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(54) Title: METHOD AND SYSTEM FOR CONCURRENT PHOTOTHERMAL ABLATION AND INTERSTITIAL PHOTODYNAMIC THERAPY

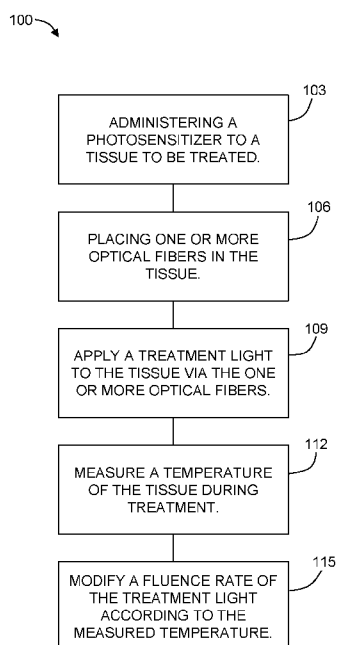


Fig. 2

(57) Abstract: The present disclosure provides a method and a system for treating a tissue using photodynamic therapy (PDT). A photosensitizer is administered to the tissue and one or more optical fibers are placed in the tissue. A treatment light is applied to the tissue by way of the one or more optical fibers. A temperature of the tissue is measured during application of the treatment light, and a fluence rate of the treatment light is modified based on the temperature of the tissue. For example, the fluence rate may be modified to be lower if the temperature of the tissue is higher than a predetermined threshold.

METHOD AND SYSTEM FOR CONCURRENT PHOTOTHERMAL ABLATION AND INTERSTITIAL PHOTODYNAMIC THERAPY

Statement Regarding Federally Sponsored Research

[0001] This invention was made with government support under CA193610 awarded by
5 the National Institutes of Health. The government has certain rights in the invention.

Cross-Reference to Related Applications

[0002] This application claims priority to U.S. provisional Application No. 62/492,171,
filed on April 29, 2017, now pending, the disclosure of which is incorporated herein by
reference.

10 Field of the Disclosure

[0003] The present disclosure relates to photodynamic therapy.

Background of the Disclosure

[0004] Photodynamic therapy (PDT), in particular interstitial photodynamic therapy (I-
PDT), offers promising outcomes for patients with refractory locally advanced cancer. The use
15 of I-PDT with porfimer sodium (Photofrin®) is approved for palliation in patients with
esophageal cancer or lung cancer with airway obstruction, who are non-candidates for surgery or
radiation therapy. In addition, I-PDT with porfimer sodium has been used, in compassionate care
settings, to treat patients with head and neck squamous cell carcinoma. A principal clinical goal
has been to shorten treatment times by administering the therapeutic light at high dose rates (*i.e.*,
20 400 mW/cm) that are clinically approved by the FDA for I-PDT with porfimer sodium.
However, the cure rate for I-PDT with porfimer sodium is limited.

[0005] PDT has also been viewed as beneficial when considering the relatively minor
nature of adverse effects. Additionally, it has been noted that PDT provides excellent cosmetic
outcomes. To date, it has been believed that during I-PDT the changes in tissue temperature do
25 not affect the response. Physicians and researchers assumed that PDT is associated with minimal
heating. The clinically approved, and used, light dose rate (400 mW/cm) for PDT or I-PDT with
porfimer sodium was chosen arbitrarily, about 25 years ago. There was no systemic study to
evaluate potential tissue heating during I-PDT. Several retrospective clinical studies suggest that

PDT and I-PDT will result in retention of functional anatomy and other benefits. While offering improved palliative outcomes for patients with such advanced diseases, there remains a need for further improvement.

Brief Summary of the Disclosure

5 **[0006]** In a first aspect, the present disclosure provides a method for treating a tissue. A photosensitizer is administered to the tissue. One or more optical fibers are placed in the tissue. For example, a portion (such as, for example, an end portion) of the one or more optical fibers are inserted in the tissue. The optical fibers may be spaced apart from one another such that a light dose may be applied to the tissue. The method includes applying a treatment light to the
10 tissue by way of the one or more optical fibers. A temperature of the tissue is measured during application of the treatment light. The fluence rate (mW/cm^2) of the treatment light is modified based on the temperature of the tissue. For example, by adjusting the light dose rate one may govern the intratumoral fluence rate within the tissue (*e.g.*, intratumoral fluence rate). For example, the fluence rate may be modified to be lower if the temperature of the tissue is higher
15 than a predetermined threshold. In some embodiments, the fluence rate is modified to maintain a tissue temperature between 50°C and 65°C . In some embodiments, the fluence rate is modified to maintain a tissue temperature of substantially 60°C . In some embodiments, the fluence rate is modified to maintain a tissue temperature between 60°C and 90°C .

[0007] In some embodiments, one or more dosimetry fibers may be placed in the tissue
20 and configured to measure light dose (J/cm^2). The optical fiber(s) and/or the dosimetry fiber(s) may be disposed within one or more light-transmitting catheters (LTCs) placed in the tissue. For example, each optical fiber may be disposed in a corresponding LTC. In another example, each of a plurality of LTCs may contain an optical fiber and a dosimetry fiber.

[0008] In another aspect, the present disclosure may be embodied as a system for treating
25 a tissue. The system includes a light source and an optical fiber operably coupled to the light source. The optical fiber is configured to deliver a light dose of treatment light to the tissue. A temperature sensor is configured to measure a temperature of the tissue. The temperature sensor may be any suitable sensor such as, for example, a thermistor, a thermal imaging sensor, a fiber optic, a magnetic resonance thermometer (providing volumetric temperature data), or the like. In
30 some embodiments, the temperature sensor is configured to measure temperature at a plurality of

locations throughout the volume of the tissue. In some embodiments, the temperature sensor comprises a plurality of temperature sensitive catheters.

[0009] A controller, such as, for example, a programmable microprocessor, is in communication with the temperature sensor and configured to modify a fluence rate of the treatment light based on a measured temperature. In some embodiments, the controller is configured to modify the fluence rate of the treatment light to maintain a tissue temperature between 50°C and 65°C. In some embodiments, the controller is configured to modify the fluence rate of the treatment light to maintain a tissue temperature of substantially 60°C. In some embodiments, the controller is configured to modify the fluence rate of the treatment light to maintain a tissue temperature between 60°C and 90°C.

[0010] The system may further include a dosimetry fiber for measuring the light dose. A spectrometer may be operably coupled to the dosimetry fiber. The system may further include an LTC, and the optical fiber and/or the dosimetry fiber may be disposed in the LTC.

[0011] In some embodiments, a second optical fiber is operably coupled to the light source and configured to deliver a second light dose of treatment light to the tissue. The controller may be configured to modify a fluence rate of the second light dose based on the measured temperature. The fluence rate of the second light dose may be modified based on a temperature at a second location of the tissue.

Description of the Drawings

[0012] For a fuller understanding of the nature and objects of the disclosure, reference should be made to the following detailed description taken in conjunction with the accompanying drawings, in which:

Figure 1 depicts a system according to an embodiment of the present disclosure;

Figure 2 is a chart showing a method according to another embodiment of the present disclosure;

Figure 3 shows a mouse being fitted with two optical fibers, each disposed within a light-transmitting catheter, for use in interstitial photodynamic therapy (I-PDT);

Figure 4 is a chart showing intratumoral heating results for a light dose of 150 mW/cm, 100 J/cm with and without photosensitizer;

Figure 5 is a chart showing intratumoral heating results for a light dose of 350 mW/cm, 100 J/cm with and without photosensitizer;

Figure 6 is a chart showing tumor size over time in populations of mice, where a control population was untreated, a second population was treated with a light dose of 150 mW/cm, 100 J/cm (control vs. light $p = < 0.0001$), and a third population was treated with I-PDT (control vs. I-PDT $p = < 0.0001$; light vs. I-PDT $p < 0.05$);

Figure 7 is a chart showing tumor size over time in populations of mice, where a control population was untreated, a second population was treated with a light dose of 350 mW/cm, 100 J/cm (control vs. light $p = < 0.0001$), and a third population was treated with I-PDT (control vs. I-PDT $p = < 0.0001$; light vs. I-PDT $p = 0.339$); and

Figure 8 is a chart showing tumor size over time in populations of mice, where a control population was untreated, a second population was treated with a light dose of 100 mW/cm, 540 J/cm (control vs. light $p = < 0.0001$), and a third population was treated with I-PDT concurrent with the same light dose as the second population (control vs. light $p = < 0.0001$; light vs. I-PDT/light $p = 0.164$).

Detailed Description of the Disclosure

[0013] As mentioned above, a perceived benefit of photodynamic therapy has been the lack of significant changes in tissue temperature. However, the present disclosure advantageously utilizes increased temperatures induced in the tissue using the I-PDT techniques disclosed herein to enhance efficacy as compared to I-PDT without an increased temperature.

[0014] With reference to Figure 2, the present disclosure may be embodied as a method **100** for treating a tissue, for example, treating a tumor, of an individual using interstitial photodynamic therapy (I-PDT) (*see* Figure 2). The method **100** includes administering **103** a photosensitizer to the tissue. The photosensitizer may be, for example, porfimer sodium (Photofrin®) or any other photosensitizer known for use in I-PDT—*e.g.*, capable of generating reactive oxygen species and radicals when activated by light in the presence of oxygen. The photosensitizer may be administered **103** by, for example, intravenous injection.

[0015] One or more optical fibers are placed **106** into the tissue to be treated. The optical fibers may be placed at locations in the tissue according to a predetermined treatment plan. In some embodiments, the optical fiber(s) are placed **106** into the tissue by way of light-

transmitting catheter(s) (LTCs) where each optical fiber is disposed in a light-transmitting catheter.

[0016] A treatment light is applied **109** to the tissue by way of the one or more optical fibers. The treatment light has a fluence (measured in, for example, joules per square
5 centimeter—J/cm²) and a fluence rate (measured in, for example, milliwatts per square centimeter—mW/cm²).

[0017] The method **100** includes measuring **112** a temperature of the tissue during application of the treatment light (*i.e.*, during “treatment”). Measurement **112** of the tissue may be performed using any technique appropriate. For example, volumetric measurement may be
10 accomplished using magnetic-resonance thermometry (MR thermometry or MRT). In another example, temperature is measured using a temperature-sensitive catheter. In embodiments where LTCs are placed in the tissue, a temperature-sensitive catheter may optionally be disposed in an LTC. Other methods for measuring **112** a temperature of a tissue may be used.

[0018] The fluence rate of the treatment light may be modified **115** based on the
15 temperature of the tissue. The fluence rate of the treatment light within the tissue (*e.g.*, intratumoral fluence rate) may be modified by adjusting the light dose rate. For example, the fluence rate may be decreased when the tissue temperature is higher than a (first) predetermined threshold. In this way, the temperature of the tissue will decrease. Similarly, the fluence rate of the treatment light may be increased if the tissue temperature is lower than a second
20 predetermined threshold, which may be the same as or different from the first predetermined threshold. By increasing the fluence rate, the tissue temperature will increase. In exemplary embodiments, the fluence rate is modified to maintain a tissue temperature of between 50–65°C, inclusive. In another exemplary embodiment, the fluence rate is modified to maintain a tissue temperature of less than 60°C. In another exemplary embodiment, the fluence rate is modified to
25 maintain a tissue temperature of substantially 60°C. By substantially, embodiments may maintain the temperature of the tissue within a desired tolerance, for example, ±5°C, ±1°C, ±0.5°C, ±0.2°C, or other tolerance levels between these exemplary values, for example, in 2°C increments. In embodiments incorporating thermal ablation, the temperature may be maintained at greater than 60°C and less than 100°C (or in some embodiments, less than 90°C) in order to
30 avoid tissue carbonization.

[0019] With reference to Figure 1, the present disclosure may be embodied as a system **10** for treating tissue **90** using I-PDT is provided. The system **10** includes a light source **12**. For example, the light source **12** may be a laser configured to emit light at a wavelength for activating a selected photosensitizer. For example, when using Photofrin, the emitted light may be 630 nm. An optical fiber **20** is operably coupled to the light source **12**. The optical fiber **20** is configured to deliver a light dose to the tissue **90**. The optical fiber **20** may have a cylindrical diffuser, a fiber with a flat-cut end, or other configuration. Embodiments of the system **10** may include additional optical fibers, for example, the embodiment depicted in Figure 1 includes a second optical fiber **20** for delivering a second light dose to the tissue **90**.

[0020] The system **10** includes a temperature sensor **30** for measuring a temperature of the tissue **90**. In some embodiments, the temperature sensor **30** may be configured to measure the temperature of the tissue **90** at more than one location, for example, more than one 3-D location within the tissue **90**. In some embodiments, the temperature sensor is a magnetic-resonance thermometer. In some embodiments, the temperature sensor comprises one or more temperature-sensitive catheters (*e.g.*, a thermistor disposed in a catheter).

[0021] In some embodiments, the system **10** may include a light-transmitting catheter **22** (*e.g.*, a transparent catheter)(an “LTC”). In such embodiments, the optical fiber(s) **20** of the system **10** may be disposed within a corresponding number of LTCs **22**. For example, each optical fiber **20** may be disposed in a lumen **23** of an LTC **22**.

[0022] The system **10** further includes a controller **40** in communication with the temperature sensor **30**. The controller **40** is configured to modify a fluence rate of the treatment light based on the temperature of the tissue **90**, as described above. In some embodiments, the controller **40** is a programmable microprocessor, programmed to modify the treatment light based on a signal received from the temperature sensor. The treatment light may be modified by adjusting the intensity of the light source, attenuating the light emitted from the light source, independently attenuating the light in each optical fiber, or any other technique for increasing or decreasing the fluence rate of the treatment light delivered to the tissue via the optical fiber(s).

[0023] Some embodiments of the presently-disclosed system may include a dosimetry fiber **25** for measuring a light dose. In embodiments wherein the system includes an LTC **22**, the dosimetry fiber **25** may be disposed in an LTC **22**, for example, within a lumen **23** of an LTC **22**. The dosimetry fiber **25** may be operably coupled to a spectrometer **27** for measuring the light

dose delivered to the tissue. In this way, a desired total dose may be delivered while also maintaining the temperature of the tissue in a desired range for effective photothermal ablation (or other synergistic effect when combined with I-PDT).

[0024] The present disclosure is further illustrated in the discussion below, which includes exemplary embodiments used to test the disclosed technique using mouse models.

Further Discussion

[0025] The mechanism of action in photodynamic therapy (PDT) involves the generation of reactive oxygen species and radicals through light activation of photosensitizer in the presence of oxygen—*i.e.*, an effective photoreaction. Previous studies demonstrated that oxygen-conserving light fluence rate (mW/cm^2) is required for an effective photoreaction. In I-PDT, multiple optical fibers with a cylindrical diffuser or optical fibers with flat cut end are inserted into the tumor. During I-PDT, the light dose rate (mW/cm) dictates the resulted fluence rate in the tumor. Thus, the light fluence rate depends on the light dose rate delivered from the optical fibers.

[0026] In the U.S., Photofrin is the only approved photosensitizer in the treatment of obstructing esophageal, non-small cell endobronchial lung cancer and high-grade dysplasia in Barrett's esophagus. The FDA-approved light dose rate for I-PDT with Photofrin is $400 \text{ mW}/\text{cm}$ length of the optical fiber cylindrical diffuser, which translates to a fluence rate of up to $800 \text{ mW}/\text{cm}^2$. This clinically-approved light dose rate induces significant thermal ablation that could overwhelm the photoreaction. However, our preclinical data suggest that this is not the case, and cure of locally advanced squamous cell carcinoma can be achieved in a mouse model treated with I-PDT and thermal ablation. In an ongoing preclinical study it was found that the laser light can induce significant heating that can induce immediate tissue ablation, at $T > 60^\circ\text{C}$, without impeding the efficacy of the I-PDT.

[0027] The inventors hypothesized that the limited cure rate for I-PDT with porfimer sodium is due to the high dose rate that could limit the photodynamic efficiency by depleting tumor oxygen levels.

[0028] As further described below, aspects of the presently-disclosed method and system were implemented for testing. In particular, *in vivo* magnetic resonance thermometry (MRT) was

used to quantify photothermal ablation during I-PDT. Time-to-event and cure rates were analyzed with Kaplan Meier curves. Safe and effective light dose rates and doses with photothermal ablation were identified.

Animal Model

- 5 **[0029]** All procedures were carried out in accordance with a protocol approved by the Institutional Animal Care and Use Committee (IACUC) at Roswell Park Cancer Institute (RPCI). Female C3H, 8–12 weeks, mice bearing locally advanced SCCVII tumors were treated when the tumors reached a size of 9–10 mm in their largest diameter, and a volume of 400–500 mm³ calculated from caliper measurements, as is known in the art.
- 10 **[0030]** The animals were randomly assigned to receive light only (no drug) or I-PDT by administering 5 mg/kg porfimer sodium 24 hours prior to light delivery. Mice were considered cured if there was no palpable tumor any time at or after 60 days post I-PDT.

Interstitial Photodynamic Therapy (I-PDT)

- 15 **[0031]** The laser light (treatment light) was delivered through one to three 0.98 mm diameter optical fibers with 20 mm cylindrical light diffuser RD20 (Medlight SA, Ecublens, Switzerland). The cylindrical light diffusers were connected to 1.0 Watt laser diode modules that emit 630±3 nm light (ML6500, Modulight Inc., Tampere, Finland). During light delivery, a custom made template was utilized to guide the placement of the laser fibers into the tumor, as shown in Figure 3.

20 ***Magnetic Resonance Thermometry***

- [0032]** Magnetic resonance thermometry (MRT) by proton resonance frequency methods was carried out in a 4.7 Tesla preclinical scanner using the ParaVision 3.0.2 imaging platform (Bruker Biospin, Billerica MA) and a 35 mm quadrature transceiver coil. Figures 4 and 5 show that there was a temperature increase during the interstitial light delivery, with and without drug.
- 25 These temperatures were averaged over the entire tumor volume.

Results

- [0033]** Figure 6 shows the percentage of mice with tumors less than 4000 mm³ over a period of 60 days post treatment. As shown in the chart, a control population was untreated, a

second population was treated with a light dose of 150 mW/cm, 100 J/cm (control vs. light $p \leq 0.0001$), and a third population was treated with I-PDT and similar dose (control vs. I-PDT $p \leq 0.0001$; light vs. I-PDT $p = 0.0004$). Figure 7 is a similar chart for populations treated with a light dose of 350 mW/cm, 100 J/cm (control vs. light $p \leq 0.0001$; control vs. I-PDT $p \leq 0.0001$; light vs. I-PDT $p = 0.339$). It can be seen that after 60 days, only 10% of mice remained with tumors less than 4,000 mm³.

[0034] Figure 8 shows the beneficial results of an embodiment of the presently-disclosed techniques using concurrent I-PDT and thermal ablation. It can be seen that the use of light without photosensitizer results in a cure rate of 40%. Despite the previous consideration that a lack of significant temperature change of the tissue was a benefit of PDT, Figure 8 shows that concurrent photothermal ablation and I-PDT resulted in a cure rate of 70%.

[0035] Although claimed subject matter is described in terms of certain embodiments, other embodiments, including embodiments that do not provide all of the benefits and features set forth herein, are also within the scope of this disclosure. Various structural, logical, process step, and electronic changes may be made without departing from the scope of the disclosure.

What is claimed is:

1. A method for treating a tissue, comprising:
 - administering a photosensitizer to the tissue;
 - providing one or more optical fibers placed in the tissue;
 - 5 applying a treatment light to the tissue by way of the one or more optical fibers, the treatment
light having a fluence rate;
 - measuring a temperature of the tissue during application of the treatment light; and
 - modifying the fluence rate of the treatment light based on the temperature of the tissue.
2. The method of claim 1, wherein the fluence rate is modified to be lower if the temperature of
10 the tissue is higher than a predetermined threshold.
3. The method of claim 1, wherein the fluence rate is modified to maintain a tissue temperature
between 50°C and 65°C.
4. The method of claim 1, wherein the fluence rate is modified to maintain a tissue temperature
of substantially 60°C.
- 15 5. The method of claim 1, wherein the fluence rate is modified to maintain a tissue temperature
between 60°C and 90°C.
6. The method of claim 1, further comprising providing one or more dosimetry fibers placed in
the tissue and configured to measure light dose.
7. The method of claim 6, wherein the optical fiber(s) and/or the dosimetry fiber(s) are disposed
20 within one or more light-transmitting catheters (LTCs) placed in the tissue.
8. A system for treating a tissue, comprising:
 - a light source;
 - an optical fiber operably coupled to the light source and configured to deliver a light dose of
treatment light to the tissue;
 - 25 a temperature sensor; and
 - a controller in communication with the temperature sensor and configured to modify a
fluence rate of the treatment light based on a measured temperature.

9. The system of claim 8, wherein the temperature sensor is configured to measure temperature at a plurality of locations throughout the volume of the tissue.

10. The system of claim 9, wherein the temperature sensor is a magnetic resonance thermometer.

11. The system of claim 9, wherein the temperature sensor comprises a plurality of temperature sensitive catheters.

12. The system of claim 8, wherein the controller is configured to modify the fluence rate of the treatment light to maintain a tissue temperature between 50°C and 65°C.

13. The system of claim 8, wherein the controller is configured to modify the fluence rate of the treatment light to maintain a tissue temperature of substantially 60°C.

10 14. The system of claim 8, wherein the controller is configured to modify the fluence rate of the treatment light to maintain a tissue temperature between 60°C and 90°C.

15. The system of claim 8, further comprising a dosimetry fiber for measuring the light dose.

16. The system of claim 15, further comprising a spectrometer operably coupled to the dosimetry fiber.

15 17. The system of claim 15, further comprising a light-transmitting catheter (LTC), and wherein the optical fiber and/or the dosimetry fiber is disposed in the LTC.

18. The system of claim 8, further comprising:

a second optical fiber operably coupled to the light source and configured to deliver a second light dose of treatment light to the tissue; and

20 wherein the controller is configured to modify a fluence rate of the second light dose based on the measured temperature.

19. The system of claim 18, wherein the fluence rate of the second light dose is modified based on a temperature at a second location of the tissue.

20. The system of claim 8, wherein the controller is a programmable microprocessor.

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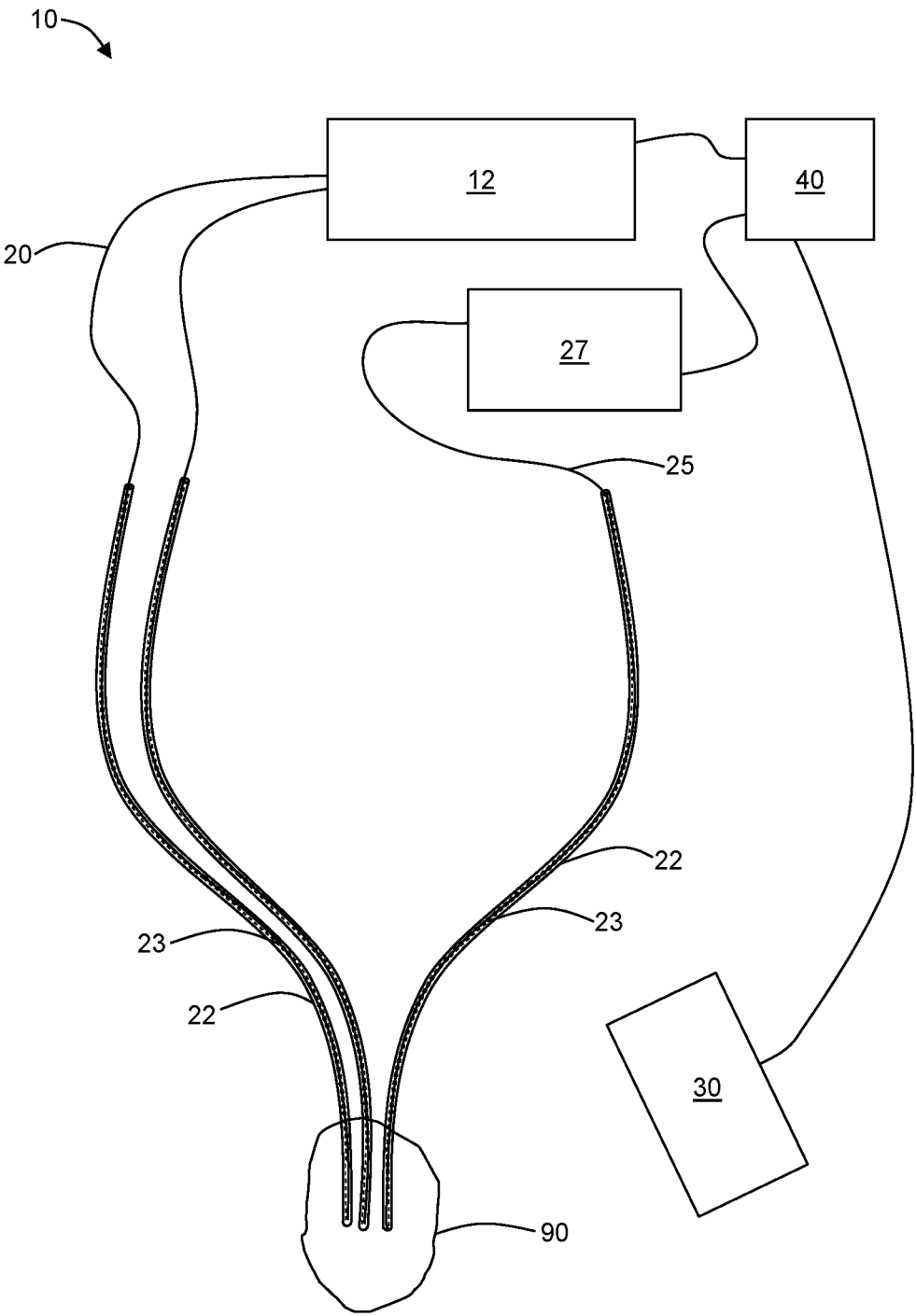


Fig. 1

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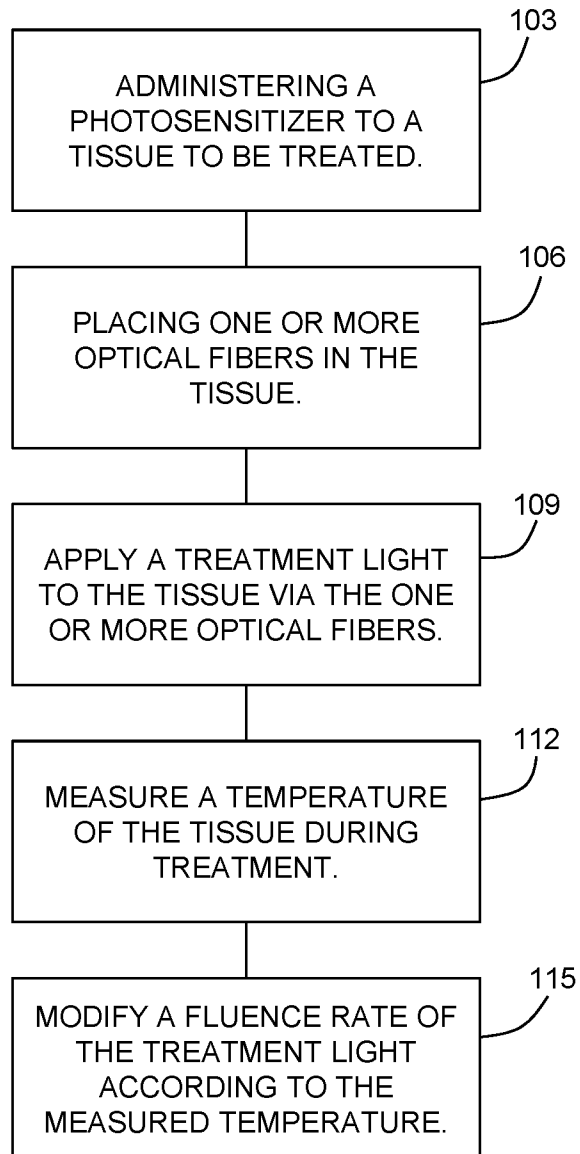


Fig. 2

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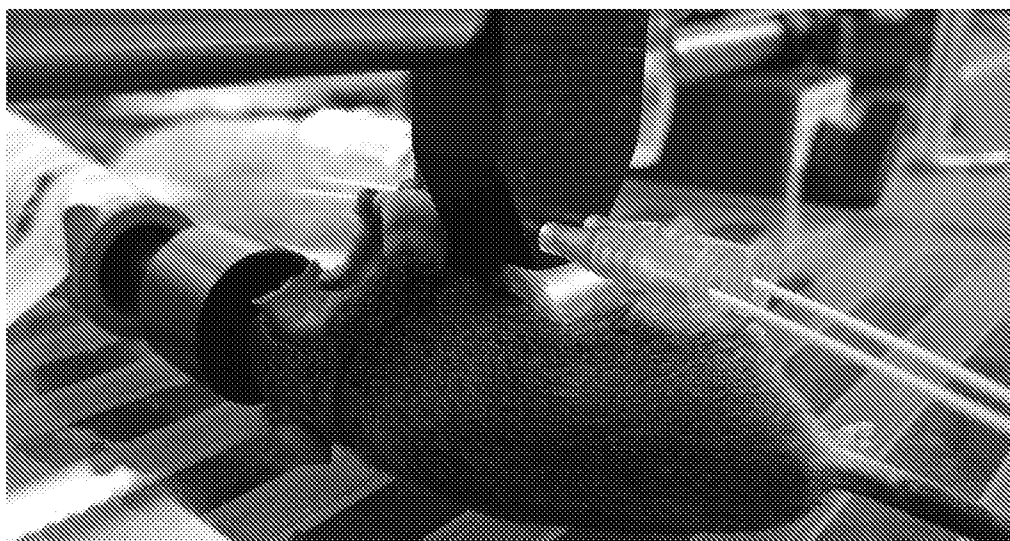


Fig. 3

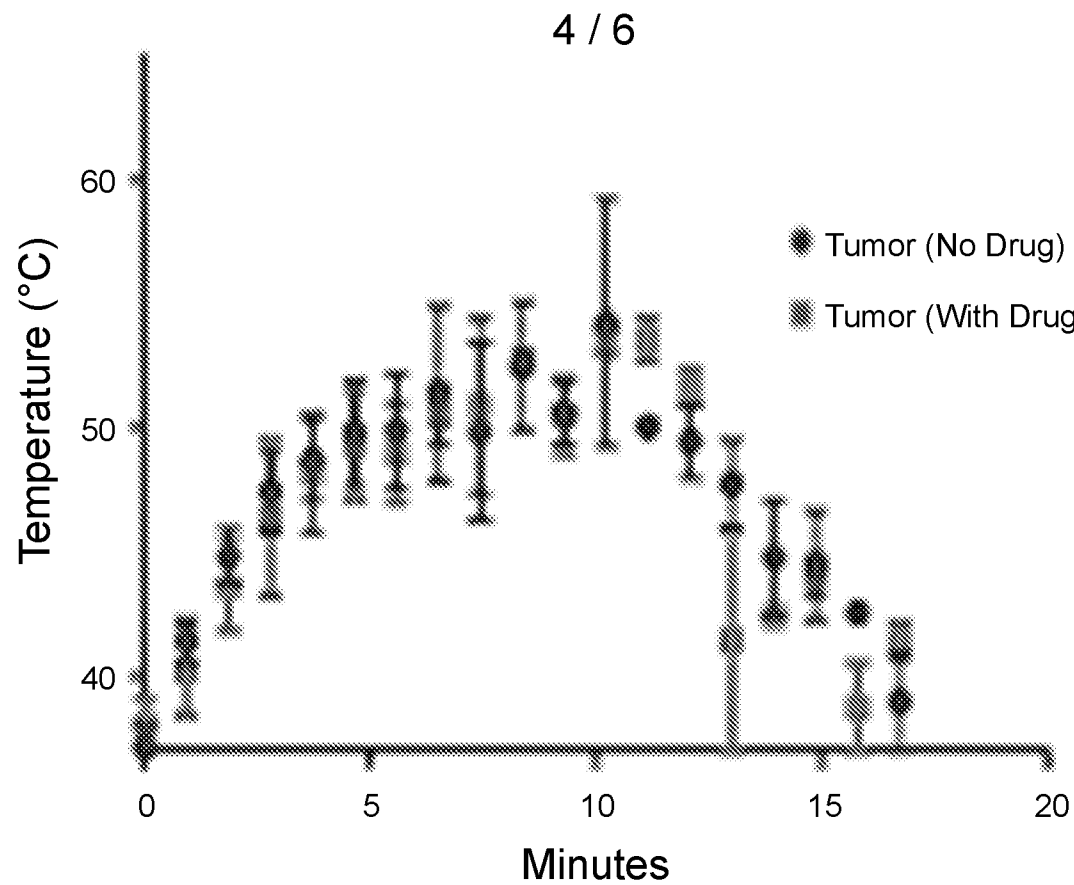


Fig. 4

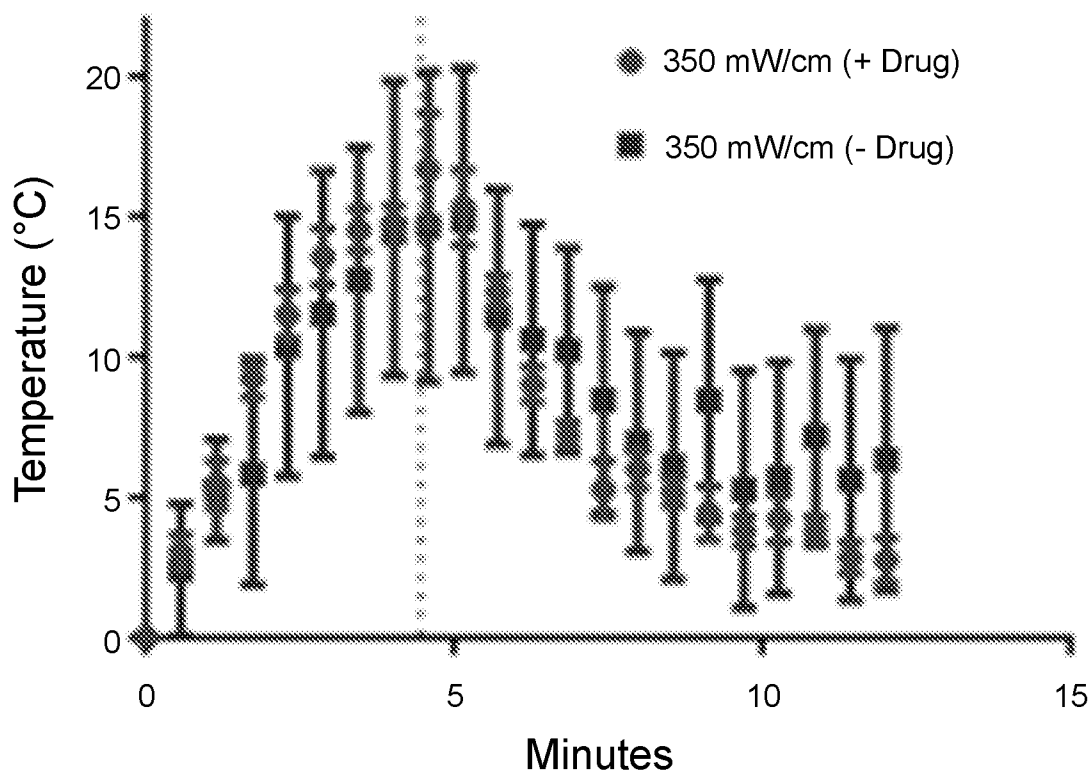


Fig. 5

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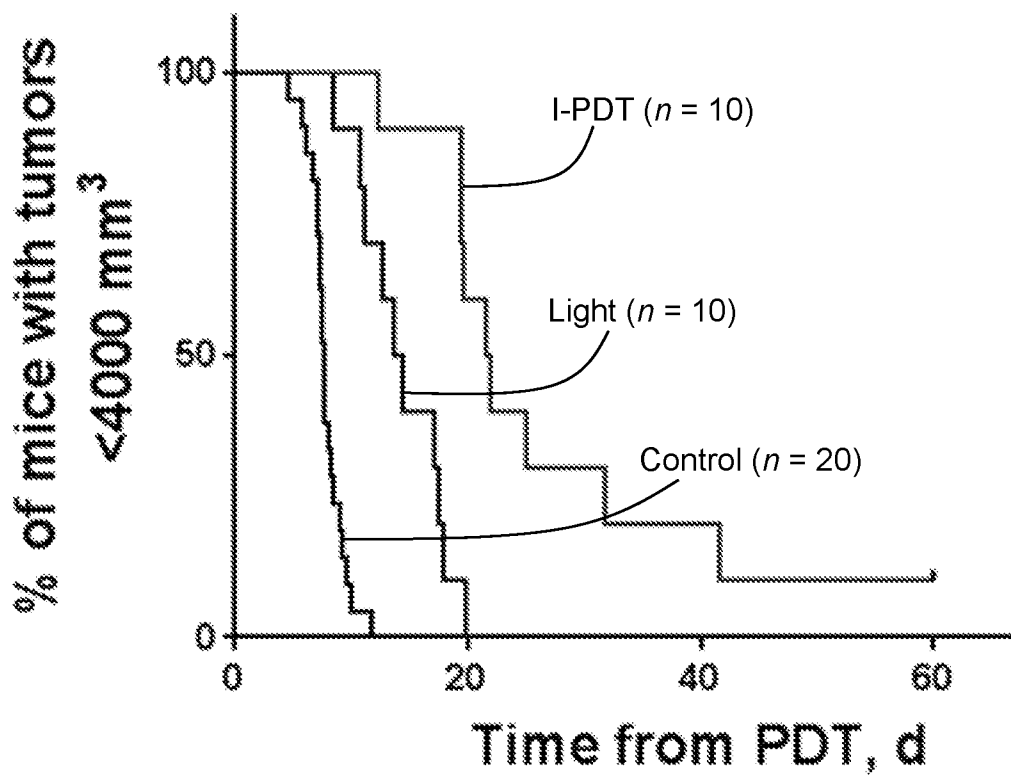


Fig. 6

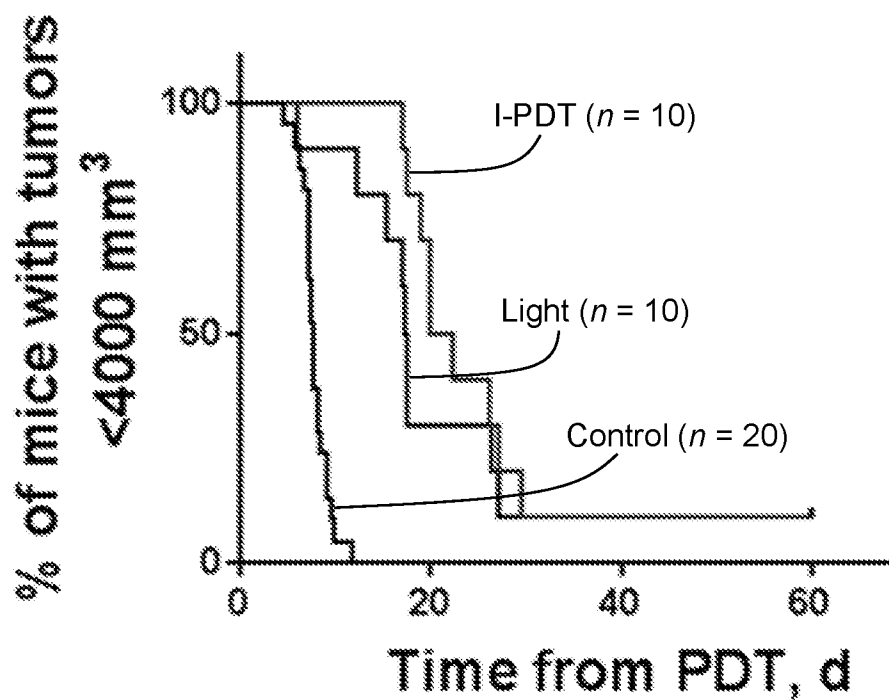


Fig. 7

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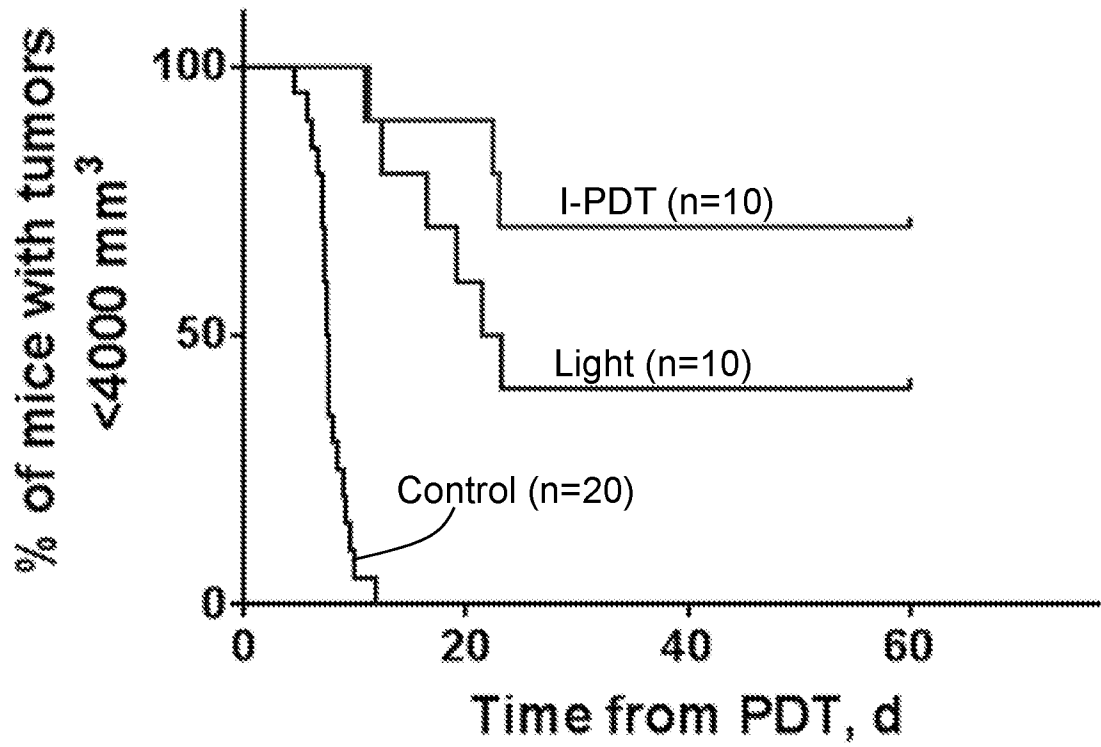


Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/30314

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 18/00 (2018.01)

CPC - A61B 2018/2005, A61B 2018/00005, A61B 2018/00041, A61B 2018/00642, A61B 2018/00666, A61B 2018/00672, A61B 2018/00678, A61B 2018/00714, A61B 2018/00791, A61B 2018/2211, A61B 18/24

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	US 5,496,308 A (BROWN et al.) 05 March 1996 (05.03.1996) Entire document, especially Abstract, col 3, ln 18-50, col 5, ln 4-64 and FIG. 2.	1, 6-7
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Y		2-5
Y	US 2006/0052661 A1 (GANNOT et al.) 09 March 2006 (09.03.2006) Entire document, especially Abstract, para[0006]-[0008], [0023]-[0032], [0281] and FIG. 1.	2-5
A	US 2009/0076489 A1 (WELCHES et al.) 19 March 2009 (19.03.2009) Entire document, especially Abstract, para[011], [0152], [0159] and FIG. 1.	1-7
A	US 2015/0230864 A1 (AMS RESEARCH CORPORATION) 20 August 2015 (20.08.2015) Entire document.	1-7

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

10 SEP 2018

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/30314

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 examined, the appropriate additional examination fees must be paid.

Group I: claims 1-7, directed towards a method for PDT based on temperature feedback

Group II: claims 8-20, directed towards a sensed temperature feedback controlled laser device

The inventions listed as Groups I - 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:

----- 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.:
1-7

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 18/30314

----- Continuation of Box III: Observations where unity of invention is lacking (Continuation of item 3 of first sheet) -----

Group I includes the special technical features of method steps including particular use steps (claim 1) administering a photosensitizer to the tissue, (claim 2) wherein the fluence rate is modified to be lower if the temperature of the tissue is higher than a predetermined threshold, not required by Group II.

Group I-II are related to an apparatus (Group II) and method(s) of using the apparatus (Group I). These groups therefore share the technical features of the apparatus of claim 8, however, these shared technical features fail to provide a contribution over the prior art of US 2009/0076489 A1 WELCHES et al. (hereinafter: Welches). Welches describes a system for treating a tissue (Abstract), comprising: a light source (laser source 14, FIG. 1; para[0112]); an optical fiber operably coupled to the light source and configured to deliver a light dose of treatment light to the tissue (optical fiber, para[0112]; i.e. of handpiece 12); a temperature sensor (sensor 14b, FIG. 1; para[0112]); and a controller in communication with the temperature sensor (controller 115, FIG. 1; para[0112]) and configured to modify a fluence rate of the treatment light based on a measured temperature (closed loop temperature feedback ... power, pulse rate, wavelength, para[0159]; see also para[0152]).

Thus, Groups I-II lack unity of invention because they do not share a same or corresponding special technical feature providing a contribution over the prior art.