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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 February 2003 (20.02.2003)

PCT

(10) International Publication Number
WO 03/014303 A3

(51) International Patent Classification[7]: A61K 38/00

(21) International Application Number: PCT/US02/24655

(22) International Filing Date: 2 August 2002 (02.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/309,841 3 August 2001 (03.08.2001) US
60/360,061 25 February 2002 (25.02.2002) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), 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 (utility model), 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:
14 August 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.

WO 03/014303 A3

(54) Title: MOLECULAR INTERACTIONS IN CELLS

(57) Abstract: The invention provides reagents and methods for inhibiting or enhancing interactions between proteins in cells, particularly interactions between a PDZ protein and a PL protein. Reagents and methods that are provided are useful for treatment of a variety of diseases and conditions in a variety of cell types.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/24655

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/00

US CL : 514/2, 12

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. : 514/2, 12,; 530/350,324, 435/ 7.24

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/69896 A (ARBOR VITA CORP.) 23 November 2000 (23.11.2000), whole document, esp. claims 1, 3, 4, 6, 16, 17, 20, and 22.	2, 5, 15-20, 23-26
Y	US 5,976,819 A (FINEKL et al.) 2 November 1999 (02.11.1999), abstract, column 2, lines 28-67, column 4, lines 16-26, and column 6, lines 23-47.	5, 15-20
Y,E	US 2002/0058607 A (SATO et al.) 16 May 2002 (16.05.2002), page 1, page 5, paragraphs 0075, 0078-0080.	2, 5, 15-20
A	DOYLE et al., Cell, June 1996, Vol. 85, pages 1067-1076	2,5,15-20, 23-26
A	SONGYANG et al., Science, January 1997, Vol. 275, pages 73-77.	2,5,12-15, 23-26
X, E	US 2002/0147306 A (LIN et al.) 10 October 2002 (10.10.2002), abstract, page 1, paragraphs 0002, 0005, page 2, paragraphs 0009, 0020, 0028.	2, 15-20, 23-26

☐ 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

28 April 2003 (28.04.2003)

Date of mailing of the international search report

09 MAY 2003

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/24655

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.: 1
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:
Please See Continuation Sheet

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.: 2, 5, 15-20, 23-26

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box I Reason 2:
Claim 1 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: The claim is drawn to a method of modulating a biological function of a cell by introducing tot the cell an agent that modifies binding between an PDZ and a PL protein. The claim further states that the PDZ and PL proteins are identified in Table 2. Table 2 does not identify protein binding pairs as indicated in the claim However, it would appear that the Applicant intended to refer to Table 7, rather than Table 2, in the claim. Thus, although claim 1 is technically indefinite, for the purposes of this search report, it is being treated as though it referred to Table 7.

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, and 23-26 drawn to methods of modulating a biological function of a cell using an agent that alters the binding between PDZ and PL proteins and to such agents.

Group II, claim(s) 21 and 22, drawn to methods of determining if a test compound is an agent that modulates PDZ/PL binding.

Group III, claim(s) 27-29, drawn to methods of treating diseases by administering a modulating agent of PDZ/PL binding.

Each of the above Groups I and III comprise multiple inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1. Therefore, if one of these Groups is elected, further election is required as stated below.

For Group I, the applicant must also elect as the invention to be examined:

one of the proteins of following Groups I-a to I-i as the PDZ protein:

I-a	a protein kinase,	I-b	a guanalyte kinase,
I-c	a tyrosine phosphatase,	I-d	a serine phosphatase,
I-e	a LIM protein,	I-f	a guanine exchange factor,
I-g	a viral oncogene interacting protein,		
I-h	an ion channel protein, or	I-i	a transporter protein;

and one of I-1 to I-14 as the PL protein:

I-1	a T-cell surface receptor,	I-2	a B- cell surface receptor,
I-3	a NK cell surface receptor,	I-4	a monocyte cell surface receptor,
I-5	a granulocyte cell surface receptor,		
I-6	a endothelial cell surface receptor,		
I-7	a G-protein linked cell surface receptor,		
I-8	a regulator of G-protein signaling,		
I-9	an adhesion protein,		
I-10	a tight junction integral membrane protein,		
I-11	a viral oncogene,	I-12	a neuron membrane transport protein,
I-13	a receptor kinase, or	I-14	a tumor suppressor protein.

For Group III, the applicant must also elect as the invention to be examined:
one of the following methods, wherein the disease being treated is

IV-a	a neurological disease,	IV-b	an immune response disease
IV-c	a muscular disease, or	IV-d	a cancer.

The inventions listed as Groups I-III 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: each of these Groups relates to a

set of methods that perform a different function relating to modulators of PDZ/PL binding. As each of these methods perform a different function, and as the applicant is entitled to joinder of only a fist method with a claimed product, the methods of each of these Groups share no common special technical feature.

The inventions listed as Groups Ia-Ii, I-1 to I-14, and IV-a to IV-d 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: although the inventions share a common feature of modulating PDZ/Pl activities using modulators of PDZ/Pl binding, this feature does not distinguish over the prior art. See e.g. , U.S. Patent 5,958,731, issued to Yue et al., disclosing agonists and antagonists of a PDZ protein, and the use of such to treat disorders associated with the PDZ protein. See also, U.S. Patent 6,174,702, issued to Lal et al. and U.S. Patent 5, 863,898, issued to Goli et al. each of which discloses the use of agonists and antagonists of LIM proteins (disclosed as a PDZ protein in the present application) to treat diseases. As the proteins are disclosed as having affects on cells, these references also teach the use of these compounds to modulate biological functions in cells. Thus, because it is known to use PDZ agonists and antagonists to treat diseases (and therefore to modulate cellular activity), this feature cannot form the basis of establishing unity of invention.