



(51) International Patent Classification:

C07K 16/28 (2006.01) *A61P 35/02* (2006.01)
A61K 39/395 (2006.01)

(21) International Application Number:

PCT/US2017/042982

(22) International Filing Date:

20 July 2017 (20.07.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/364,811 20 July 2016 (20.07.2016) US

(71) Applicant: **JANSSEN PHARMACEUTICA NV**
[BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

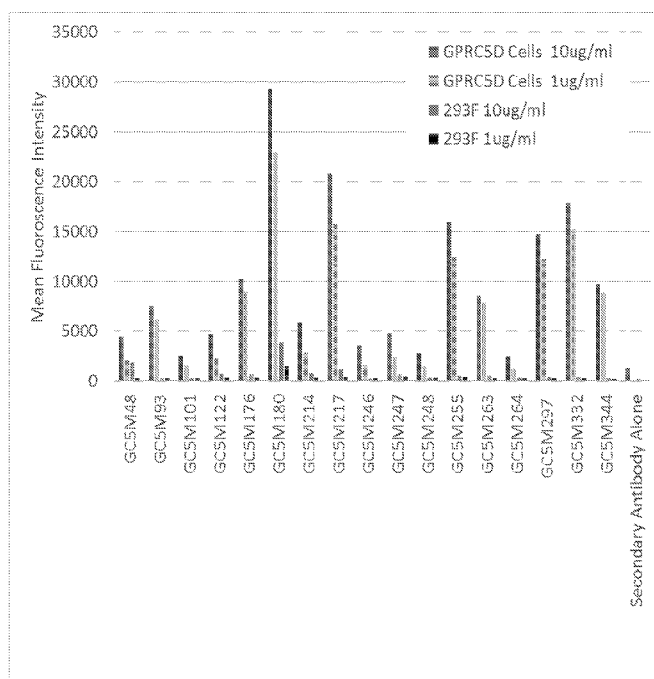
(72) Inventor; and

(71) Applicant: **ATTAR, Ricardo** [US/US]; 1400 McKean Road, Spring House, Pennsylvania 19477 (US).

(72) Inventors: **CHIN, Diana**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **EDAVETTAL, Suzanne**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **GAUDET, Francois**; 3210 Merryfield Row, La Jolla, 92121 (UA). **LI, Yingzhe**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **LUISTRO, Leopoldo**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **MAJEWSKI, Nathan**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **MEN-DONCA, Mark**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **PILLARISETTI, Kondandaram**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **TEPLYAKOV, Alexey**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **TORNETTA, Mark**;

(54) Title: ANTI- GPRC5D ANTIBODIES, BISPECIFIC ANTIGEN BINDING MOLECULES THAT BIND GPRC5D AND CD3, AND USES THEREOF

Figure 1



(57) Abstract: Provided herein are antibodies that specifically bind to GPRC5D. Also described are related polynucleotides capable of encoding the provided GPRC5D-specific antibodies or antigen-binding fragments, cells expressing the provided antibodies or antigen-binding fragments, as well as associated vectors and detectably labeled antibodies or antigen-binding fragments. In addition, methods of using the provided antibodies are described. For example, the provided antibodies may be used to diagnose, treat, or monitor GPRC5D-expressing cancer progression, regression, or stability; to determine whether or not a patient should be treated for cancer; or to determine whether or not a subject is afflicted with GPRC5D-expressing cancer and thus may be amenable to treatment with a GPRC5D-specific anti-cancer therapeutic, such as the multispecific antibodies against GPRC5D and CD3 described herein.



1400 McKean Road, Spring House, Pennsylvania 19477 (US).

(74) **Agent:** SHIRTZ, Joseph F. et al.; JOHNSON & JOHNSON, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (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, 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, 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 applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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:**

01 March 2018 (01.03.2018)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/042982

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/28 A61K39/395 A61P35/02 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 A61K		
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, Sequence Search, 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 2016/090329 A2 (SLOAN KETTERING INST CANCER [US]; EUREKA THERAPEUTICS INC [US]) 9 June 2016 (2016-06-09)	1-6,8, 12-26,64
Y	tables 1-32, examples 1-6	27-29, 32, 43-63,65

X	WO 2016/036937 A1 (JANSSEN PHARMACEUTICA NV [BE]) 10 March 2016 (2016-03-10)	64,65
Y	Seq ID No. 184, 190	27-29, 32,49-63

-/--		
☒ 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 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 5 January 2018		Date of mailing of the international search report 02/02/2018
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Bernhardt, Wiebke

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/042982

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "Human GPRC5D APC-conjugated Antibody", 12 October 2015 (2015-10-12), XP055408560, Retrieved from the Internet: URL:https://resources.rndsystems.com/pdfs/ datasheets/fab6300a.pdf [retrieved on 2017-09-21]	1-6,8, 12-26,64
Y	abstract	27-29, 32, 43-63,65
A	----- RUDIHOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity", PROCEEDINGS NATIONAL ACADEMY OF SCIENCES PNAS, NATIONAL ACADEMY OF SCIENCES, US, vol. 79, no. 6, 1 March 1982 (1982-03-01), pages 1979-1983, XP002683593, ISSN: 0027-8424, DOI: 10.1073/PNAS.79.6.1979 abstract	1-6,8, 12-29, 32,43-65
A	----- WO 2005/086568 A2 (MORPHOSYS AG [DE]; LITZENBURGER TOBIAS [DE]; URBAN MARGIT [DE]) 22 September 2005 (2005-09-22) fig. 3 Seq ID No. 17	1-6,8, 12-29, 32,43-65
X	----- EP 1 468 694 A1 (SUMITOMO PHARMA [JP]) 20 October 2004 (2004-10-20) paragraphs [0027] - [0030], examples	1-6,8, 12-26
A	----- COHEN YOSSIE ET AL: "GPRC5D is a promising marker for monitoring the tumor load and to target multiple myeloma cells.", HEMATOLOGY (AMSTERDAM, NETHERLANDS) NOV 2013, vol. 18, no. 6, November 2013 (2013-11), pages 348-351, XP009195526, ISSN: 1607-8454 abstract, tables 1-2	1-6,8, 12-29, 32,43-65
	----- -/-	

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/042982

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOHANNA ATAMANIUK ET AL: "Overexpression of G protein-coupled receptor 5D in the bone marrow is associated with poor prognosis in patients with multiple myeloma", EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, vol. 42, no. 9, 1 September 2012 (2012-09-01), pages 953-960, XP055408451, GB ISSN: 0014-2972, DOI: 10.1111/j.1365-2362.2012.02679.x abstract -----	1-6,8, 12-29, 32,43-65

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/042982

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.:

1-6, 8, 12-29, 32, 43-65
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: 29(completely); 1-6, 12-28, 43-65(partially)

An isolated antibody, or antigen-binding fragment thereof, that binds specifically to GPRC5D comprising the 6 CDRs with Seq ID No. 1, 5, 9, 13, 16, 19 (i.e. the CDRs of antibody designated GC5B81 according to table 1); an isolated GPRC5D x CD3 bispecific antibody comprising said CDRs; an isolated cell expressing said antibody or bispecific antibody; a medical use of said bispecific antibody; a pharmaceutical composition comprising said bispecific antibody; a method for generating said bispecific antibody; an isolated synthetic polynucleotide encoding a chain of said bispecific antibody; a kit comprising said bispecific antibody or said polynucleotide

2-3. claims: 1-28, 30-65(all partially)

An isolated antibody, or antigen-binding fragment thereof, that binds specifically to GPRC5D comprising the 6 CDRs of antibody designated GC5B465 to GC5B599 according to table 1, respectively; an isolated GPRC5D x CD3 bispecific antibody comprising said CDRs; an isolated cell expressing said antibody or bispecific antibody; a medical use of said bispecific antibody; a pharmaceutical composition comprising said bispecific antibody; a method for generating said bispecific antibody; an isolated synthetic polynucleotide encoding a chain of said bispecific antibody; a kit comprising said bispecific antibody or said polynucleotide

4. claims: 32(completely); 1-5, 8, 12-28, 43-65(partially)

An isolated antibody, or antigen-binding fragment thereof, that binds specifically to GPRC5D comprising the 6 CDRs with Seq ID No. 4, 8, 12, 15, 18 and 21 (i.e. the CDRs of antibody designated GC5B596 according to table 1), respectively; an isolated GPRC5D x CD3 bispecific antibody comprising said CDRs; an isolated cell expressing said antibody or bispecific antibody; a medical use of said bispecific antibody; a pharmaceutical composition comprising said bispecific antibody; a method for generating said bispecific antibody; an isolated synthetic polynucleotide encoding a chain of said bispecific antibody; a kit comprising said bispecific antibody or said polynucleotide

5-13. claims: 1-28, 30-65(all partially)

An isolated antibody, or antigen-binding fragment thereof, that binds specifically to GPRC5D comprising the 6 CDRs of antibody designated GC5B382 to GC5B601 according to table 1,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

respectively; an isolated GPRC5D x CD3 bispecific antibody comprising said CDRs; an isolated cell expressing said antibody or bispecific antibody; a medical use of said bispecific antibody; a pharmaceutical composition comprising said bispecific antibody; a method for generating said bispecific antibody; an isolated synthetic polynucleotide encoding a chain of said bispecific antibody; a kit comprising said bispecific antibody or said polynucleotide

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/042982

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016090329	A2	09-06-2016	
		AU 2015357535 A1	29-06-2017
		CA 2969886 A1	09-06-2016
		CN 107206077 A	26-09-2017
		EP 3227324 A2	11-10-2017
		KR 20170108945 A	27-09-2017
		SG 11201704552T A	28-07-2017
		WO 2016090329 A2	09-06-2016
WO 2016036937	A1	10-03-2016	
		AR 101765 A1	11-01-2017
		AU 2015311931 A1	16-03-2017
		CA 2959171 A1	10-03-2016
		CN 107074956 A	18-08-2017
		CR 20170079 A	27-04-2017
		EP 3189081 A1	12-07-2017
		JP 2017529838 A	12-10-2017
		KR 20170049554 A	10-05-2017
		PE 15562017 A1	27-10-2017
		PH 12017500472 A1	31-07-2017
		SG 11201701599U A	30-03-2017
		TW 201625687 A	16-07-2016
		US 2016068605 A1	10-03-2016
		UY 36289 A	01-04-2016
		WO 2016036937 A1	10-03-2016
WO 2005086568	A2	22-09-2005	NONE
EP 1468694	A1	20-10-2004	
		AU 2002367145 A1	15-07-2003
		EP 1468694 A1	20-10-2004
		JP WO2003055507 A1	28-04-2005
		US 2005019320 A1	27-01-2005
		WO 03055507 A1	10-07-2003