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(71) Applicant: **LUDWIG INSTITUTE FOR CANCER RESEARCH LTD** [US/US]; 666 Third Avenue, New York, NY 10017 (US).

(72) Inventors: **VAN SNICK, Jacques**; c/o Ludwig Institute for Cancer Research, Avenue Hippocrate 74-UCL 7459, B-1200 Brussels (BE). **UYTTENHOVE, Catherine**; c/o Ludwig Institute for Cancer Research, Avenue Hippocrate 74-UCL 7459, B-1200 Brussels (BE).

(74) Agent: **DIETZEL, Christine E.**; Klauber & Jackson L.L.C., 25 East Spring Valley Avenue - Suite 160, Maywood, NJ 07607 (US).

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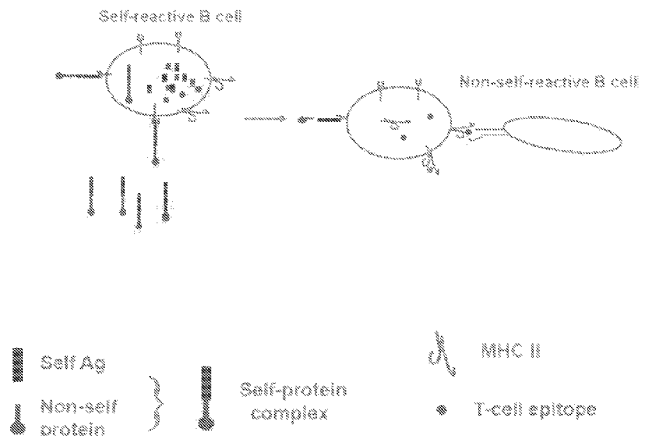
— *with international search report (Art. 21(3))*

— *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))*

[Continued on next page]

(54) Title: TGF-β3 SPECIFIC ANTIBODIES AND METHODS AND USES THEREOF

FIGURE 1



(57) Abstract: Specific binding members, particularly antibodies and fragments thereof, which bind to transforming growth factor beta 3 (TGF-β3) are provided, particularly recognizing human and mouse TGF-β3, particularly antibodies and fragments that do not recognize or bind TGF-β1 or TGF-β2. Particular antibodies are provided which specifically recognize and neutralize TGF-β3. These antibodies are useful in the diagnosis and treatment of conditions associated with activated or elevated TGF-β3, including cancer, and for modulating immune cells and immune response, including immune response to cancer or cancer antigens. The anti-TGF-β3 antibodies, variable regions or CDR domain sequences thereof, and fragments thereof may also be used in therapy in combination with chemotherapeutics, immune modulators, or anti-cancer agents and/or with other antibodies or fragments thereof. Antibodies of this type are exemplified by the novel antibodies hereof, including antibody MTGF-β3-9, MTGF-β3-12, MTGF-β3-16, MTGF-β3-17 and MTGF-β3-19, whose sequences are provided herein.

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

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/36965

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/00, 16/22; C12Q 1/68 (2016.01)
CPC - C07K 16/00, 16/22; C12Q 1/68
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 16/00, 16/22; C12Q 1/68 (2016.01)
CPC: C07K 16/00, 16/22, 2317/21, 2317/64, 2317/76, 2316/96, 2317/565, 2317/567; C12Q 1/68

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); EBSCO Discovery; PubMed; Google; Google Scholar; Google Patents; The Lens; ENA; NCBI Blast; KEYWORDS: isolated, antibody, neutralize, human, mouse, TGF-BETA3

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2014/0127230 A1 (LEDBETTER, S et al.) May 8, 2014; paragraphs [0004], [0014], [0042], [0050], [0074]	1-2 --- 10-11, 13-14, 16, 17/10-11, 17/13-14, 17/16, 18/10-11, 18/13-14, 18/16, 19/10-11, 19/13-14, 19/16, 20/10-11, 20/13-14, 20/16
Y	US 2006/0222643 A1 (TSUNODA, H et al.) October 5, 2006; claim 16	10, 13, 14, 16, 17/10, 17/13-14, 17/16, 18/10, 18/13-14, 18/16, 19/10, 19/13-14, 19/16, 20/10, 20/13-14, 20/16
Y	US 2006/0039913 A1 (DAS, A et al.) February 23, 2006; paragraph [0012]; claim 2	11, 14, 17/11, 17/14, 17/16, 18/11, 18/14, 18/16, 18/11, 19/14, 19/16, 20/11, 20/14, 20/16
Y	US 2010/0285034 A1 (GREGORY) November 11, 2010;	16, 17/16, 18/16, 19/16, 20/16
Y	US 2005/0176933 A1 (CHEN, Z et al.) August 11, 2005;	16, 17/16, 18/16, 19/16, 20/16

☒ 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	Date of mailing of the international search report
03 November 2016 (03.11.2016)	02 DEC 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/36965

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0003254 A1 (HATTORI, K et al.) January 7, 2010;	4-7, 12, 15, 17/4-7, 17/12, 17/15, 18/4-7, 18/12, 18/15, 19/4-7, 19/12, 19/15, 20/4-7, 20/12, 20/15
A	US 2014/0199301 A1 (ERDAG, B et al.) July 17, 2014; claim 16	4-9, 12, 15, 17/4-9, 17/12, 17/15, 18/4-9, 18/12, 18/15, 19/4-9, 19/12, 19/15, 20/4-9, 20/12, 20/15
A	US 2005/0079170 A1 (LE GALL, F et al.) April 14, 2005; paragraph [0013]	15, 17/15, 18/15, 19/15, 20/15
A	US 2010/0235938 A1 (XU, D et al.) September 16, 2010; paragraph [0281]	8-9, 17/8-9, 18/8-9, 19/8-9, 20/8-9
A	US 2013/0236471 A1 (BOEHRINGER INGELHEIM GMBH) Sep 12, 2013; claim 6	4-7, 12, 15, 17/4-7, 17/12, 17/15, 18/4-7, 18/12, 18/15, 19/4-7, 19/12, 19/15, 20/4-7, 20/12, 20/15
A	US 2011/0142859 A1 (EBENS, A et al.) June 16, 2011; claim 1	4-7, 12, 15, 17/4-7, 17/12, 17/15, 18/4-7, 18/12, 18/15, 19/4-7, 19/12, 19/15, 20/4-7, 20/12, 20/15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/36965

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.: 21-44
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 Supplemental Page-***-

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.:

1-16, 17/3-16, 18/3-16, 19/3-16, 20/3-16 ; SEQ ID NOs: 1-9, 23, 25, 31, 33, 39, 41

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
Information on patent family members

International application No.
PCT/US16/36965

-***-Continued from Box III -***-

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.

Groups I+, Claims 1-20 and SEQ ID NOs: 1-6, 24 and 25 are directed toward an isolated antibody molecule or fragment thereof which recognizes human and mouse transforming growth factor beta 3 (TGF-B3); and antibodies that bind to the same epitope, or which compete therewith.

The antibody will be searched to the extent that it encompasses a light chain variable region comprising a CDR1 sequence encompassing SEQ ID NO: 1 (first exemplary LCDR1), a CDR2 sequence encompassing SEQ ID NO: 2 (first exemplary LCDR2), and a CDR3 sequence encompassing SEQ ID NO: 3 (first exemplary LCDR3); and a heavy chain variable region sequence comprising a CDR1 sequence encompassing SEQ ID NO: 4 (first exemplary HCDR1), a CDR2 sequence encompassing SEQ ID NO: 5 (first exemplary HCDR2), and a CDR3 sequence encompassing SEQ ID NO: 6 (first exemplary HCDR3); a light chain variable region sequence encompassing SEQ ID NO: 25 (first exemplary light chain variable region) and a heavy chain variable region encompassing SEQ ID NO: 24 (first exemplary heavy chain variable region). Applicant is invited to elect additional set(s) of CDRs with specified SEQ ID NO: for each CDR, or specified substitution(s) at specified site(s) of a CDR SEQ ID NO:, with associated VL and/or VH, represented by SEQ ID NO(s), to be searched. Additional set(s) of antibody CDRs and accompanying VL and/or VH sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1, 2, 3 (in-part), 4 (in-part), 5 (in-part), 6 (in-part), 7 (in-part), 8 (in-part), 9 (in-part), 10 (in-part), 11 (in-part), 12 (in-part), 13 (in-part), 14 (in-part), 15 (in-part), 16 (in-part), 17 (in-part), 18 (in-part), 19 (in-part) and 20 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 1 (LCDR1), SEQ ID NO: 2 (LCDR2), SEQ ID NO: 3 (LCDR3); SEQ ID NO: 4 (HCDR1), a SEQ ID NO: 5 (HCDR2), SEQ ID NO: 6 (HCDR3); SEQ ID NO: 25 (light chain variable region) and SEQ ID NO: 24 (heavy chain variable region). Applicants must specify the claims that encompass any additionally elected sequences. 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/examined. An exemplary election would be a light chain CDR1 encompassing SEQ ID NO: 10 (first exemplary elected LCDR1), a CDR2 encompassing SEQ ID NO: 11 (first exemplary elected LCDR2), a CDR3 encompassing SEQ ID NO: 12 (first exemplary LCDR3), and corresponding light chain variable region sequence encompassing SEQ ID NO: 29 (first exemplary elected light chain variable region sequence).

No technical features are shared between the antibody CDR and corresponding light/heavy chain sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: an isolated antibody molecule or fragment thereof which recognizes human and mouse transforming growth factor beta 3 (TGF-B3) and which neutralizes activity of TGF-B3; an isolated antibody that binds to the same epitope of human TGF-B3; an isolated antibody that competes with the antibody in an assay comprising the following steps: (a) incubating TGF-B3 coated ELISA plates with a first antibody or antigen-binding fragment thereof in unlabeled form; (b) adding a biotinylated antibody or antigen-binding fragment thereof to the TGF-B3 coated ELISA plates and incubating TGF-B3 coated ELISA plates; and (c) detecting the binding of the antibody or antigen-binding fragment thereof; wherein the competition is exhibited as reduced binding of first antibody to human TGF-B3 by more than 60%.

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from Box III -***-

However, these shared technical features are previously disclosed by US 2014/0127230 A1 to Ledbetter et al. (hereinafter 'Ledbetter').

Ledbetter discloses an isolated antibody molecule or fragment thereof which recognizes human (an isolated antibody molecule or fragment thereof which recognizes human; paragraph [0014]) and mouse (mouse; paragraph [0004], wherein mouse TGFB3, being identical to human, presents the same epitopes) transforming growth factor beta 3 (TGF-B3) (transforming growth factor beta 3 (TGF-B3); paragraph [0014]) and which neutralizes activity of TGF-B3 (which neutralizes activity of TGF-B3; paragraph [0074]); an isolated antibody that binds to the same epitope of human TGF-B3 (an isolated antibody that binds to the same epitope of human TGF-B3; paragraphs [0014], [0044]); an isolated antibody that competes with the antibody (an isolated antibody that competes with the antibody; paragraph [0044]) in an assay comprising the following steps: (a) incubating TGF-B3 coated ELISA plates (in an assay comprising the following steps: (a) incubating TGF-B3 coated ELISA plates; paragraphs [0014], [0044], [0174]) with a first antibody or antigen-binding fragment thereof in unlabeled form (with a first antibody or antigen-binding fragment thereof in unlabeled form; paragraph [0174]); (b) adding a biotinylated antibody or antigen-binding fragment thereof to the TGF-B3 coated ELISA plates ((b) adding a biotinylated antibody or antigen-binding fragment thereof to the TGF-B3 coated ELISA plates; paragraphs [0149], [0174]) and incubating TGF-B3 coated ELISA plates (incubating TGF-B3 coated ELISA plates; paragraph [0174]); and (c) detecting the binding of the antibody or antigen-binding fragment thereof (detecting the binding of the antibody or antigen-binding fragment thereof; paragraph [0174]); wherein the competition is exhibited as reduced binding of first antibody to human TGF-B3 by more than 60%.

Ledbetter does not disclose wherein the competition is exhibited as reduced binding of first antibody to human TGF-B3 by more than 60%. However, it would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Ledbetter to have indicated wherein at least one antibody competed with a first antibody in a manner so as to reduce binding of first antibody to human TGF-B3 by more than 60%, in order to establish a threshold for competition indicating an antibody with a higher affinity for the target epitope than the first antibody, thereby enabling the selection of antibodies with improved affinity and potentially greater therapeutic efficacy.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Ledbetter reference, unity of invention is lacking.