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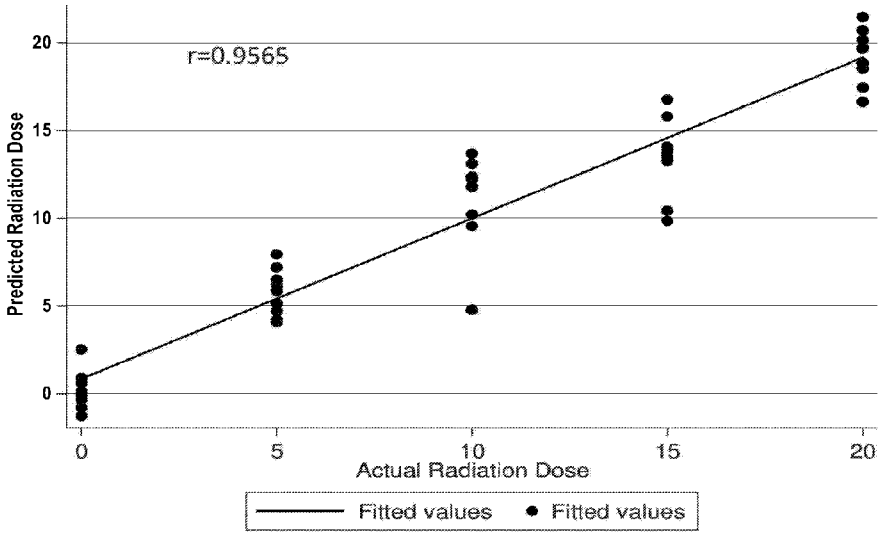
(54) Title: PANEL OF INFLAMMASOME PROTEINS AS RADIATION BIODOSIMETER

FIGURE 22



(57) Abstract: The present invention relates to a panel of inflammasone biomarkers for detecting exposure to ionizing radiation and/or for determining absorbed dose of ionizing radiation in a subject exposed thereto.

[Continued on next page]

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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).

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/44817

A. CLASSIFICATION OF SUBJECT MATTER

IPC - G01N 33/573, G01N 33/50, G01N 33/534 (2021.01)

CPC - G01N 33/573, G01N 33/6893, G01N 2800/40, G01N 2800/50, G01N 2800/52

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.
Y	WO 2011/127056 A2 (UAB RESEARCH FOUNDATION) 13 October 2011 (13.10.2011) Abstract; pg 3, ln 9-14; pg 4, ln 31-34; pg 5, ln 24-29; pg 5, ln 31-33; pg 7, ln 33- pg 8, ln 1; pg 11, ln 29- 33; pg 13, ln 15-17	1-32, 37-50
Y	WEI et al., The role of NLRP3 inflammasome activation in radiation damage, Biomedicine and Pharmacotherapy, October 2019, Vol. 118, p 1-5; Especially: Abstract	1-32, 37-50
Y	EL-SAGHIRE et al., Low doses of ionizing radiation induce immune-stimulatory responses in isolated human primary monocytes, International Journal of Molecular Medicine, 30 September 2013, Vol. 32, No 6, p 1407-1414; Especially: Abstract	5, 39

☐ 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
"D" document cited by the applicant in the international application
"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
7 December 2021	JAN 25 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

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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 searched, the appropriate additional search fees must be paid.

Group I: claims 1-32, 37-50, drawn to a method of detecting whether a subject has been exposed to ionizing radiation, comprising: measuring levels of one or more inflammasome biomarkers.

Group II: claims 33-36, drawn to a device and a biodosimeter panel.

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:

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.:
1-32, 37-50

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

International application No.

PCT/US 21/44817

Continuation of Box No. III (Observations where unity of invention is lacking):

Special Technical Features

Group I includes the special technical feature of a method which differs from the special technical feature of a composition, as disclosed by Group II.

Common Technical Features

The inventions of Groups I-II share the technical feature of detecting whether a subject has been exposed to ionizing radiation.

However, these shared technical features do not represent a contribution over prior art in view of WO 2011/127056 A2 to UAB Research Foundation (hereinafter "UAB"), in view of the article entitled "The role of NLRP3 inflammasome activation in radiation damage" by Wei et al. (hereinafter "Wei").

UAB teaches (instant claim 1) a method of detecting whether a subject has been exposed to ionizing radiation, comprising:
a) obtaining a biological sample from the subject; and
b) measuring levels of one or more biomarkers in the biological sample, wherein a change in levels as compared to a non-irradiated control indicates the subject has been exposed to ionizing radiation (pg 3, ln 9-14 "In one aspect, the method of the invention comprises a method of identifying a mammalian subject exposed to ionizing radiation, comprising: detecting the presence of, and/or quantifying the level of, one or more biomarker nucleic acids or proteins in a blood sample or blood derived sample from the subject, wherein the presence of the biomarker, or a level or concentration of the biomarker above a pre-determined threshold is indicative of ionizing radiation exposure in the subject"). UAB fails to teach wherein the biomarkers are inflammasome biomarkers selected from the group consisting of NLRP3, ASC, HMGB 1, IL-1(3, IL-6, IL-8, sICAM, and sVCAM.

Wei teaches wherein NLRP3 is induced following radiation (Abstract "Radiotherapy (RT) is currently one of the leading treatment for various cancers and it may cause injury to healthy tissue, with both short-term and long-term side effects. Inflammatory responses play an important role in the adverse reactions of early and late ionizing radiation. Nucleotide-binding domain and leucine-rich-repeat containing family pyrin 3 (NLRP3) inflammasome as a multi-protein complex that activates caspase-1 can give rise to the proinflammatory cytokines such as interleukin-18 (IL-18) and interleukin-1 beta (IL-1beta) maturation."). Given the observation that NLRP3 is increased after radiation induced tissue damage, it would have been obvious to an artisan of ordinary skill in the art identify NLRP3 using the method taught by UAB, to identify subjects negatively impacted by ionizing radiation.

As said technical features were known in the art at the time of the invention, these cannot be considered special technical features 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.