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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))*

- (88) **Date of publication of the international search report:**
31 December 2014

(54) **Title:** METHODS FOR TREATING CANCER

(57) **Abstract:** The disclosure features a method of treating cancer by lowering a patient's two gene score (TGS), particularly by increasing the number of tumor-infiltrating leukocytes. In addition, a TGS animal model and uses thereof are provided.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/30676

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/68, G01N 33/48, G01N 33/50 (2014.01)

CPC - C12Q 1/6883, C12Q 1/6827, C12Q 1/6816, C12Q 2600/156, C12Q 1/6869, C07H 21/00

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)

CPC- C12Q 1/6883, C12Q 1/6827, C12Q 1/6816, C12Q 2600/156, C12Q 1/6869, C07H 21/00

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

CPC- C12Q 1/6837, A61K 38/00, C12Q 1/6897, C12Q 1/6883, C12Q 1/6895, C12Q 1/6886, C12Q 2600/158, C07K 14/47, G06F 19/18, G06F 19/24, G06F 19/20; USPC- 435/6.1, 435/6.11, 435/6.14, 702/19, 506/7, 424/133.1, 514/283, 514/34, 514/110, 514/179

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: PACHYNSKI, Russe11 K; KOHRT, Ho1brook E.YONEHIRO, Jason; Non-Hodgkin lymphoma; Diffuse large B-cell lymphoma DLBCL, R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, International Prognostic Index, Comblmmune

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Alizadeh, et al. Prediction of survival in diffuse large B-cell lymphoma based on the expression of 2 genes reflecting tumor and microenvironment. Blood 2011, 118(5):1350-8) Abstract, pg 1350, col 1; pg 1351, col 2; pg 1354; pg 1355, Fig 3 and its legend; pg 1356; Supplemental Materials, Fig S3 and its legend	1-7, 9-18 ----- 8
Y	Desbois, et al. Natural killer cells in non-hematopoietic malignancies. Front Immunol. 2012, 3:395; pg 8, last para to pg 9, 1st para	8

☐ 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

05 October 2014 (05.10.2014)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/30676

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.

Group I: claims 1-18, drawn to a method of treating a patient diagnosed with a malignant tumor and having a first two gene score (TGS), wherein the first TGS indicates the patient is high risk, intermediate risk, or low risk, the method comprising administering a therapeutic that leads to an increased number of tumor-infiltrating leukocytes.

***** 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.:
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.:
1-18

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.

***** Supplemental Sheet *****

In Continuation of Box III. Observations where unity of invention is lacking

Group II: claims 19-37, drawn to a method of modeling TGS in a non-human animal comprising:

- (a) obtaining a first sample from a tumor in a non-human animal,
- (b) determining a TGS,
- (c) observing a clinical outcome of the non-human animal, and
- (d) correlating the clinical outcome with the TGS, thereby producing a TGS animal model (claims 19-30), and a method of identifying a composition that lowers a TGS, the method comprising:
 - (a) obtaining a first sample from a tumor in a non-human animal,
 - (b) contacting the tumor in vivo with a composition,
 - (c) obtaining a second sample from the tumor,
 - (d) determining the TGS of the first sample and the second sample,wherein the composition lowers the TGS of the tumor if the TGS of the second sample is less than the TGS of the first sample (claims 31-37).

The inventions listed as Groups I and II 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 do not include the special technical feature of a method of modeling TGS in a non-human animal comprising:

- (a) obtaining a first sample from a tumor in a non-human animal, (b) determining a TGS, (c) observing a clinical outcome of the non-human animal, and (d) correlating the clinical outcome with the TGS, thereby producing a TGS animal model (claims 19-30) or a method of identifying a composition that lowers a TGS by (a) obtaining a first sample from a tumor in a non-human animal, (b) contacting the tumor in vivo with a composition, (c) obtaining a second sample from the tumor, (d) determining the TGS of the first sample and the second sample, wherein the composition lowers the TGS of the tumor if the TGS of the second sample is less than the TGS of the first sample (claims 31-37), as required by Group II.

The inventions of Group II do not include the special technical feature of a method of treating a patient diagnosed with a malignant tumor and having a first TGS indicating that the patient is high, intermediate, or low risk, the method comprising administering a therapeutic that leads to an increased number of tumor-infiltrating leukocytes, as required by Group I.

Common Technical Features

The inventions of Groups I and II share the technical feature of a method of determining TGS in a subject and correlating it with the risk for subject. However, this shared technical feature does not represent a contribution over prior art as being anticipated by an article titled "Prediction of survival in diffuse large B-cell lymphoma based on the expression of 2 genes reflecting tumor and microenvironment" by Alizadeh, et al. (Blood 2011, 118(5):1350-8) (hereinafter "Alizadeh").

Alizadeh discloses a method of determining TGS in a subject (pg 1354, col 1, "We next examined the prognostic strength of the bivariate model combining expression of the tumor biomarker LMO2... with the microenvironment marker TNFRSF9, weighting the 2 genes based on their independent contributions from multivariate Cox regression in the training cohort (DLBCL1). We calculated TGS as follows: $TGS = (-0.32 \times LMO2) + (-0.29 \times TNFRSF9)$ ") and correlating it with the risk for subject (pg 1354, col 1, "This score effectively predicted OS [overall survival] in patients treated with R-CHOP ($P < .0001$; Figure 3A-C). For each incremental unit rise of the TGS, there was a 2.7-fold (95% confidence interval [CI] 2.0-3.8) increase in relative risk of death. Tertiles of the TGS stratified patients with distinct outcomes (supplemental Figure 5), with corresponding 2-year OS rates of 56%, 77%, and 91% (Figure 3A)"). As said technical feature was known in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the groups.

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