The present invention relates to methods for diagnosing transplant rejection, or a condition associated with transplant rejection, such as, primary graft dysfunction in a subject, to antigen probe arrays for performing such a diagnosis, and to antigen probe sets for generating such arrays.
## INTERNATIONAL SEARCH REPORT

### A. CLASSIFICATION OF SUBJECT MATTER

<table>
<thead>
<tr>
<th>IPC(8)</th>
<th>G01 N 33/53 (2012.01)</th>
</tr>
</thead>
</table>

USPC - 435/7.1 : 436/501

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)
USPC: 435/7.1 : 436/501

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/7.1 : 436/501

(keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google; PubMed

Search terms: primary graft dysfunction, primary graft failure, organ transplant rejection, TEP1, EGFR, MBP, MUC1, autoantibodies, kit, diagnosis

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<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>X A</td>
<td>US 2008/0254481 A1 (LOVE et al.) 16 October 2008 (16.10.2008) para [0020], [0033]; Table 1</td>
<td>34</td>
</tr>
<tr>
<td>A</td>
<td>HAGEDORN et al. Chronic rejection of a lung transplant is characterized by a profile of specific autoantibodies. Immunology. July 2010 (07.2010), Vol. 130, No. 3, pages 427-435; abstract; pg 429, para 4; pg 429, para 5 - pg 430, para 2; Table 1</td>
<td>1-6, 12-18, 22-33, 35</td>
</tr>
<tr>
<td>A</td>
<td>PLANQUE et al. Autoantibodies to the epidermal growth factor receptor in systemic sclerosis, lupus, and autoimmune mice. FASEB J. February 2003 (02.2003), Vol. 17, No. 2, pages 136-143; abstract; pg 136, para 2</td>
<td>1-6, 12-18, 22-33, 35</td>
</tr>
</tbody>
</table>

* 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

**S** document member of the same patent family

Date of the actual completion of the international search
31 July 2012 (31.07.2012)

Date of mailing of the international search report
08 August 201?

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: IS/AUS, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer.
Lee W. Young

Form PCT/ISA/2 10 (second sheet) (July 2009)
INTERNATIONAL SEARCH REPORT

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:

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 1-1: claims 1-35, directed to a method of diagnosing primary graft dysfunction or organ transplantation rejection in a subject in need thereof, comprising: determining the reactivity of antibodies in a sample obtained from the subject to a plurality of antigens selected from the group consisting of: TEP1, EGFR, MBP, MLANA, MUC1, MYCL1, PLCG1, RB1, CERK, CYP3A4, SOC3, PRKCA, HSP90AA1, IFGR, HSPD1, TARP and TP 53, thereby determining the reactivity pattern of the sample to the plurality of antigens; and comparing said reactivity pattern of the sample to a control reactivity pattern, wherein a significant difference between said reactivity pattern of the sample compared to the control reactivity pattern is an indication that the subject is afflicted with primary graft dysfunction; wherein the first invention is limited to the smallest number of markers constituting a "plurality": three markers; further wherein the markers comprise the first three markers listed: TEP1, EGFR and MBP. (claims 1-5, 12-17, and 22-35)(Applicants may opt for additional markers to be searched by specifying the marker and paying an additional invention fee for each elected marker).

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. IEI 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, 12-18, and 22-35; limited to TEP1, EGFR, MBP, and MUC1
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.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)
**INTERNATIONAL SEARCH REPORT**

**DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
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</table>

Form PCT/ISA/2 10 (continuation of second sheet) (July 2009)
Continuation of Box III - observations where unity of invention is lacking:

The inventions listed as Groups 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:

The common technical feature of the claims of Group I+ is indicated above in the Group description; wherein the special technical feature of each subgroup is the particular marker or plurality of markers used.

The above common technical elements do not represent an improvement over the prior art of the article entitled "Antibodies to Self-Antigens Predispose to Primary Lung Allograft Dysfunction and Chronic Rejection" by Bharat et al. (hereinafter "Bharat") teaches wherein adult lung transplant recipients were diagnosed for primary graft dysfunction, and wherein samples from the subjects were assessed for the presence of antibodies to a plurality of antigens (Antibodies to self-antigens k-alpha-1 tubulin, collagen type V, and collagen I were quantitated using standardized enzyme-linked immunosorbent assays; methods), and wherein the presence of pretransplant antibodies to self-antigens correlated with increased risk of PGD, in comparison to subjects without pretransplant antigens (Results). Although Bharat does not specifically recite diagnosis of PGD, nor refer to the quantitation of the plurality of antibodies as a "pattern", and comparing said pattern to a control pattern, as indicated above, Bharat teaches comparing the antibody amounts in subjects demonstrating PGD to those not demonstrating PGD, it would have been obvious to a person skilled in the art to consider the subjects not demonstrating PGD to be controls, and to consider the quantitation of the antibodies taught by Bharat to represent a pattern that, when compared to the controls, would have produced a profile that would have been associated with a diagnosis of PGD, and to use said profile as a means of diagnosing PGD, or a high risk thereof.

Therefore, the inventions of Groups I+ lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.