



(51) International Patent Classification:

*C07K 16/30* (2006.01)    *G01N 33/574* (2006.01)  
*A61K 39/395* (2006.01)    *A61K 47/48* (2006.01)  
*G01N 33/68* (2006.01)    *A61K 39/00* (2006.01)  
*A61K 38/45* (2006.01)

(21) International Application Number:

PCT/US2016/034633

(22) International Filing Date:

27 May 2016 (27.05.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/166,760    27 May 2015 (27.05.2015)    US

(71) Applicants: **LA JOLLA BIOLOGICS, INC.** [US/US];  
10421 Pacific Center Court, Suite 100, San Diego, CA  
92121 (US). **TANVEX BIOLOGICS CORP.**; 33F.,  
No.99, Sec. 1, Xintai 5th Rd., Xizhi Dist., New Taipei City  
221 (TW).

(72) Inventors: **LEE, Yu-ching**; 250 Wuxing Street, Taipei  
City, 110 (TW). **YANG, Yi-Yuan**; 250 Wuxing Street,  
Taipei City, 110 (TW). **YEN, Yun**; 1301 Oaklawn Road,  
Arcadia, CA 91006 (US).

(74) Agent: **NORTON, Vicki, G.**; Duane Morris LLP, Suite  
2900, 750 B Street, San Diego, CA 92101 (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, DK, DM,  
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,  
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,  
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).

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))

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

16 February 2017

(54) Title: ANTIBODIES AGAINST GLYPICAN-3 AND THEIR USES IN CANCER DIAGNOSIS AND TREATMENT

(57) Abstract: The present invention relates to anti-GPC3 antibodies and their applications. The invention investigates the potential inhibitory effect of anti-GPC3 antibodies on tumor growth, proliferation, migration and their applications for diagnostic and therapeutic purposes.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/34633

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a.  forming part of the international application as filed:  
 in the form of an Annex C/ST.25 text file.  
 on paper or in the form of an image file.
- b.  furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c.  furnished subsequent to the international filing date for the purposes of international search only:  
 in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).  
 on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2.  In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of 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/US 16/34633

**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.: 44, 45  
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 Supplemental Sheet to continue .....

- 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 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.:  
 ..... See Supplemental Sheet to continue .....
- 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.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/34633

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - C07K 16/30, A61K 39/395, G01N 33/68, A61K 38/45, G01N 33/574, A61K 47/48, A61K 39/00 (2016.01) CPC - C07K 16/303, C07K 16/3069, C07K 16/30, A61K 47/48638, A61K 47/48569, A61K 38/45 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(8) - C07K 16/30, A61K 39/395, G01N 33/68, A61K 38/45, G01N 33/574, A61K 47/48, A61K 39/00 (2016.01) CPC - C07K 16/303, C07K 16/3069, C07K 16/30, A61K 47/48638, A61K 47/48569, A61K 38/45 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched CPC - G01N 33/57492, G01N 33/57449, G01N 33/57438, G01N 33/57423, A61K 2039/505, C07K 2317/73, C07K 2317/92, C07K 2317/76, C07K 2317/622, C07K 2317/569, C07K 2317/56, C07K 2317/55, C07K 2317/54, C07K 2317/24, G01N 2333/705, G01N 2458/00 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST(PGPB,USPT,USOC,EPAB,JPAB); PatBase, Google/Scholar: Glypican-3, Glypican-3, GPC3, DGSX, GTR2-2, MXR7, OCI-5, SDYS, SGB, SGBS, SGBS1, or heparan sulphate proteoglycan, HSPG, hepatocellular carcinoma, antibody GenCore 6.4.1: SEQ ID NO: 1, 3, 5, 7, 10, 12, 15, 16, 18, 20, 23, 25, 28, 30, 36, 38																			
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>																			
<table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>US 2007/0083334 A1 (Mintz, et al.) 12 April 2007 (12.04.2007) SEQ ID NO 1022717, amino acids 10-24, 63.4% identity to SEQ ID NO:10</td> <td>1-5, 10, 11, 13-17, 19, 20, 23, 24, 26, 28-32, (35,37,41,43)/(1-5,10,11,13-17,19,20,23,24,26,28-32), 36/(35), (38-40)/37, 42/41</td> </tr> <tr> <td>A</td> <td>WO 2010/126590 A1 (COLD SPRING HARBOR LAB, et al.) 04 November 2010 (04.11.2010) pg 86, SEQ ID NO:19, amino acids 134-256, 87.0% identity to SEQ ID NO: 28; pg 117, SEQ ID NO:309, amino acids 22-126, 82.4% identity to SEQ ID NO: 36</td> <td>11, 20, 31</td> </tr> <tr> <td>A</td> <td>WO 2014/016737 A9 (PFIZER) 04 September 2014 (04.09.2014) Claim 11, SEQ ID NO 23, amino acids 97-109, 73.8% identity to SEQ ID NO:12</td> <td>1-4, 7, 9-13, 16-18, 20-22, 25-27, 29-32, (35,37,41,43)/(1-4,7,9,10-13,16-18,20-22,25-27,29-32), 36/35, (38-40)/37, 42/41</td> </tr> <tr> <td>A</td> <td>US 2014/0099317 A1 (Suri, et al.) 10 April 2014 (10.04.2014) SEQ ID NO:153, 87.2% identity to SEQ ID NO:30</td> <td>11, 31</td> </tr> <tr> <td>A</td> <td>US 2014/0205612 A1 (Chan-Hui, et al.) 24 July 2014 (24.07.2014) claim 70, SEQ ID NO: 393, 82.4% identity to SEQ ID NO:38</td> <td>20</td> </tr> </tbody> </table>	Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	US 2007/0083334 A1 (Mintz, et al.) 12 April 2007 (12.04.2007) SEQ ID NO 1022717, amino acids 10-24, 63.4% identity to SEQ ID NO:10	1-5, 10, 11, 13-17, 19, 20, 23, 24, 26, 28-32, (35,37,41,43)/(1-5,10,11,13-17,19,20,23,24,26,28-32), 36/(35), (38-40)/37, 42/41	A	WO 2010/126590 A1 (COLD SPRING HARBOR LAB, et al.) 04 November 2010 (04.11.2010) pg 86, SEQ ID NO:19, amino acids 134-256, 87.0% identity to SEQ ID NO: 28; pg 117, SEQ ID NO:309, amino acids 22-126, 82.4% identity to SEQ ID NO: 36	11, 20, 31	A	WO 2014/016737 A9 (PFIZER) 04 September 2014 (04.09.2014) Claim 11, SEQ ID NO 23, amino acids 97-109, 73.8% identity to SEQ ID NO:12	1-4, 7, 9-13, 16-18, 20-22, 25-27, 29-32, (35,37,41,43)/(1-4,7,9,10-13,16-18,20-22,25-27,29-32), 36/35, (38-40)/37, 42/41	A	US 2014/0099317 A1 (Suri, et al.) 10 April 2014 (10.04.2014) SEQ ID NO:153, 87.2% identity to SEQ ID NO:30	11, 31	A	US 2014/0205612 A1 (Chan-Hui, et al.) 24 July 2014 (24.07.2014) claim 70, SEQ ID NO: 393, 82.4% identity to SEQ ID NO:38	20	<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																	
A	US 2007/0083334 A1 (Mintz, et al.) 12 April 2007 (12.04.2007) SEQ ID NO 1022717, amino acids 10-24, 63.4% identity to SEQ ID NO:10	1-5, 10, 11, 13-17, 19, 20, 23, 24, 26, 28-32, (35,37,41,43)/(1-5,10,11,13-17,19,20,23,24,26,28-32), 36/(35), (38-40)/37, 42/41																	
A	WO 2010/126590 A1 (COLD SPRING HARBOR LAB, et al.) 04 November 2010 (04.11.2010) pg 86, SEQ ID NO:19, amino acids 134-256, 87.0% identity to SEQ ID NO: 28; pg 117, SEQ ID NO:309, amino acids 22-126, 82.4% identity to SEQ ID NO: 36	11, 20, 31																	
A	WO 2014/016737 A9 (PFIZER) 04 September 2014 (04.09.2014) Claim 11, SEQ ID NO 23, amino acids 97-109, 73.8% identity to SEQ ID NO:12	1-4, 7, 9-13, 16-18, 20-22, 25-27, 29-32, (35,37,41,43)/(1-4,7,9,10-13,16-18,20-22,25-27,29-32), 36/35, (38-40)/37, 42/41																	
A	US 2014/0099317 A1 (Suri, et al.) 10 April 2014 (10.04.2014) SEQ ID NO:153, 87.2% identity to SEQ ID NO:30	11, 31																	
A	US 2014/0205612 A1 (Chan-Hui, et al.) 24 July 2014 (24.07.2014) claim 70, SEQ ID NO: 393, 82.4% identity to SEQ ID NO:38	20																	
<table border="1"> <tbody> <tr> <td>* Special categories of cited documents:</td> <td>"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</td> </tr> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"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</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"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</td> </tr> <tr> <td>"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>"&amp;" document member of the same patent family</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </tbody> </table>		* Special categories of cited documents:	"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	"A" document defining the general state of the art which is not considered to be of particular relevance	"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	"E" earlier application or patent but published on or after the international filing date	"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	"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)	"&" document member of the same patent family	"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							
* Special categories of cited documents:	"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																		
"A" document defining the general state of the art which is not considered to be of particular relevance	"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																		
"E" earlier application or patent but published on or after the international filing date	"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																		
"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)	"&" document member of the same patent family																		
"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																			
Date of the actual completion of the international search 28 November 2016	Date of mailing of the international search report <b>28 DEC 2016</b>																		
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774																		

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/34633

In Continuation of Box III. 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.

Group I+: claims 1-43, directed to an isolated anti-GPC3 antibody (claims 1-34), a pharmaceutical composition comprising thereof (claims 35,36); a method of treating cancer (claims 37-40); a method of diagnosing cancer (claims 41-43). The anti-GPC3 antibody, a pharmaceutical composition comprising the antibody and a method of using the antibody will be searched to the extent that the anti-GPC3 antibody comprises HC CDR1 of SEQ ID NO:1, HC CDR2 of SEQ ID NO:5, HC CDR3 of SEQ ID NO:10; LC CDR1 of SEQ ID NO:15, LC CDR2 of SEQ ID NO:18, LC CDR3 of SEQ ID NO:23, HC of SEQ ID NO:28, LC of SEQ ID NO:36. It is believed that claims 1-5, 10, 11, 13-17, 19, 20, 23, 24, 26, 28-32, (35,37,41,43)/(1-5,10,11,13-17,19,20,23,24,26,28-32), 36/(35)/(1-5,10,11,13-17,19,20,23,24,26,28-32), (38-40)/37/(1-5,10,11,13-17,19,20,23,24,26,28-32), 42/41/(1-5,10,11,13-17,19,20,23,24,26,28-32) encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass an anti-GPC3 antibody comprising HC CDR1 of SEQ ID NO:1, HC CDR2 of SEQ ID NO:5, HC CDR3 of SEQ ID NO:10; LC CDR1 of SEQ ID NO:15, LC CDR2 of SEQ ID NO:18, LC CDR3 of SEQ ID NO:23, HC of SEQ ID NO:28, LC of SEQ ID NO:36, a pharmaceutical composition comprising the antibody and a method of using the antibody. An additional antibody(ies) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected antibody(ies). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be an anti-GPC3 antibody, a pharmaceutical composition comprising the antibody and a method of using the antibody comprising HC CDR1 of SEQ ID NO:2, HC CDR2 of SEQ ID NO:6, HC CDR3 of SEQ ID NO:11; LC CDR1 of SEQ ID NO:16, LC CDR2 of SEQ ID NO:19, LC CDR3 of SEQ ID NO:24, HC of SEQ ID NO:29, LC of SEQ ID NO:37, i.e., claims 1-4, 6, 10-12, 14-21, 25-27, 29-32, (35,37,41,43)/(1-4,6,10-12,14-21,25-27,29-32), 36/35/(1-4,6,10-12,14-21,25-27,29-32), (38-40)/37/(1-4,6,10-12,14-21,25-27,29-32), 42/41/(1-4,6,10-12,14-21,25-27,29-32).

The inventions listed as Group I+ 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:

#### Special Technical Features

The special technical feature of each invention of Group I+ is a specific combination of HC CDRs1-3 and LC CDRs 1-3.

#### Common Technical Features

The inventions of Group I+ share the technical feature of an isolated anti-GPC3 antibody. Some inventions of Group I+ share the technical feature of a pharmaceutical composition comprising the antibody. Some inventions of Group I+ share the technical feature of a method of treating cancer or a method of diagnosing liver cancer. However, this shared technical feature does not represent a contribution over prior art as being anticipated by WO 2013/181543 A1 to THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPT. OF HEALTH AND HUMAN SERVICES (hereinafter "USHHS") (05 December 2013).

USHHS discloses an isolated anti-GPC3 antibody (claims 1-6), a pharmaceutical composition comprising thereof (claim 19, "A composition comprising a therapeutically effective amount of the isolated immunoconjugate of any one of claims 13-18 in a pharmaceutically acceptable carrier"), a method of treating cancer (claim 21, "A method of inhibiting tumor growth or metastasis, comprising selecting a subject with a cancer that expresses GPC3 and administering to the subject a therapeutically effective amount of the composition of claim 12 or claim 19, thereby inhibiting tumor growth or metastasis"), and a method of diagnosing liver cancer (claim 22, claim 25, "The method of any one of claims 22-24, wherein the cancer is hepatocellular carcinoma (HCC)..."). As said technical features were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the groups.

The inventions of Group I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

#### Note re item 4:

Claims 44, 45 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

In Continuation of BOX III. Observations where unity of invention is lacking (item 3):

1-5, 7, 9-32, (35-43)/(1-5,7,9-32), restricted to an anti-GPC3 antibody comprising HC CDR1 of SEQ ID NO:1, HC CDR2 of SEQ ID NO:5, HC CDR3 of SEQ ID NO:10; LC CDR1 of SEQ ID NO:15, LC CDR2 of SEQ ID NO:18, LC CDR3 of SEQ ID NO:23, HC of SEQ ID NO:28, LC of SEQ ID NO:36 or HC CDR1 of SEQ ID NO:3, HC CDR2 of SEQ ID NO:7, HC CDR3 of SEQ ID NO:12; LC CDR1 of SEQ ID NO:16, LC CDR2 of SEQ ID NO:20, LC CDR3 of SEQ ID NO:25, HC of SEQ ID NO:30, LC of SEQ ID NO:38