003)

PCT

(10) International Publication Number
WO 2003/001883 A3

(51) International Patent Classification[7]: C12N 15/11, A01K 67/00, C12P 21/00, G01N 33/00

(21) International Application Number: PCT/US2002/020270

(22) International Filing Date: 25 June 2002 (25.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/301,102 26 June 2001 (26.06.2001) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/301,102 (CON)
Filed on 26 June 2001 (26.06.2001)

(71) Applicant *(for all designated States except US)*: **DELTAGEN, INC.** [US/US]; 740 Bay Road, Redwood City, CA 94063 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **WISOTZKEY, Robert, G.** [US/US]; 5408 Ruth Avenue, Oakland, CA 94601 (US).

(74) Agents: **BURKE, John, E.** et al.; Deltagen, Inc., 740 Bay Road, Redwood City, CA 94063 (US).

(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, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, 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:
22 January 2004

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.

WO 2003/001883 A3

(54) Title: GABA B1A RECEPTOR DISRUPTIONS, COMPOSITIONS AND METHODS RELATING THERETO

(57) Abstract: The present invention relates to compositions and methods relating to the characterization, function, and uses of GABA-B1A. Specifically, the present invention provides transgenic animals comprising disruptions in GABA-B1A receptors. The present invention also provides methods of identifying agents that modulate GABA-B1A, useful models, and potential for various disease states and disease conditions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/20270

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/11; A01K 67/00; C12P 21/00; G01N 33/00
US CL : 800/3, 4, 8, 18, 21; 536/23.1; 435/325

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)
U.S. : 800/3, 4, 8, 18, 21; 536/23.1; 435/325

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)
EAST, medline biosis caplus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OLSEN et al. Function of GABAA receptors: insights from mutant and knockout mice. GABA in the Nervous System (2000), pg 81-96. Editors Martin and Olsen. Publisher: lippincott Williams & Wilkins, Philadelphia, PA. See entire article.	1-20
A	SULLIVAN et al. Coexpression of full-length gamma-aminobutyric acid-B (GABA-B) receptors with truncated receptors with truncated receptors and metabotropic glutamate receptor 4 supports the GABA-B heterodimer as the functional receptor. J. Pharmacol. and Exp. Therapeutics. 2000. Vol. 293, No. 2. pg 460-467. See entire article.	1-20
P	HIRST et al. Molecular and pharmacological characterisation of the GABAB1 knockout mouse. Soc. Neurosci. Abstracts, 2001, Vol. 27, No. 2, pg 1854. See entire abstract.	1-20
P	PANGALOS et al. Epileptogenesis and pre-pulse inhibition in GABAB1 deficient mice. Society Neurosci. Abstracts. 2001. Vol. 27. No. 2. pg 1855. See entire abstract.	1-20
X	PROSSER et al. Epileptogenesis and enhanced prepulse inhibition in GABA-B1-deficient mice. Mol. Cellular Neurosci. June 2001. Vol. 17. pg 1059-1070. See entire article.	1-20
A	SANGER et al. GABA(B) receptor function in the ileum and urinary bladder of wildtype and GABA(B1) subunit in null mice. Auton Autacoid Pharmacol. June 2002. Vol. 22. No. 3. pg 147-154. See entire article.	1-20

☒ 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 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
11 July 2003 (11.07.2003)	22 SEP 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Deborah Reynolds Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/20270

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim 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. ☐ Claim 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:
Please See Continuation 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.: 1-20

Remark on Protest

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

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-20, drawn to a mouse having a disruption in a GABA-B1A gene.

Group II, claim(s) 21-27, drawn to a construct comprising a first and second portion of a GABA-B1A gene and a selectable marker located between the first and second portions and cells having a disruption in a GABA-B1A gene.

Group III, claim(s) 28, 29 and 33, drawn to a method using GABA-B1A to test agents that modulate a phenotype.

Group IV, claim(s) 30-32, drawn to a method of using animals to test agents that modulate a phenotype.

Group V, claim(s) 34, drawn to a method of using a preparation from a mouse having a disruption in a GABA-B1A gene.

Group VI, claim(s) 35, drawn to GABA-B1A protein.

Group VII, claim(s) 36, drawn to a method of making a pharmaceutical agent that modulates GABA-B1A.

Group VIII, claim(s) 37, drawn to phenotypic data.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
Inventions I-V and VIII are not a contribution to the art. Prosser (Molecular and Cellular Neuroscience. June 2001, Vol. 17. No. 6. pg 1059-1070) taught a mouse having a disruption in a GABA-B1A gene as claimed.
Inventions I-II, IV, V or VIII and III, VI or VII do not share a "special technical feature" because inventions I-II, IV, V and VIII require a disruption in a GABA-B1A gene which is not required in IV, VII or VIII.

Inventions III and V or VI lack unity because the GABA-B1A protein is not a contribution over the prior art. Sullivan (2000, J. Pharmacol Exp Ther, Vol. 293, pg 460-467) taught a GABA-B1A protein.

Inventions III, V or VI and VII or VIII do not share the same "special technical feature" because the protein required for III, V or VI is not required for the method of making a pharmaceutical or the data required for Inventions VII or VIII.