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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 (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description (Rules 13bis.4(d)(i) and 48.2(a)(viii))*

(88) **Date of publication of the international search report**:
12 January 2017

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(54) **Title**: TIGIT-BINDING AGENTS AND USES THEREOF

(57) **Abstract**: Agents that specifically bind TIGIT are disclosed. The TIGIT-binding agents may include polypeptides, antibodies, and/or bispecific agents. Also disclosed are methods of using the agents for enhancing the immune response and/or treatment of diseases such as cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/34549

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 14/47, C07K 16/18 (2016.01)
CPC - C07K 14/4702, C07K 16/18
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)
IPC(8)- C07K 14/47, C07K 16/18 (2016.01)
CPC- C07K 14/4702, C07K 16/18

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 424/193.1, 530/387.9 (keyword search, terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar
Search Terms Used: TIGIT, antibody, epitope, Q62, D63, extreacellular, PVR

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X – A	US 2009/0258013 A1 (Clark et al.) 15 October 2009 (15.10.2009) para [0011]-[0015]	150, 152, 153/(150,152) — 1-2, 4, 5(1,2,4), 6, 17-18, 23-24, 94
A	Stanietsky et al."The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity" PNAS (October 20, 2009) vol. 106, no. 42, 17858-17863; pg 17858, col 2, para 2, Fig. S1 legend	1-2, 4, 5(1,2,4), 6, 17-18, 23-24, 94
A	US 2012/0213774 A1 (Fertig et al.) 23 August 2012 (23.08.2012) abstract, para [0007], SEQ ID NO: 7	1-2, 4, 5(1,2,4), 6, 17-18, 23-24, 94
A	US 2014/0271664 A1 (Garcia-Martinez et al.) 18 September 2014 (18.09.2014) abstract, para [0275], SEQ ID NO: 262	1-2, 4, 5(1,2,4), 6, 17-18, 23-24, 94
A	US 2004/0185040 A1 (Garcia-Martinez et al.) 23 September 2004 (23.09.2004) abstract, para [0153], SEQ ID NO; 78	1-2, 4, 5(1,2,4), 6, 17-18, 23-24, 94
A	US 2007/0072797 A1 (Robinson et al.) 29 March 2007 (29.03.2007) para [0067], SEQ ID NO: 23	1-2, 4, 5(1,2,4), 6, 17-18, 23-24, 94

☐ Further documents are listed in the continuation of Box C. ☐

* 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
09 November 2016	05 DEC 2016
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 16/34549

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.: 9-16, 31-93, 95-123, 131-132, 134-138, 146-149, 154-209, 211-214, 216-239
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:

- Please see extra sheet for continuation -

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.:

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.:
1-2, 4, 5(1,2,4), 6, 17-18, 23-24, 94, 150, 152, 153(150,152) limited to SEQ ID NOs: 7-12, 17, 18, 26, 28, 79

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.

Continuation of:

Box NO 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. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-8, 17-30, 94, 124-130, 133, 139-145, 150-153, 210, 215, 240-242, directed to an isolated antibody that specifically binds the extracellular domain (epitope) of TIGIT, comprising heavy chain variable region and light chain variable region polypeptides; and plasmids encoding thereof. The isolated TIGIT antibody will be searched to the extent that the anti-TIGIT antibody encompasses the first named antibody comprising heavy chain CDRs (SEQ ID NOs: 7-9), light chain CDRs (SEQ ID NOs: 10-12), heavy chain variable region SEQ ID NO: 17, light chain variable region SEQ ID NO: 18; heavy chain SEQ ID NO: 26, light chain SEQ ID NO: 28 (antibody 313R11 and 313/R12), and binds to epitope SEQ ID NO: 79 [see instant Specification, pg 41, Table 1, pg 146, para [0702], sequence listings]. It is believed that claims 1-2, 4, 5(in part), 6, 17-18, 23-24, 94, 150, 152, 153(in part) encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass antibody 313R11 and 313R12 comprising SEQ ID NOs: 7-12, 17, 18, 26, 28, 79. Additional anti-TIGIT antibody(ies) will be searched upon the payment of additional fee(s). 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 antibody 313M26 and 313M32 comprising heavy chain CDRs (SEQ ID NOs: 57-59), light chain CDRs (SEQ ID NOs: 60-62), heavy chain variable region SEQ ID NO: 63, light chain variable region SEQ ID NO: 64, heavy chain SEQ ID NO: 70, light chain SEQ ID NO: 72, epitope SEQ ID NO: 79 (claims 126-129, 133, 139-145, 150, 152, 153(in part), 210, 240, 241). [NOTE, claims 25-30 are excluded from the first invention, because antibody 313R19 is deposited with ATCC as PTA-122180 and PTA-122181, see instant Specification, para [0596]]

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 inventions of Group I+ each include the special technical feature of an unique anti-TIGIT antibody (CDRs, H chain, L chain, epitope, ATCC deposit) recited therein. Each of the inventions of Group I+ requires a unique anti-TIGIT antibody, not required by the other inventions

Common Technical Features

The inventions of Group I+ share the technical feature of an isolated antibody that specifically binds the extracellular domain (epitope) of TIGIT, comprising heavy chain variable region and light chain variable region polypeptides; and plasmids encoding thereof. However, these shared technical features do not represent a contribution over prior art in view of the article titled "The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity" by Stanietsky et al. (hereafter 'Stanietsky') [PNAS October 20, 2009 vol. 106 no. 421page 7858?17863]. Stanietsky teaches an isolated antibody that specifically binds the extracellular domain (epitope) of TIGIT (pg 17858, col 2, para 2, Mice were injected with the TIGIT-Ig fusion protein (described in Figs. S1 and S2) and hybridomas supernatants were tested for specific recognition of the YTS/TIGIT transfectants. Seven different mAbs were obtained that recognized YTS/TIGIT but not the parental YTS cells (Fig. 1A) in moderate (mAb 1?3) and high (mAb 4?7) modes of recognition; Fig. S1 legend, The TIGIT-Ig fusion protein, composed of the extracellular domain of the TIGIT receptor fused to the Fc portion of human IgG1). US 2013/0251720 A1 to GENETECH, INC (hereafter 'Genetech') also teaches anti-TIGIT antibody comprising HVR (hypervariable region, or CDRs), heavy chain and light chain (para [0017], [0110]). Genetech does not specifically teaches a plasmid encoding said antibody heavy chain and light chain, however, it would have been obvious to one of ordinary skill in the art to have obtained plasmids comprising the heavy chain or light chain of an antibody, as commonly practiced in the art.

As said technical features were known in the art at the time of the invention, these cannot be considered special technical feature that would otherwise unify the groups.

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