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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a
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- with international search report (Art. 21(3))
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[Continued on next page]

(54) **Title:** MEANS AND METHODS FOR DIAGNOSTICS AND THERAPEUTICS OF DISEASES

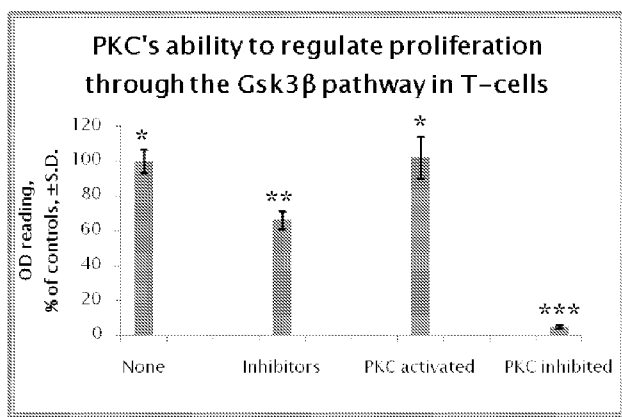


Figure 8

(57) **Abstract:** The present invention discloses a method of detecting T-cell proliferation in a subject comprising the steps of (a) obtaining a sample from said subject; and (b) profiling at least one parameter selected from the group consisting of: the activation level of GSK-3β, the expression level of GSK-3β and the activation or expression level of related members of pathways in which GSK-3β plays a part. It is a core aspect of the invention, wherein a significant deviation from normal values indicates cellular proliferation. The present invention further discloses kits for detecting T-cell proliferation.



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INTERNATIONAL SEARCH REPORT

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International application No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - G01N 33/535 (2013.01)

USPC - 435/7.92

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) - C12N 5/071, 5/0783, 9/12; C12Q 1/48, 1/68; G01N 33/50, 33/53, 33/533, 33/535 (2013.01)

USPC - 435/6.11, 6.19, 7.2, 7.24, 7.92, 194, 372.3

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

CPC - C12N 5/071, 5/0783, 9/12; C12Q 1/48, 1/68; G01N 33/50, 33/53, 33/533, 33/535 (2013.01)

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

Patbase, Google Patent, PubMed, Google Scholar, Google

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 2008/0213240 A1 (ALESSI et al) 04 September 2008 (04.09.2008) entire document | 1, 2, 4, 5, 9, 10, 14-16, 21-23, 25, 26, 32, 33, 35-39, 41-45, 47, 48, 50, 51, 53-55, 59, 61, 62, 64, 66, 74-76 3, 6-8, 17-20, 24, 27-31, 34, 40, 46, 49, 52, 56-58, 60, 63, 69-73 |
| Y | US 2005/0075276 A1 (RUDD) 07 April 2005 (07.04.2005) entire document | 3, 18-20, 40, 60, 63 |
| Y | PODAR et al., "Targeting PKC in multiple myeloma: in vitro and in vivo effects of the novel, orally available small-molecule inhibitor enzastaurin (LY317615.HCl)," Blood, 15 February 2007 (15.02.2007), Vol. 109, No. 4, Pgs. 1669-1677. entire document | 6-8 |
| Y | US 2008/0306069 A1 (WYATT et al) 11 December 2008 (11.12.2008) entire document | 17, 52 |
| Y | US 2002/0197657 A1 (BJORKLUND et al) 26 December 2002 (26.12.2002) entire document | 24, 56 |
| Y | US 2010/0183586 A1 (HORI et al) 22 July 2010 (22.07.2010) entire document | 27-31, 57, 58, 71, 73 |

 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

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INTERNATIONAL SEARCH REPORT

international application no.

PCT/IL2013/050237

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| Y | US 2011/0129896 A1 (TER HAAR et al) 02 June 2011 (02.06.2011) entire document | 34, 46, 49 |
| Y | WO 2009/069980 A2 (HAN et al) 04 June 2009 (04.06.2009) entire document | 69-72 |
| Y | WO 2003/004612 A2 (GHOSH et al) 16 January 2003 (16.01.2003) entire document | 8 |

INTERNATIONAL SEARCH REPORT

international application no.

PCT/IL2013/050237

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:

See Extra Sheet

- 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.:

- 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.

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 need to be paid.

Group I: claims 1-68 and 73-76 are drawn to a method and kit for detecting, diagnosing, and regulating T-cell proliferation disorders in a subject by measuring GSK-3- β expression.

Group II: claims 69-72 are drawn to a protein chip comprising an array of bound antibodies, biomarkers, or antigens useful in determining the expression of proteins associated with T-cell proliferation.

The inventions listed in 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:

The special technical features of Group I, a method and kit for detecting, diagnosing, and regulating T-cell proliferation disorders in a subject by measuring GSK-3- β expression, are not present in Group II; and the special technical features of Group II, a protein chip comprising an array of bound antibodies, biomarkers, or antigens useful in determining the expression of proteins associated with T-cell proliferation in a sample, are not present in Group I.

Additionally, Groups I and II share the technical features of measuring expression levels of proteins associated with T-cell proliferation in a sample. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2008/0213240 A1 to Alessi et al. discloses measuring expression levels of proteins associated with T-cell proliferation in a sample (Para. [0023] The method of the invention can also be used for identifying activators or inhibitors of GSK3. The invention also provides a method for screening for inhibitors or activators of enzymes that catalyze the phosphorylation of RAC-PKA DNA construct expressing human GSK3B with the EFMPME (EE) (SEQ ID NO: 18) epitope tag at the N-terminus was prepared. A standard PCR reaction was carried out using as a template the human GSK3 beta cDNA clone in the pBluescript SK+vector; Para. [0154] The fractions (0.05 mL) assayed with the synthetic peptide GRPRTSSFAEG SEQ ID NO: 5, which corresponds to the sequence of GSK3 surrounding the serine (bold type) whose phosphorylation triggers the inactivation of GSK 3 alpha (Ser21) and GSK3 beta (Ser9); Para. [0127] compounds which demonstrate elevated levels of kinase inhibition may then be further assessed by determining the immunosuppressive or anti-proliferative properties thereof directly, for instance, by means of a cell proliferation inhibition assay. Such an assay preferably involves physical determination of T-cell proliferation in cells which have been subjected to kinase activation by a phosphatase inhibitor).

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