



(51) International Patent Classification:

C12Q 1/68 (2006.01) *C40B* 40/08 (2006.01)
C40B 40/06 (2006.01) *G06F* 19/20 (2011.01)

(21) International Application Number:

PCT/US2017/016482

(22) International Filing Date:

3 February 2017 (03.02.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/290,657 3 February 2016 (03.02.2016) US

(71) Applicant: THE SCRIPPS RESEARCH INSITUTE
[US/US]; 10550 North Torrey Pines Road, La Jolla, CA
92037 (US).(72) Inventors: SALOMON, Daniel, R.; 4728 Reedley Ter-
race, San Diego, CA 92130 (US). KURIAN, Sunil, M.;
10963 Tobago Road, San Diego, CA 92126 (US). MOD-
ENA, Brian, D.; 645 Front Street, Unit 710, San Deigo,
CA 92101 (US).(74) Agents: FITTING, Thomas et al.; The Scripps Research
Institute, 10550 North Torrey Pines Road, TPC-8, La Jolla,
CA 92037 (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, 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).

Published:

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

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

5 October 2017

(54) Title: MOLECULAR ASSAYS FOR REGULATING IMMUNOSUPPRESSION, AVERTING IMMUNE-MEDIATED RE-
JECTION AND INCREASING GRAFT SURVIVAL

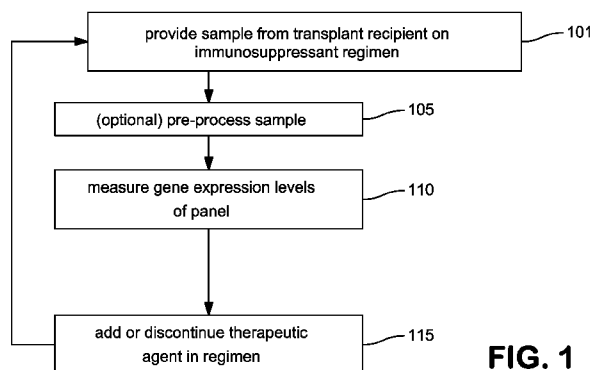


FIG. 1

(57) Abstract: Disclosed herein are methods of detecting, predicting or monitoring immune-mediated rejection, immunosuppression, or risk of graft loss in a transplant recipient undergoing an immunosuppression regimen. These methods may be useful even in patients with kidney damage not thought to result from ongoing immune activation. Also provided are molecular profiles that more sensitively detect ongoing immune-mediated injury and are a better indicator of later graft loss than standard microscopic biopsy examination.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/16482

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C12Q 1/68; C40B 40/06, 40/08; G06F19/20 (2017.01)

CPC - C12Q 1/68, 1/6809, 1/6816, 1/6874, 1/6876, 1/6881; C40B 40/06, 40/08; G06F 19/20

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/035367 A1 (THE SCRIPPS RESEARCH INSTITUTE et al.) 12 March 2015; paragraphs [0006], [0038]-[0039], [0043], [0047], [0053], [0055], [0061], [0069], [0085], [00244], [00249], [00297], [00301], [00303]	1, 31/, 4-5, 45, 47-48 ----- 49 - 52
Y	US 2009/0304705 A1 (GRASS, P) 10 December 2009; paragraphs [0007], [0155], [0183]	49 - 52
A	US 2010/0190166 A1 (HALLORAN, PF) 29 July 2010; page 10, table 4; page 11, table 4; page 13, table 6	2, 3/2, 46

☐ 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

19 May 2017 (19.05.2017)

Date of mailing of the international search report

08 JUN 2017

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

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/16482

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.: 6-44, 53-67
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.:
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.:
Groups I+, Claims 1-5, 45-52, DOCK2, CD53, ARHGAP30, CD2 and BIN2

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/US17/16482

-Continued from 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.

Groups I+, Claims 1-5, 45-52, DOCK2, CD53, ARHGAP30, CD2 and BIN2 are directed toward methods of administering immunosuppressant drugs, managing an immunosuppression regimen and detecting, monitoring or prognosing immune-mediated rejection or inadequate immunosuppression in a kidney transplant recipient.

The methods will be searched to the extent that the marker panel encompasses DOCK2 (first exemplary marker), CD53 (second exemplary marker), ARHGAP30 (third exemplary marker), CD2 (fourth exemplary marker) and BIN2 (fifth exemplary marker). Applicant is invited to elect additional marker(s) to be searched. Additional marker(s) will be searched upon the payment of additional fees. It is believed that claims 1, 2 (in part), 3-5, 45, 46 (in part) and 47-52 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass DOCK2 (first marker), CD53 (second marker), ARHGAP30 (third marker), CD2 (fourth marker) and BIN2 (fifth marker). Applicants must specify the claims that encompass any additionally elected marker(s). 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 marker encompassing CD48 (first exemplary elected marker).

No technical features are shared between the markers of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a method of managing an immunosuppression regimen and administering immunosuppressant drugs comprising: (a) obtaining a biological sample comprising nucleic acids, wherein the biological sample is obtained from a kidney transplant recipient on an immunosuppression drug regimen and wherein the nucleic acids comprise expression products from a panel of genes that are commonly dysregulated in acute and chronic rejection; (b) diagnosing immune-mediated rejection or inadequate immunosuppression in the kidney transplant recipient based on levels of the expression products from the panel of genes, wherein the panel of genes is specifically selected to detect immune-mediated rejection or inadequate immunosuppression in a kidney transplant subject irrespective of histological findings; and (c) adjusting the immunosuppression drug regimen administered to the kidney transplant recipient based on the levels of the expression products from the panel of genes specifically selected to detect immune-mediated rejection or inadequate immunosuppression in a kidney transplant subject irrespective of histological findings; detecting the presence or absence of immune-mediated rejection in the kidney transplant recipient without distinguishing between acute and chronic rejection, wherein the detecting is based on levels of the expression products from the panel of genes commonly regulated in acute and chronic rejection; wherein the panel is selected from a single set of up to 250 markers, and wherein the single set of up to 250 markers specifically detects immune-mediated rejection or inadequate immunosuppression in subjects with subclinical acute rejection, clinical acute rejection, subclinical chronic rejection, or clinical chronic rejection; a method of detecting, monitoring or prognosing immune-mediated rejection or inadequate immunosuppression in a kidney transplant recipient comprising: (a) obtaining a biological sample comprising nucleic acids, wherein the biological sample is obtained from a kidney transplant recipient on an immunosuppression drug regimen; (b) performing an assay on the nucleic acids to determine expression levels of a panel of genes, wherein the panel of genes is specifically selected to detect immune-mediated rejection or inadequate immunosuppression in a kidney transplant subject irrespective of histological findings; and (c) detecting, monitoring or prognosing immune-mediated rejection or inadequate immunosuppression based on the expression levels of the panel of genes specifically selected to detect immune-mediated in a kidney transplant subject irrespective of histological findings in the subject.

However, these shared technical features are previously disclosed by WO 2015/035367 A1 to The Scripps Research Institute et al. (hereinafter 'Scripps')

Scripps discloses a method of managing an immunosuppression regimen (a method of managing an immunosuppression regimen; paragraph [0038]) and administering immunosuppressant drugs (administering immunosuppressant drugs; paragraph [0054]) comprising: (a) obtaining a biological sample comprising nucleic acids (comprising: (a) obtaining a biological sample comprising nucleic acids; abstract, paragraphs [0006], [0058]), wherein the biological sample is obtained from a kidney transplant recipient (wherein the biological sample is obtained from a kidney transplant recipient; paragraph [0006]) on an immunosuppression drug regimen (on an immunosuppression drug regimen; paragraph [0038]) and wherein the nucleic acids comprise expression products from a panel of genes (wherein the nucleic acids comprise expression products from a panel of genes; paragraph [0069]) that are commonly dysregulated (that are known to be dysregulated in association with a diagnosis (that are commonly dysregulated); paragraph [00262]) in acute (in acute; paragraph [0006]) and chronic rejection (and chronic rejection; paragraph [0043]); (b) diagnosing immune-mediated rejection or inadequate immunosuppression in the kidney transplant recipient (diagnosing immune-mediated rejection or inadequate immunosuppression in the kidney transplant recipient; paragraphs [0010], [0038]) based on levels of the expression products from the panel of genes (based on levels of the expression products from the panel of genes; paragraphs [0006], [0038], [0069]), wherein the panel of genes is specifically selected to detect immune-mediated rejection or inadequate immunosuppression in a kidney transplant subject irrespective of histological findings (wherein the panel of genes is selected to detect subclinical rejection or immune-mediated rejection (wherein the panel of genes is specifically selected to detect immune-mediated rejection or inadequate immunosuppression in a kidney transplant subject irrespective of histological findings); paragraphs [0006], [0038], [0069]); and (c) adjusting the immunosuppression drug regimen administered to the kidney transplant recipient based on the levels of the expression products from the panel of genes (adjusting the immunosuppression drug regimen administered to the kidney transplant recipient based on the levels of the expression products from the panel of genes; paragraphs [0038], [0069]) specifically selected to detect immune-mediated rejection or inadequate immunosuppression in a kidney transplant subject irrespective of histological findings (selected to detect subclinical rejection or immune-mediated rejection (specifically selected to detect immune-mediated rejection or inadequate immunosuppression in a kidney transplant subject irrespective of histological findings); paragraphs [0006], [0038], [0069]);

-Continued on Next Supplemental Page-

-***-Continued from Previous Supplemental Page:

detecting the presence or absence of immune-mediated rejection in the kidney transplant recipient (detecting the presence or absence of immune-mediated rejection in the kidney transplant recipient; paragraphs [0006], [0038]), wherein the detecting is based on levels of the expression products from the panel of genes commonly regulated in acute and chronic rejection (wherein the detecting is based on the levels of expression products known to be associated with a rejection diagnosis, including acute and chronic rejection (wherein the detecting is based on levels of the expression products from the panel of genes commonly regulated in acute and chronic rejection); paragraphs [0006], [0043], [0069], [00262]); wherein the panel is selected from a single set of up to 250 markers (wherein the panel is selected from a single set of up to 250 markers; paragraph [0074]), and wherein the single set of up to 250 markers specifically detects immune-mediated rejection or inadequate immunosuppression in subjects with subclinical acute rejection, clinical acute rejection, subclinical chronic rejection, or clinical chronic rejection (wherein the single set of up to 250 markers specifically detects immune-mediated rejection or inadequate immunosuppression in subjects with subclinical acute rejection, clinical acute rejection, subclinical chronic rejection, or clinical chronic rejection; paragraphs [0006], [0038], [0043], [0069], [0074]); a method of detecting, monitoring or prognosing immune-mediated rejection or inadequate immunosuppression in a kidney transplant recipient (a method of detecting, monitoring or prognosing immune-mediated rejection or inadequate immunosuppression in a kidney transplant recipient; paragraphs [0010], [0038]) comprising: (a) obtaining a biological sample comprising nucleic acids (comprising: (a) obtaining a biological sample comprising nucleic acids; abstract, paragraphs [0006], [0058]), wherein the biological sample is obtained from a kidney transplant recipient (wherein the biological sample is obtained from a kidney transplant recipient; paragraph [0006]) on an immunosuppression drug regimen (on an immunosuppression drug regimen; paragraph [0038]); (b) performing an assay on the nucleic acids to determine expression levels of a panel of genes ((b) performing an assay on the nucleic acids to determine expression levels of a panel of genes; paragraphs [0006], [0069]), wherein the panel of genes is specifically selected to detect immune-mediated rejection or inadequate immunosuppression in a kidney transplant subject irrespective of histological findings (wherein the panel of genes is selected to detect subclinical rejection or immune-mediated rejection (wherein the panel of genes is specifically selected to detect immune-mediated rejection or inadequate immunosuppression in a kidney transplant subject irrespective of histological findings); paragraphs [0006], [0038], [0069]); and (c) detecting, monitoring or prognosing immune-mediated rejection or inadequate immunosuppression based on the expression levels of the panel of genes (detecting, monitoring or prognosing immune-mediated rejection or inadequate immunosuppression based on the expression levels of the panel of genes; paragraphs [0010], [0038], [0069]) specifically selected to detect immune-mediated in a kidney transplant subject irrespective of histological findings in the subject (specifically selected to detect immune-mediated in a kidney transplant subject irrespective of histological findings in the subject; paragraphs [0006], [0038], [0069]). Scripps further discloses distinguishing between at least two conditions (distinguishing between at least two conditions; paragraphs [0006]), including wherein one of the two conditions is transplant rejection (including wherein one of the two conditions is transplant rejection; paragraph [0006]), and one condition is transplant dysfunction without rejection (one condition is transplant dysfunction without rejection; paragraphs [0005], [0006]).

Scripps does not disclose: without distinguishing between acute and chronic rejection. However, based on the disclosure of Scripps, 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 Scripps to have considered distinguishing between two conditions, or three conditions, where at least one condition was normal functioning, and one condition included transplant rejection, as disclosed by Scripps, to have included both acute and chronic rejection within the classification of transplant rejection, in order to better enable a determination of an appropriate course of treatment or lack of alteration of treatment of a patient.

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 Scripps reference, unity of invention is lacking.