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(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, 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, KN, KP, KR, 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.

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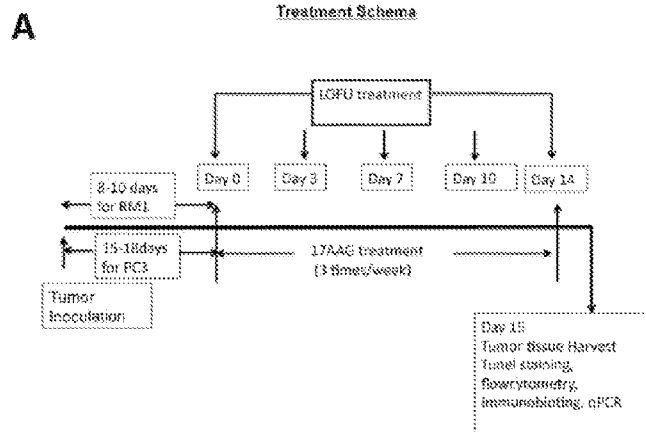
ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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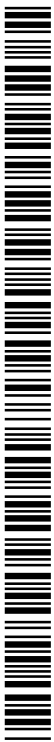
- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report: 4 May 2017

(54) Title: LOW INTENSITY FOCUSED ULTRASOUND FOR TREATING CANCER AND METASTASIS



(57) Abstract: Systems and methods for treating cancer and for preventing metastasis using low intensity focused ultrasound in combination with an anti-cancer therapy are disclosed.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/35440

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
  - a.  forming part of the international application as filed:
    - in the form of an Annex C/ST.25 text file.
    - on paper or in the form of an image file.
  - b.  furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
  - c.  furnished subsequent to the international filing date for the purposes of international search only:
    - in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
    - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2.  In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

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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.: 8-11, 18, 20-36, 40-79, 81  
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.:  
Group I, Claims 1-7, 12-17, 19, 80, and 82

**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/US16/35440

-\*\*\*-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.

Group I, Claims 1-7, 12-17, 19, 80, and 82 are directed toward methods of increasing the efficacy of a chemotherapy in a subject; treating a tumor in a subject, and a system therefor.

Group II, Claims 37-39 are directed toward methods of sensitizing a tumor to an anti-cancer therapy and reducing the effective dose of an anti-cancer chemotherapy required to treat a tumor.

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: the special technical features of Group I include wherein the chemotherapeutic drug effects endoplasmic reticulum (ER) stress, not present in Group II; the special technical features of Group II include reducing the effective dose of a chemotherapy, not present in Group I.

Groups I and II share the technical features including: administering to a subject undergoing anti-cancer chemotherapy an amount of low intensity focused ultrasound (LOFU); and an anti-cancer chemotherapy to treat a tumor.

However, these shared technical features are previously disclosed by WO 2015/077005 A1 to Sonify Biosciences, LLC (hereinafter 'Sonify').

Sonify discloses administering to a subject undergoing anti-cancer chemotherapy an amount of low intensity focused ultrasound (LOFU) (administering to a subject undergoing anti-cancer chemotherapy an amount of low intensity focused ultrasound (LOFU); abstract; paragraph [0037]); and an anti-cancer chemotherapy to treat a tumor (anti-cancer chemotherapy to treat skin cancer (a tumor); paragraph [0037]).

Since none of the special technical features of the Groups I and II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Sonify reference, unity of invention is lacking.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/35440

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - A61B 5/06, 8/08; A61K 47/42, 49/22 (2017.01) CPC - A61B 5/061, 5/066, 8/0825, 8/085; A61K 47/42, 49/22 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC(8): A61B 5/06, 8/08; A61K 47/42, 49/22, 6/00, 39/395; A61P 31/12, 31/18, 35/00; G01N 33/574; C12Q 1/68; C07K 16/18 (2017.01) CPC: A61B 5/061, 5/066, 8/0825, 8/085, 18/20; A61K 47/42, 49/22, 45/06, 38/00; C12N 2799/04, 9/1029; A61F 9/0079; A61N 5/062 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; Pubmed; EBSCO; IEEE Keywords: cancer, tumor, acoustic, ultrasound, radiation, immunotherapy, chemotherapy, treat*		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	(SAHA, S et al.) Low Intensity Focused Ultrasound (LOFU) Modulates Unfolded Protein Response and Sensitizes Prostate Cancer to 17AAG. <i>Oncoscience</i> . 03 June, 2014; Vol. 1, No. 6; pages 434-445; abstract; page 435, column 1, paragraph 3 - column 2, paragraph 2; page 440, column 1, paragraph -column 2, paragraph 1; page 441, column 1, paragraph 2 - column 2, paragraph 2; 442, column 1, paragraphs 1-4	1-2, 4, 5/4, 12, 15, 19, 82
Y	(YU, KD et al.) Identification of Prognosis-Relevant Subgroups in Patients with Chemoresistant Triple Negative Breast Cancer. <i>Clinical Cancer Research</i> . 15 May, 2013; Vol. 19, No. 10; pages 1-18; abstract; page 2, paragraph 2; page 7, paragraph 4; DOI: 10.1158/1078-0432.CCR-12-2986.	3, 5/3, 6-7, 13-14, 16, 17/12-14
Y	(CANCER RESEARCH INSTITUTE) Focused Ultrasound and Immunotherapy Workshop. New York; 11 February, 2015; pages 1-13; page 5, paragraph 1; downloaded from the internet < <a href="https://d3nqfeqdaoni.cloudfront.net/images/pdf/FUS_Immunotherapy_Workshop_Summary.pdf">https://d3nqfeqdaoni.cloudfront.net/images/pdf/FUS_Immunotherapy_Workshop_Summary.pdf</a> >.	3, 5/3, 6-7
Y	(LAN, J et al.) Ablative Hypofractionated Radiotherapy Normalizes Tumor Vasculature in Lewis Lung Carcinoma Mice Model. <i>Radiation Research</i> . 12 March, 2013; Vol. 179, No. 4; pages 458-464; abstract; page 461, column 2, paragraph 2; DOI: 10.1667/RR3116.1.	13, 17/13
Y	US 2010/0092424 A1 (SANGHVI, NT et al.) 15 April, 2010; paragraph [0081].	14, 17/12-14
Y	(JEONG, JS et al.) Ultrasound Transducer and System for Real-Time Simultaneous Therapy and Diagnosis for Noninvasive Surgery of Prostate Tissue. <i>IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control</i> . September, 2009; Vol. 56, No. 9; pages 1-20; page 3, paragraphs 1, 5	16
A		80
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> 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		Date of mailing of the international search report
14 February 2017 (14.02.2017)		17 MAR 2017
Name and mailing address of the ISA/US		Authorized officer
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Shane Thomas  PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US16/35440

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	(SEN, HT et al.) A Cooperatively Controlled Robot for Ultrasound Monitoring of Radiation Therapy. Proceedings of the IEEE/RSJ International Conference on Intelligent Robots and Systems. November, 2013; Vol. 2013; pages 1-20; abstract; page 2, paragraph 3.	80
P, X	WO 2016/196741 A2 (MONTEFIORE MEDICAL CENTER) 08 December, 2016; whole document	1-4, 5/3-4, 6-7, 12-16, 17/12-14, 19, 80, 82