

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 August 2009 (13.08.2009)

(10) International Publication Number
WO 2009/099961 A3

(51) International Patent Classification:

C07K 16/00 (2006.01) C07K 19/00 (2006.01)
C07K 16/10 (2006.01)

(21) International Application Number:

PCT/US2009/032692

(22) International Filing Date:

30 January 2009 (30.01.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/063,245 31 January 2008 (31.01.2008) US

(71) Applicant (for all designated States except US): **THE GOVERNMENT OF THE UNITED STATES OF AMERICA** as represented by **THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; National Institutes Of Health, Office Of Technology Transfer, 6011 Executive Blvd., Suite 325, Rockville, MD 20852-3804 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **DIMITROV, Dimiter, S.** [US/US]; 1019 Storrington Drive, Frederick, MD 21702 (US).

(74) Agent: **CONNOLLY, Jodi, L.**; Klarquist Sparkman, LLP, One World Trade Center, Suite 1600, 121 Sw Salmon Street, Portland, OR 97204 (US).

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

CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

— with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:

1 October 2009

(54) Title: ENGINEERED ANTIBODY CONSTANT DOMAIN MOLECULES

(57) Abstract: Described herein are engineered antibody constant domain molecules, such as CH2 or CH3 domain molecules, comprising at least one mutation, or comprising at least one complementarity determining region (CDR), or a functional fragment thereof, grafted in a loop region of the CH2 domain. The CH2 domain molecules described herein are small, stable, soluble, exhibit little to no toxicity and are capable of binding antigen.



WO 2009/099961 A3

INTERNATIONAL SEARCH REPORT

International application No PCT/US2009/032692
--

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07K16/00 C07K16/10 C07K19/00

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)
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, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/072620 A (RUEKER FLORIAN [AT]; WOZNIAK-KNOPP GORDANA [AT]) 13 July 2006 (2006-07-13) examples 1-10 claim 30 page 29, line 2 - line 10 page 41	1-8, 12-31, 43, 44, 46-62, 64
X	WO 2006/114700 A (BIOREN INC [US]; CREA ROBERTO [US]; CAPPUCCILLI GUIDO [US]; TAKEUCHI T) 2 November 2006 (2006-11-02) sequences 1,12	43, 44, 47, 48
X	US 2007/148170 A1 (DESJARLAIS JOHN R [US] ET AL) 28 June 2007 (2007-06-28) sequences 25-27	43, 44, 47, 48
	----- -/--	

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 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. *8* document member of the same patent family
---	---

Date of the actual completion of the international search 17 July 2009	Date of mailing of the international search report 03/08/2009
--	---

Name and mailing address of the ISA/ European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Fax: (+31-70) 340-3016	Authorized officer <p style="text-align: center;">Bumb, Peter</p>
--	---

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2009/032692

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material
 - on paper
 - in electronic form
 - c. time of filing/furnishing
 - contained in the international application as filed
 - filed together with the international application in electronic form
 - furnished subsequently to this Authority for the purpose of search
2. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/032692

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/076319 A (CENTOCOR INC [US]; O'NEIL KARYN T [US]; PICHA KRISTEN [US]; STOJANOVIC) 5 July 2007 (2007-07-05) sequences 43,45 -----	43,44, 47,48
X	US 2005/136049 A1 (LEDBETTER JEFFREY A [US] ET AL) 23 June 2005 (2005-06-23) page 113, line 29 - line 32 -----	43,44, 47,48
X	US 5 965 709 A (PRESTA LEONARD G [US] ET AL) 12 October 1999 (1999-10-12) sequence 60 -----	43,44, 47,48
P,X	WO 2008/100470 A (TRANSTECH PHARMA INC [US]; MJALLI ADNAN M M [US]; TIAN YE E [US]; WEBS) 21 August 2008 (2008-08-21) sequence 14 figure 1E -----	43,44, 47,48
P,X	WO 2008/153745 A (AMGEN INC [US]; WALKER KENNETH W [US]; GEGG COLIN V JR [US]) 18 December 2008 (2008-12-18) sequences 1, 107, 108 page 26 -----	43,44, 47,48
A	WO 2006/036834 A (AMGEN INC [US]) 6 April 2006 (2006-04-06) page 74 examples 1,13 -----	
A	FEIGE M J ET AL: "Folding Mechanism of the CH2 Antibody Domain" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 344, no. 1, 12 November 2004 (2004-11-12), pages 107-118, XP004609207 ISSN: 0022-2836 cited in the application the whole document -----	
A	THIES M J W ET AL: "The alternatively folded state of the antibody CH3 domain" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 309, no. 5, 22 June 2001 (2001-06-22), pages 1077-1085, XP004479201 ISSN: 0022-2836 the whole document -----	
	-/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/032692

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	<p>THIES M J W ET AL: "Folding and Oxidation of the Antibody Domain CH3" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 319, no. 5, 21 June 2002 (2002-06-21), pages 1267-1277, XP004449701 ISSN: 0022-2836 the whole document</p> <p>-----</p>	
A	<p>US 6 277 375 B1 (WARD ELIZABETH SALLY [US]) 21 August 2001 (2001-08-21) column 31, line 35 - line 38 column 46, line 43 - column 47, line 32</p> <p>-----</p>	
A	<p>SKERRA A: "ENGINEERED PROTEIN SCAFFOLDS FOR MOLECULAR RECOGNITION" JOURNAL OF MOLECULAR RECOGNITION, HEYDEN & SON LTD., LONDON, GB, vol. 13, no. 4, 1 July 2000 (2000-07-01), pages 167-187, XP009019725 ISSN: 0952-3499 the whole document</p> <p>-----</p>	
A	<p>LIPOVSEK ET AL: "Evolution of an Interloop Disulfide Bond in High-Affinity Antibody Mimics Based on Fibronectin Type III Domain and Selected by Yeast Surface Display: Molecular Convergence with Single-Domain Camelid and Shark Antibodies" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 368, no. 4, 17 April 2007 (2007-04-17), pages 1024-1041, XP022030013 ISSN: 0022-2836 the whole document</p> <p>-----</p>	
P,A	<p>GONG RUI ET AL: "Engineered human antibody constant domains with increased stability." THE JOURNAL OF BIOLOGICAL CHEMISTRY 22 MAY 2009, vol. 284, no. 21, 22 May 2009 (2009-05-22), pages 14203-14210, XP002537697 ISSN: 0021-9258 the whole document</p> <p>-----</p>	1-64

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/032692

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 allsearchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-35, 49-59 (all complete), 60, 64 (both in part)

Introduction of mutations or CDR into loops of CH2 or CH3 in order to provide an antigen binding polypeptide.

2. claims: 36-42, 63 (all complete); 60, 64 (both in part)

Introduction of an additional disulfide bridge into CH2 or CH3 in order to increase stability.

3. claims: 43-48, 61-62 (all complete); 60, 64 (both in part)

Truncation (i.e. by the full 7 amino acids) of CH2 or CH3 without antigen-binding activity in order to provide monomeric domains with improved stability

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/032692

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006072620 A	13-07-2006	AT 423140 T	15-03-2009
		AT 414718 T	15-12-2008
		AT 425186 T	15-03-2009
		AU 2006204459 A1	13-07-2006
		BR PI0606399 A2	23-06-2009
		CA 2594356 A1	13-07-2006
		CN 101098891 A	02-01-2008
		DK 1772465 T3	25-05-2009
		DK 1752471 T3	16-03-2009
		DK 1699826 T3	06-07-2009
		EA 200701443 A1	28-02-2008
		EP 1772465 A1	11-04-2007
		EP 1752471 A1	14-02-2007
		EP 1699826 A1	13-09-2006
		EP 2028193 A1	25-02-2009
		ES 2321861 T3	12-06-2009
		ES 2320374 T3	21-05-2009
		HR 20090087 T3	31-03-2009
		HR 20090228 T3	31-05-2009
		JP 2008526809 T	24-07-2008
		KR 20070092242 A	12-09-2007
SI 1752471 T1	30-04-2009		
SI 1772465 T1	30-06-2009		

WO 2006114700 A	02-11-2006	CA 2605697 A1	02-11-2006
		EP 1877441 A2	16-01-2008
		JP 2008538908 T	13-11-2008

US 2007148170 A1	28-06-2007	AU 2006299429 A1	12-04-2007
		CA 2624189 A1	12-04-2007
		EP 1931709 A2	18-06-2008
		US 2008206867 A1	28-08-2008
		WO 2007041635 A2	12-04-2007

WO 2007076319 A	05-07-2007	CA 2634784 A1	05-07-2007
		EP 1968645 A2	17-09-2008

US 2005136049 A1	23-06-2005	NONE	

US 5965709 A	12-10-1999	NONE	

WO 2008100470 A	21-08-2008	AR 065373 A1	03-06-2009
		CL 4602008 A1	22-08-2008
		US 2008199467 A1	21-08-2008
		UY 30925 A1	30-09-2008

WO 2008153745 A	18-12-2008	US 2009118181 A1	07-05-2009

WO 2006036834 A	06-04-2006	AU 2005289685 A1	06-04-2006
		BR PI0516011 A	19-08-2008
		CA 2580796 A1	06-04-2006
		CN 101103045 A	09-01-2008
		EA 200700623 A1	28-12-2007
		EP 1797127 A2	20-06-2007
		JP 2008514201 T	08-05-2008
		KR 20070057975 A	07-06-2007

US 6277375 B1	21-08-2001	US 2002098193 A1	25-07-2002