

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/013160 A3

- (51) International Patent Classification⁷: **A61K 39/00**
- (21) International Application Number:
PCT/US2003/024458
- (22) International Filing Date: 5 August 2003 (05.08.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/401,293 5 August 2002 (05.08.2002) US
60/419,982 21 October 2002 (21.10.2002) US
- (71) Applicant (for all designated States except US): **UNIVERSITY OF ROCHESTER** [US/US]; 601 Elmwood Avenue, Box 706, Rochester, NY 14642 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **SMITH, Harold, C.** [US/US]; 1056 Fransworth Road South, Rochester, NY 14623 (US). **SOWDEN, Mark, P.** [US/US]; 94 Phaeton Drive, Penfield, NY 14526 (US). **DEWHURST, Stephen** [US/US]; 157 Glen Ellyn Way, Rochester, NY 14618 (US). **KIM, Baek** [US/US]; 45 Embassy Drive, Rochester, NY 14618 (US). **WEDEKIND, Joseph** [US/US]; 1111 Lac de Ville Blvd., Apt. 110, Rochester, NY 14642 (US).
- (74) Agents: **HODGES, Robert, A.** et al.; Needle & Rosenberg, P.C., 999 Peachtree Street, Suite 1000, Atlanta, GA 33309-3915 (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, 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 (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, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, 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
— 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:
26 January 2006
- 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: PROTEIN TRANSDUCING DOMAIN/DEAMINASE CHIMERIC PROTEINS, RELATED COMPOUNDS, AND USES THEREOF

(57) Abstract: Disclosed are compositions for chimeric proteins comprising a protein transduction domain and a deaminase domain, mimetics or analog thereof, and uses of same.

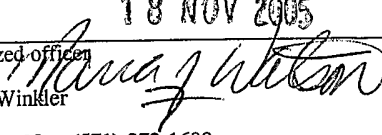


WO 2004/013160 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/24458

A. CLASSIFICATION OF SUBJECT MATTER																	
IPC(7)	: A61K 39/00																
US CL	: 424/185.1																
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. : 424/185.1																	
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) Please See Continuation Sheet																	
C. DOCUMENTS CONSIDERED TO BE RELEVANT																	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.															
Y, P --- A, P	US 2002/0164743 A1 (HONJO et al.) 07 November 2002 (07.11.2002), see claims.	37 ----- 38-40															
Y --- A	EP 1 174 509 A1 (KANSAI TECHNOLOGY LICENSING ORGANIZATION Co.) 23 January 2002 (23.01.2002)	37 ----- 38-40															
X --- Y	YANG et al. Apolipoprotein B mRNA editing and the reduction in synthesis and secretion of the atherogenic risk factor, apolipoprotein B100 can be effectively targeted through TAT-mediated protein transduction. Molecular Pharmacology. February 2002, Vol. 61, No. 2, pages 269-276.	1, 16, ----- 2-15, 17-27, 33-36, 47-78															
Y	JAYAN et al. Increased RNA editing and inhibition of hepatitis delta virus replication by high-level expression of ADAR1 and ADAR2. Journal of Virology April 2002, Vol. 76, No. 8, pages 3819-3827.	1-27, 33-36, 47-78															
Y	WYBRANIETZ et al. Enhanced suicide gene effect by adenoviral transduction of a VP22-cytosine deaminase (CD) fusion gene. Gene Therapy. 2001, Vol. 8, No. 21, pages 1654-1664.	1-27, 33-36, 47-78															
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																	
* Special categories of cited documents: <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;">"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td style="width: 5%; border: none;">"T"</td> <td style="width: 45%; border: none;">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</td> </tr> <tr> <td style="border: none;">"E" earlier application or patent published on or after the international filing date</td> <td style="border: none;">"X"</td> <td style="border: none;">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</td> </tr> <tr> <td style="border: none;">"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)</td> <td style="border: none;">"Y"</td> <td style="border: none;">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</td> </tr> <tr> <td style="border: none;">"O" document referring to an oral disclosure, use, exhibition or other means</td> <td style="border: none;">"&"</td> <td style="border: none;">document member of the same patent family</td> </tr> <tr> <td style="border: none;">"P" document published prior to the international filing date but later than the priority date claimed</td> <td style="border: none;"></td> <td style="border: none;"></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"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	"E" earlier application or patent published on or after the international filing date	"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	"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)	"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	"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed		
"A" document defining the general state of the art which is not considered to be of particular relevance	"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															
"E" earlier application or patent published on or after the international filing date	"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															
"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)	"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															
"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family															
"P" document published prior to the international filing date but later than the priority date claimed																	
Date of the actual completion of the international search 08 September 2005 (08.09.2005)		Date of mailing of the international search report 18 NOV 2005															
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner of Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230		Authorized officer  Ulrike Winkler Telephone No. (571)-272-1600															

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, T	LEE et al. Transduction of yeast cytosine deaminase mediated by HIV-1 Tat basic domain into tumor cells induces chemosensitivity to 5-fluorocytosine. <i>Experimental and Molecular Medicine</i> . 2004, Vol. 36, No. 1, pages 43-51.	1-27, 33-36, 47-78
A, P	HARRIS et al. RNA editing enzyme APOBEC1 and some of its homologs can act as DNA mutators. <i>Molecular Cell</i> . 2002, Vol. 10, No. 5, pages 1247-1253.	1-124
Y	ERBS et al. In vivo cancer gene therapy by adenovirus-mediated transfer of a bifunctional yeast cytosine deaminase/uracil phosphoribosyltransferase fusion gene. <i>Cancer Research</i> . 2000, Vol. 60, No. 14, pages 3813-3822.	1-27, 33-36, 47-78
Y, P	HARRIS et al. DNA deamination: not just a trigger for antibody diversification but also a mechanism for defense against retroviruses. <i>Nature Immunology</i> . July 2003, Vol. 4, No. 7, pages 641-643.	79-124
Y	SCHWARTZ et al. Peptide-mediated cellular delivery. <i>Current Opinion in Molecular Therapeutics</i> . 2000, Vol. 2, No. 2.	1, 2, 3, 16, 22, 23, 33, 47, 48, 63, 66-77
Y, P	ZHANG et al. The cytidine deaminase CEM15 induces hypermutation in newly synthesized HIV-1 DNA. <i>Nature</i> . July 2003, Vol. 424, pages 94-98.	28-32
--- A, P		----- 37-46
Y	SHEEHY et al. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. <i>Nature</i> . 8 August 2002, Vol. 418, pages 646-650. Epub 2002 Jul 14.	1-36, 47-78

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/24458

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.:

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) 1-15, 47-65, 28-32, drawn to a chimeric protein comprising a protein transduction domain and a deaminase domain. Administering the chimeric protein to a cell to inhibit HIV infectivity.

Group II, claim(s) 16-27, drawn to a chimeric protein that edits DNA.

Group III, claim(s) 33-36, 66-78, drawn to a nucleic acid that encodes a chimeric protein.

Group IV, claim(s) 37-46, drawn to a method of screening for a viral RNA mimetic.

Group V, claim(s) 79-97, drawn to a method of inducing class switch in immunoglobulins.

Group VI, claim(s) 98-104, drawn to a method of inducing an immune response to an antigen.

Group VII, claim(s) 105-124, drawn to a method of treating a subject having hyper IgM syndrome or having B lymphocyte lymphoma.

The inventions listed as Groups I-VII 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:

According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The invention listed as Groups I-VII do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. The technical feature of Group I (claim 1) is a chimeric protein comprising a protein transduction domain and a deaminase domain. Yang et al. (Molecular Pharmacology, February 2002) disclose a modified APOBEC-1 protein, a deaminase, that is fused to the protein transducing domain of HIV-Tat. The fusion protein is able to target into liver cells and is able to catalyze the apoB mRNA editing. Thus, the Yang et al. reference teaches a chimera that is able to enter cell and is functional in the modified cells. Jayan et al. (Journal of Virology, April 2002) teach that deaminases act on viral RNA and an overexpression of the deaminase results in inhibition of viral replication. The ordinary artisan would expect that the that the structure taught by Yang et al can be modified with any deaminase in order to produce a chimeric protein that is able to edit viral RNA. While the Jayan et al. provides the motivation for using a deaminase structure that effects viral RNA and modify the structure so that it may easily enter cells. Therefore, the technical feature of Group I (claim 1) is shown to lack an inventive step and does not make a contribution over the prior art.

Continuation of B. FIELDS SEARCHED Item 3:

WEST, DERWENT, MEDLINE

inventor search, CEM15, APOBEC3G, APOBEC1, ADER, RNA editing, protein transduction, deaminase.

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