

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number
WO 2019/018451 A3

(43) International Publication Date
24 January 2019 (24.01.2019)

(51) International Patent Classification:
A61K 38/17 (2006.01)

(21) International Application Number:

PCT/US2018/042569

(22) International Filing Date:

17 July 2018 (17.07.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/533,272 17 July 2017 (17.07.2017) US

(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF COLORADO** [US/US]; 1800 Grant Street, 8th Floor, Denver, CO 80203 (US).

(72) Inventors: **XUE, Ding**; 978 Arapahoe Circle, Louisville, CO 80027 (US). **PENG, Yu**; School of Life Sciences, Tsinghua University, Beijing, 100084 (CN). **ZHANG, Man**; School of Life Sciences, Tsinghua University, Beijing, 100084 (CN). **ZHENG, Lingjun**; 1850 Athens Street, Apt. 3, Boulder, CO 80302 (US). **LIANG, Qian**; School of Life Sciences, Tsinghua University, Beijing, 100084 (CN). **LI, Hanzeng**; 978 Arapahoe Circle, Louisville, CO 80027 (US). **YU, Jau-Song**; Graduate Institute of Biomedical Sciences, College of Medicine, Chang Gung University, Taoyuan, 333 (TW). **CHEN, Jeng-Ting**; Graduate Institute of Biomedical Sciences, College of Medicine, Chang Gung University, Taoyuan, 333 (TW).

(74) Agent: **KERR, David, S.**; Berg Hill Greenleaf Ruscitti LLP, 1712 Pearl Street, Boulder, CO 80302 (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, JO, 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))
- 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:

14 March 2019 (14.03.2019)

(54) Title: COMPOSITIONS AND METHODS FOR PREVENTING AND TREATING RADIATION-INDUCED BYSTANDER EFFECTS CAUSED BY RADIATION OR RADIOTHERAPY

(57) Abstract: The invention provides novel compositions and methods for the treatment of Radiation-Induced Bystander Effects (RIBE), resulting from radiation exposure. In one preferred embodiment the inventions includes novel therapeutic agents, including but not limited to quercetin and quercetin analogs, as well as E64, CA074, CA074Me, that interfere with the activity of Cathepsin B.



WO 2019/018451 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/42569

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/17 (2018.01)
CPC - A61K 38/16, A61K 38/17

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 --- Y	Ozyurt et al. 'Quercetin protects radiation-induced DNA damage and apoptosis in kidney and bladder tissues of rats', Free Radical Research, 14 August 2014 (14.08.2014), Vol.48, pages1247-1255; Title, p1248, p1250	1-8, 12, 17-24, 44-45, 47, 157-165, 168-170 ----- 9-11, 13-16, 25-28, 165-167, 171-173
Y	Lin et al. 'Combination of quercetin with radiotherapy enhances tumor radiosensitivity in vitro and in vivo', Radiotherapy and Oncology, 25 November 2011 (25.11.2011), Vol.104, pages395-400; Title	9-11, 25-28, 165-167, 171-173
Y	Zwicky et al. 'Cathepsin B expression and down-regulation by gene silencing and antisense DNA in human chondrocytes', Biochemical Journal, 01 October 2002 (01.10.2002), Vol.367, pag	13-14, 16
Y	Gondi et al. 'Cathepsin B as a Cancer Target', Expert Opinion on Therapeutic Targets, 08 January 2013 (08.01.2013), Vol.17, pages281-291; p5	13, 15
A	Wang et al. 'Quercetin, a flavonoid with anti-inflammatory activity, suppresses the development of abdominal aortic aneurysms in mice', European Journal of Pharmacology, 19 June 2012 (19.06.2012), Vol.690, pages133-141; Abstract	3, 12, 45, 159, 168-169
A	Alapati et al. 'uPAR and cathepsin B knockdown inhibits radiation-induced PKC integrated integrin signaling to the cytoskeleton of glioma-initiating cells', International Journal of Oncology, 24 May 2012 (24.05.2012), pages599-610; Title	13
A	Piao et al. 'Hyperoside Protects Cells against Gamma Ray Radiation-Induced Apoptosis in Hamster Lung Fibroblast', Natural Product Sciences, June 2013, Vol.19, pages127-136; Abstract	1-28, 44-45, 47, 157-173

 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

13 November 2018

Date of mailing of the international search report

30 JAN 2019

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:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571 272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/42569

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/0020902 A1 (Giuliani et al.) 26 January 2012 (26.01.2012); entire document	1-28, 44-45, 47, 157-173
A	US 2010/0257636 A1 (Warpeha et al.) 07 October 2010 (07.10.2010); entire document	1-28, 44-45, 47, 157-173

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/42569

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.: 35-43, 48-56, 61-69, 74-82, 84, 122-130, 135-143, 148-156, 174-177
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 Supplemental Box

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.:
1-28, 44-45, 47, 157-173

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 18/42569

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 1-34, 44-47, 57-60, 70-73, 83, 85-121, 131-134, 144-147, and 157-173 directed to a method for treating radiation-induced bystander effects in a subject caused by exposure to radiation, comprising administering to the subject a therapeutically effective amount of quercetin, isoquercetin, hyperoside, rutin, rhamnetin, isorhamnetin, solophenol D, uralenol, icaritin, rhamnazin, quercetin 3,7,3',4' tetrasulfate, E64, CA074, CA074Me, or an analog thereof in claims 1, 83, and 157. The method will be searched to the extent that it encompasses the method for treating radiation-induced bystander effects in a subject caused by exposure to radiation, comprising administering to the subject a therapeutically effective amount of quercetin. It is believed that claims 1-11(in part), 12-16, 17(in part), 18-28, 44-45, 47, 157-167(in part), 168, 169(in part), 170-173 read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional methods of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected method. 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. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the method for treating radiation-induced bystander effects in a subject caused by exposure to radiation, comprising administering to the subject a therapeutically effective amount of E64 (i.e., claims 85-95, 118-121, 157-173(in part)).

Group II: claims 178-195 directed to a method of assessing the efficacy or effectiveness of a radiation treatment, the method comprising:
- providing a kit for detecting in a sample of cells from a patient, a level of gene expression of a marker gene selected from the group consisting of:
i. a marker gene having at least 85% sequence identify with cathepsin B (CTSB) gene, or homologs or variants thereof;
ii. a polynucleotide which is fully complementary to at least a portion of the marker gene i; or
iii. polypeptides encoded by the marker genes of i; or
iv. fragments of polypeptides of i

The group of inventions listed above 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:

Group I+ includes the technical feature of a method for treating radiation-induced bystander effects in a subject caused by exposure to radiation, comprising administering to the subject a therapeutically effective amount of quercetin, isoquercetin, hyperoside, rutin, rhamnetin, isorhamnetin, solophenol D, uralenol, icaritin, rhamnazin, quercetin 3,7,3',4' tetrasulfate, E64, CA074, CA074Me, or an analog thereof containing the same, which is not required by any other invention of Group I+.

Group II includes the technical feature of a method of assessing the efficacy or effectiveness of a radiation treatment, not required by Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of method for treating radiation-induced bystander effects in a subject caused by exposure to radiation, comprising administering to the subject a therapeutically effective amount of quercetin, isoquercetin, hyperoside, rutin, rhamnetin, isorhamnetin, solophenol D, uralenol, icaritin, rhamnazin, quercetin 3,7,3',4' tetrasulfate, E64, CA074, CA074Me, or an analog thereof containing the same.

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over the journal article entitled 'Hyperoside Protects Cells against Gamma Ray Radiation-Induced Apoptosis in Hamster Lung Fibroblast' by Piao et al. (hereinafter 'Piao'). Piao teaches hyperoside protects cells against radiation-induced apoptosis in vitro (Abstract "hyperoside defend cells against gamma-ray radiation-induced apoptosis by inhibiting oxidative stress"), but does not teach wherein hyperoside protects cells against radiation-induced apoptosis in vivo. However, it would have been obvious to one of ordinary skill in the art to be motivated to perform the in vivo experimentation by routine experimentation, by administering hyperoside to a subject treated by radiation, in order to elucidate the efficacy of hyperoside in vivo.

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ and II. The inventions of Group I+ and II thus lack unity under PCT Rule 13.

Note

claims 35-43, 48-56, 61-69, 74-82, 84, 122-130, 135-143, 148-156, 174-177 are determined unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Claim 193 dependency is lacking clarity, "The method of claim 192, 186, and further comprising...". For the purposes of completing this ISR, claim 193 is assumed to read as "The method of claim 192 or 186, and further comprising..."