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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
06 June 2019 (06.06.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/106592 A3

(51) International Patent Classification:
C07K 14/705 (2006.01) *G01N 33/53* (2006.01)

(21) International Application Number:
PCT/IB2018/059449

(22) International Filing Date:
29 November 2018 (29.11.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/593,080 30 November 2017 (30.11.2017) US

(71) Applicant: **GRIFOLS DIAGNOSTIC SOLUTIONS INC.** [US/US]; 4560 Horton Street, Emeryville, California 94608 (US).

(72) Inventors: **BERRY, Jody**; 4209 Sullivan Trail, Easton, Pennsylvania 18040 (US). **BOOTH, Elizabeth**; 1529 Russell St. Apt 21, Berkeley, California 94703 (US). **ANTONY GEORGE, Joyee**; 2149, Otis Drive, Apt. 110, Alameda, California 94501 (US). **NASCIMENTO, Elisabete**; 1545 Floribunda Ave. Apt 115, Burlingame, California 94010 (US). **NAGORE CASAS, Daniel**; Parque Tecnologico De Bizkaia, Ibaizabal Bidea, Edificio 504, 48160 Derio (ES).

(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, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

(54) Title: IMMUNOASSAYS AND ENGINEERED PROTEINS FOR MONITORING ANTIBODY TREATMENTS TO THE IMMUNE CHECKPOINT INHIBITORS PD1 AND PD-L1

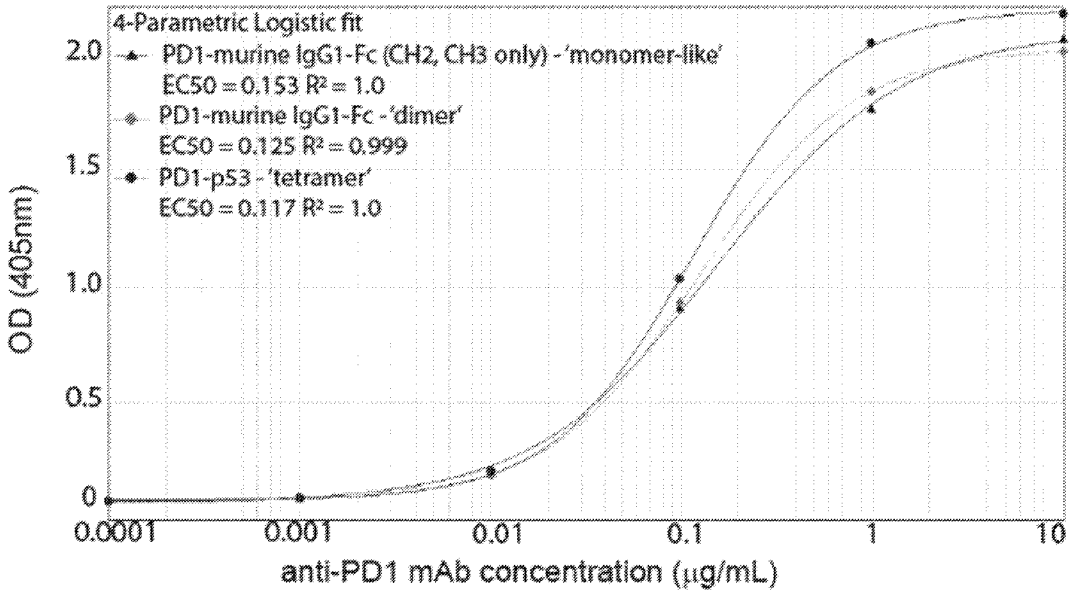

FIG. 4A

(57) Abstract: Fusion proteins comprising an extracellular domain of PD1 (programmed cell death protein-1) protein and/or an extracellular domain of PD-L1 (programmed cell death-ligand 1 protein (CD274 or B7-H1)) protein. Portions of the extracellular domains are expressed in specific configurations and purified as protein and used in immunoassays to monitor the circulating levels of biotherapeutic antibodies to these proteins. Also described is a method of determining the amount of circulating levels of a biotherapeutic antibody in a biological sample obtained from a patient, wherein a patient has undergone at least one dose of immunotherapy.

WO 2019/106592 A3

[Continued on next page]

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *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:
18 July 2019 (18.07.2019)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/059449

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/705 G01N33/53
ADD.

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 G01N

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)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, 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 2015/195531 A2 (EINSTEIN COLL MED [US]) 23 December 2015 (2015-12-23)	1,12,13
Y	paragraph [0355]	2-11,27, 29

X	WO 2011/161699 A2 (AURIGENE DISCOVERY TECH LTD [IN]; SASIKUMAR POTTAYIL GOVINDAN NAIR [IN]) 29 December 2011 (2011-12-29)	1,12,13
Y	example 16	2-11,27, 29

Y	WO 2017/058115 A1 (ASIA BIOTECH PTE LTD [SG]) 6 April 2017 (2017-04-06) examples 1, 2, 13 sequence No. 11, 14, 23	1-13,27, 29

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] 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 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
17 May 2019	31/05/2019

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, Fax: (+31-70) 340-3016	Bernhardt, Wiebke

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/059449

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 2 092 069 A2 (CENTELION [FR]) 26 August 2009 (2009-08-26) paragraph [0047], Seq ID No. 7 and 8	6,7

Y	US 2012/328693 A1 (LAN KENG-LI [TW] ET AL) 27 December 2012 (2012-12-27) example 11, paragraphs [0079], [0089], [0091], [0094] Seq ID No. 19, 26, figure 13b	6,7, 19-22

Y	JONAS SCHAEFER ET AL: "Minibodies", 1 January 2010 (2010-01-01), ANTIBODY ENGINEERING, SPRINGER-VERLAG, BERLIN/HEIDELBERG, DE, PAGE(S) 85 - 99, XP009511060, ISBN: 978-3-642-01146-7 table 7.1, table 7.2	1-29

Y	PLUCKTHUN A ET AL: "New protein engineering approaches to multivalent and bispecific antibody fragments", IMMUNOTECHNOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, NL, vol. 3, no. 2, 1 June 1997 (1997-06-01), pages 83-105, XP004126672, ISSN: 1380-2933, DOI: 10.1016/S1380-2933(97)00067-5 pages 95-96, figure 1	1-29

X	EP 3 147 298 A1 (GENEXINE INC [KR]; POSTECH ACADEMY-INDUSTRY FOUND [KR]) 29 March 2017 (2017-03-29)	14,15,25
Y	example 1, in particular paragraph [0104]	16-24, 26,28,29

X	SONG MY ET AL: "Protective effects of Fc-fused PD-L1 on two different animal models of colitis", 20150201, vol. 64, no. 2, 1 February 2015 (2015-02-01), pages 260-271, XP009186769, ISSN: 0017-5749, DOI: 10.1136/GUTJNL-2014-307311	14,15,25
Y	page 261, right-hand col.	16-24, 26,28,29

X	CN 105 999 223 A (4TH MILITARY MEDICAL UNIV CHINESE PLA) 12 October 2016 (2016-10-12)	14,15,25
Y	example 1, figures 1, 4	16-24, 26,28,29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/059449

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 all searchable 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: 1-13, 27(completely); 29(partially)

   A fusion protein comprising an extracellular domain of PD-1 and an oligomerization domain selected from (i) murine IgG1 Fc domain, (ii) murine IgG2A fc domain, (iii) GCN4 trimer domain, (iv) clathrin trimer domain, and (v) p53 tetramer domain; a method of determining the amount of an antibody comprising the use of said fusion protein

   ---

2. claims: 14-26, 28(completely); 29(partially)

   A fusion protein comprising an extracellular domain of PD-L1 and an oligomerization domain selected from (i) murine IgG1 Fc domain, (ii) murine IgG2A Fc domain, (iii) GcN4 trimer domain, (iv) clathrin trimer domain, and (v) p53 tetramer domain; a method of determining the amount of an antibody comprising the use of said fusion protein

   ---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2018/059449

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015195531 A2	23-12-2015	AU 2015277460 A1	24-11-2016
		BR 112016027897 A2	24-10-2017
		CA 2947489 A1	23-12-2015
		CN 106456733 A	22-02-2017
		EP 3157552 A2	26-04-2017
		EP 3480213 A1	08-05-2019
		EP 3483179 A1	15-05-2019
		JP 2017519491 A	20-07-2017
		KR 20170030484 A	17-03-2017
		SG 11201609876T A	27-01-2017
		TW 201613966 A	16-04-2016
		US 2017058015 A1	02-03-2017
		US 2018282392 A1	04-10-2018
		WO 2015195531 A2	23-12-2015
WO 2011161699 A2	29-12-2011	AU 2011268484 A1	31-01-2013
		CA 2803859 A1	29-12-2011
		CN 103096915 A	08-05-2013
		CU 20120176 A7	31-05-2013
		EA 201300005 A1	31-03-2014
		EP 2585099 A2	01-05-2013
		IL 223678 A	31-08-2017
		JP 2013534922 A	09-09-2013
		JP 2017008065 A	12-01-2017
		KR 20140002594 A	08-01-2014
		NZ 605533 A	24-12-2014
		SG 186809 A1	28-02-2013
		US 2011318373 A1	29-12-2011
		WO 2011161699 A2	29-12-2011
		ZA 201300313 B	26-10-2016
WO 2017058115 A1	06-04-2017	BR 112018006547 A2	11-12-2018
		CA 3000638 A1	06-04-2017
		CN 108368175 A	03-08-2018
		EP 3356416 A1	08-08-2018
		JP 2018529368 A	11-10-2018
		KR 20180083318 A	20-07-2018
		US 2018282412 A1	04-10-2018
		WO 2017058115 A1	06-04-2017
EP 2092069 A2	26-08-2009	AR 063975 A1	04-03-2009
		AT 509106 T	15-05-2011
		AU 2007326985 A1	05-06-2008
		BR PI0719290 A2	25-02-2014
		CA 2668932 A1	05-06-2008
		CL 2007003411 A1	04-07-2008
		CO 6190564 A2	19-08-2010
		CR 10777 A	23-07-2009
		CY 1112435 T1	09-12-2015
		DK 2092069 T3	29-08-2011
		EA 200970515 A1	30-12-2009
		EC SP099361 A	30-06-2009
		EP 2092069 A2	26-08-2009
		GT 200900137 A	02-09-2011
		HR P20110503 T1	31-08-2011
		JP 2010510801 A	08-04-2010
		KR 20090102769 A	30-09-2009
		MA 31143 B1	01-02-2010

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2018/059449

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		MY 145914 A	15-05-2012
		PE 12502008 A1	07-10-2008
		PT 2092069 E	29-07-2011
		RS 51911 B	29-02-2012
		SI 2092069 T1	30-09-2011
		SV 2009003272 A	05-02-2010
		TN 2009000184 A1	18-10-2010
		TW 200839012 A	01-10-2008
		US 2010061979 A1	11-03-2010
		US 2012195851 A1	02-08-2012
		US 2014030265 A1	30-01-2014
		WO 2008065543 A2	05-06-2008
US 2012328693 A1	27-12-2012	CN 102836441 A	26-12-2012
		CN 107519486 A	29-12-2017
		TW 201300529 A	01-01-2013
		US 2012328693 A1	27-12-2012
		US 2014105934 A1	17-04-2014
		US 2017028040 A1	02-02-2017
EP 3147298 A1	29-03-2017	CN 106573987 A	19-04-2017
		EP 3147298 A1	29-03-2017
		JP 2017519520 A	20-07-2017
		KR 20150135148 A	02-12-2015
		US 2017189476 A1	06-07-2017
CN 105999223 A	12-10-2016	NONE	