

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
14 October 2004 (14.10.2004)

PCT

(10) International Publication Number  
**WO 2004/087730 A3**

(51) International Patent Classification<sup>7</sup>: **C12Q 1/68**,  
C07H 21/00, C07K 9/00, C12P 21/00, C07K 14/82

(21) International Application Number:  
PCT/US2004/009648

(22) International Filing Date: 29 March 2004 (29.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/458,192 27 March 2003 (27.03.2003) US  
60/535,781 12 January 2004 (12.01.2004) US

(71) Applicant (for all designated States except US): **THE  
JOHNS HOPKINS UNIVERSITY** [US/US]; 100 N.  
Charles Street, 5th Floor, Baltimore, MD 20201 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MERRYMAN,  
Charles, E.** [US/US]; 2501 Jim Kohler Road, Syberville,  
MD 21784 (US). **GREEN, Rachel, D.** [US/US]; 4303  
Wickford Road, Baltimore, MD 21210 (US).

(74) Agents: **COLLINS, Anne, J.** et al.; Hamilton, Brook,  
Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133,  
Concord, MA 01742-9133 (US).

(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG,  
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,  
ZW.

(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Euro-  
pean (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,  
GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK,  
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,  
ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

(88) Date of publication of the international search report:  
9 June 2005

(15) Information about Correction:

Previous Correction:

see PCT Gazette No. 07/2005 of 17 February 2005, Sec-  
tion II

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

(54) Title: METHOD FOR PRODUCING DIVERSE LIBRARIES OF ENCODED POLYMERS

(57) Abstract: Described are aminoacyl tRNA analogues which comprise a tRNA, and an amino acid which acts as an acceptor and donor substrate for ribosome-directed translation, thus, incorporating unusual monomers into non-standard polymers by the action of ribosomes. Also described are methods for producing such tRNA analogues; non-standard polymers; libraries of encoded polymers; methods of screening the libraries; and target members and their uses. A key advantage of synthesizing non-standard polymer libraries of the present invention with aminoacyl tRNA analogues is that large libraries of high complexity can be easily made and functional library members (e.g. novel drugs) readily identified.

WO 2004/087730 A3

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/009648

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC 7	C12Q1/68	C07H21/00 C07K9/00 C12P21/00 C07K14/82
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC 7 C12Q C07H C07K C12P		
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, CHEM ABS Data, BIOSIS, WPI Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KILLIAN, JENNIFER A. ET AL: "Ribosome-mediated incorporation of hydrazinophenylalanine into modified peptide and protein analogs" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, 120(13), 3032-3042 CODEN: JACSAT; ISSN: 0002-7863, 1998, XP002323506 * Schema 1-7 * abstract  ----- -/--	12-16, 21-27, 32-38, 42-49, 63-65
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> 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 *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	
7 April 2005	21/04/2005	
Name and mailing address of the ISA	Authorized officer	
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	Gohlke, P	

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/US2004/009648

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROBERTSON S A ET AL: "A GENERAL AND EFFICIENT ROUTE FOR CHEMICAL AMINOACYLATION OF TRANSFER RNAs" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 113, no. 7, 1991, pages 2722-2729, XP001064836 ISSN: 0002-7863 abstract; figures 3,4 -----	1-65
A	HECKLER, THOMAS G. ET AL: "Ribosomal binding and dipeptide formation by misacylated tRNAs" BIOCHEMISTRY, 27(19), 7254-62 CODEN: BICHAW; ISSN: 0006-2960, 1988, XP002323507 page 7256, left-hand column, last paragraph - right-hand column, paragraph THIRD * page 7257 Scheme I * -----	1-65
A	BAIN, J. D. ET AL: "Site-specific incorporation of nonnatural residues during in vitro protein biosynthesis with semi-synthetic aminoacyl-tRNAs" BIOCHEMISTRY, 30(22), 5411-21 CODEN: BICHAW; ISSN: 0006-2960, 1991, XP002323508 cited in the application the whole document -----	1-65
A	US 2002/031762 A1 (MERRYMAN CHARLES EVERETT ET AL) 14 March 2002 (2002-03-14) claims; figures 1a,1b,2 -----	1-65
A	CHO J H ET AL: "LiOH-mediated N-monoalkylation of alpha-amino acid esters and a dipeptide ester using activated alkyl bromides" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 43, no. 7, 11 February 2002 (2002-02-11), pages 1273-1276, XP004333902 ISSN: 0040-4039 abstract -----	21,63
A	RON, D. ET AL: "N-Methylated analogs of Ac'Nle28,31!CCK(26-33): synthesis, activity, and receptor selectivity" JOURNAL OF MEDICINAL CHEMISTRY ( 1992 ), 35(15), 2806-11 CODEN: JMCMAR; ISSN: 0022-2623, 1992, XP002323509 page 2806, right-hand column, line 11 - page 2807, left-hand column, line 14; figure 1 -----	21-63

-/--

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/009648

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BOWMAN W R ET AL: "A Facile Method for the N-Alkylation of alpha-Amino Esters" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 53, no. 46, 17 November 1997 (1997-11-17), pages 15787-15798, XP004106426 ISSN: 0040-4020 abstract	21,63
A	----- CHRUMA J J ET AL: "General Method for the Synthesis of N-Methyl Amino Acids and N-Alkyl Amino Esters from O'Donnell's Schiff Bases" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 38, no. 29, 21 July 1997 (1997-07-21), pages 5085-5086, XP004082951 ISSN: 0040-4039 abstract	21,63
P,X	----- FRANKEL, ADAM ET AL: "Encodamers Unnatural Peptide Oligomers Encoded in RNA" CHEMISTRY & BIOLOGY, 10(11), 1043-1050 CODEN: CBOLE2; ISSN: 1074-5521, 2003, XP002323510 the whole document	12-65
P,X	----- MERRYMAN CHUCK ET AL: "Transformation of aminoacyl tRNAs for the in vitro selection of "drug-like" molecules" CHEMISTRY & BIOLOGY (CAMBRIDGE), vol. 11, no. 4, April 2004 (2004-04), pages 575-582, XP002323511 ISSN: 1074-5521 the whole document	1-65
P,X	----- WO 03/059926 A (UNIVERSITY OF MASSACHUSETTS; ZHANG, BILIANG; CUI, ZHIYONG) 24 July 2003 (2003-07-24) cited in the application page 7, lines 17-28; claims	12-16, 21-27,63

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/009648

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002031762 A1	14-03-2002	US 2003022213 A1	30-01-2003
WO 03059926 A	24-07-2003	AU 2002359799 A1	30-07-2003
		WO 03059926 A2	24-07-2003