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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399

CONFIRMATION NO. 3488

22428
FOLEY & LARDNER LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

PUBLICATION NOTICE

OC000000109736825

Title:METHODS FOR PHOTODYNAMIC THERAPY

Publication No.US-2019-0216927-A1
Publication Date:07/18/2019

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Biofrontera Exhibit 1002
Biofrontera Inc. et al. v. DUSA Pharmaceuticals, Inc.
IPR2022-00056

001

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	07/23/2019	10357567	067286-0399	3488

22428 7590 07/02/2019

FOLEY & LARDNER LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Scott LUNDAHL, Lexington, MA;
DUSA Pharmaceuticals, Inc., Wilmington, MA;
Michael Guttadauro, Carlisle, MA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Appl. No.:	15/869,164
Filing Date:	1/12/2018
Examiner:	Ahmed M FARAH
Art Unit:	3762
Confirmation Number:	3488

COMMENTS ON STATEMENTS OF REASONS FOR ALLOWANCE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The allowance is sincerely appreciated. The Applicant understands that the allowance is based on the actual language of each claim (which were carefully examined) and each individual claim is limited only by the actual language of that claim.

Respectfully submitted,

Date June 6, 2019

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5426
Facsimile: (202) 672-5399

Glenn Law
Attorney for Applicant
Registration No. 34,371

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 06/03/2019

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WASHINGTON, DC 20007-5109

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399	3488

TITLE OF INVENTION: METHODS FOR PHOTODYNAMIC THERAPY

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	09/03/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
FARAH, AHMED M	3792	607-088000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Foley & Lardner LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: DUSA Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Wilmington, MA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 19-0741

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date June 6, 2019

Typed or printed name Glenn Law Registration No. 34,371

Electronic Patent Application Fee Transmittal

Application Number:	15869164
Filing Date:	12-Jan-2018
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Filer:	Glenn Law/Effie Hale
Attorney Docket Number:	067286-0399

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1000**

Electronic Acknowledgement Receipt

EFS ID:	36223769
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Customer Number:	22428
Filer:	Glenn Law/Effie Hale
Filer Authorized By:	Glenn Law
Attorney Docket Number:	067286-0399
Receipt Date:	06-JUN-2019
Filing Date:	12-JAN-2018
Time Stamp:	14:53:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1000
RAM confirmation Number	060719INTEFSW14542900
Deposit Account	190741
Authorized User	Effie Hale

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.20 (Post Issuance fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Comments.pdf	79162 ba1d7d43a3251c385f096ab234d3382f0a827928	no	1
Warnings:					
Information:					
2	Issue Fee Payment (PTO-85B)	IssueFee.pdf	204516 7de9d36d3cde6c672f4108f663034f6cd9d30a2a	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30201 018d9d85c0c7803271899d4a957e95d01c5fdc01	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	313879		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 06/03/2019

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER
FARAH, AHMED M

ART UNIT	PAPER NUMBER
3792	

DATE MAILED: 06/03/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399	3488

TITLE OF INVENTION: METHODS FOR PHOTODYNAMIC THERAPY

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	09/03/2019

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

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Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399	3488

TITLE OF INVENTION: METHODS FOR PHOTODYNAMIC THERAPY

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	09/03/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
FARAH, AHMED M	3792	607-088000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

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❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399	3488

22428 7590 06/03/2019

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
FARAH, AHMED M	
ART UNIT	PAPER NUMBER
3792	

DATE MAILED: 06/03/2019

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/869,164	Applicant(s) LUNDAHL et al.	
	Examiner AHMED M FARAH	Art Unit 3792	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the amendment filed on 04/12/2019.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☑ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/AHMED M FARAH/
Primary Examiner, Art Unit 3792

Continuation of 3. The allowed claim(s) is/are: 1,5-8,16,19-20 and 24-25

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Reasons for Allowance

2. The following is an examiner's statement of reasons for allowance: the prior art of record does not teach a photodynamic therapy method for enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into a tissue, the method comprising: topically applying ALA to a treatment area to be treated with photodynamic therapy; after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize trans-epidermal water loss from the treatment area; and removing the low density polyethylene barrier applied to the treatment area prior to applying light to the treatment area. The prior art further fails to teach a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, wherein the treatment area is located on a hand or a forearm as claimed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AHMED M FARAH whose telephone number is (571)272-4765. The examiner can normally be reached on Mon - Fri. 9:30AM -10:30 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is

encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jackson can be reached on 571-272-4697. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AHMED M FARAH/
Primary Examiner, Art Unit 3792

May 13, 2019

Notice of References Cited	Application/Control No. 15/869,164	Applicant(s)/Patent Under Reexamination LUNDAHL et al.	
	Examiner AHMED M FARAH	Art Unit 3792	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20180311507-A1	11-2018	Barolet; Daniel	A61N5/0616	1/1
*	B	US-20120129879-A1	05-2012	Cantrell; Gary L.	A61K9/0075	514/282
*	C	US-20130274834-A1	10-2013	Barolet; Daniel	A61N5/062	607/88
*	D	US-9492681-B2	11-2016	Aydt; Ewald	A61F9/00834	1/1
*	E	US-9186349-B2	11-2015	Rajagopalan; Raghavan	A61K31/397	1/1
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/869,164	LUNDAHL et al.
	Examiner	Art Unit
	AHMED M FARAH	3792

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61N5/06 A61N5/0616 A61N5/062 A61N2005/0662 A61N2005/0663 A61N2005/067	08/05/2018	AF
A61K41/0057 A61K41/0061 A61K41/0071 A61K41/0076	08/05/2018	AF
A61K31/74 A61K31/745 A61K31/75 A61K31/756	08/05/2018	AF
updated	05/13/2019	AF

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**
607	88,89,96,100	08/05/2018	AF
128	898	08/05/2018	AF
	updated	05/13/2019	AF

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
EAST search: IS&R, BRS, and CPC forms, see the attached Search History.	05/13/2019	AF

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
607	88,89,96,100	05/13/2019	AF
128	898	05/13/2019	AF

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/869,164	LUNDAHL et al.
	Examiner	Art Unit
	AHMED M FARAH	3792

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/869,164	LUNDAHL et al.
	Examiner	**Art Unit**
	AHMED M FARAH	3792

CPC								
Symbol							**Type**	**Version**
A61K	/	41	/	0061			F	2013-01-01
A61P	/	17	/	12			I	2018-01-01
A61K	/	9	/	0014			I	2013-01-01
A61N	/	5	/	062			I	2013-01-01
A61K	/	31	/	75			I	2013-01-01
A61N	/	2005	/	0659			A	2013-01-01
A61N	/	2005	/	0663			A	2013-01-01
A61N	/	2005	/	0652			A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/AHMED M FARAH/ Primary Examiner, Art Unit 3792	13 May 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	Fig. 3

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/869,164	LUNDAHL et al.
	Examiner	**Art Unit**
	AHMED M FARAH	3792

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61N	/	5	/	06

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
607	88

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 10	
/AHMED M FARAH/ Primary Examiner, Art Unit 3792 (Primary Examiner)	13 May 2019 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure Fig. 3

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/869,164	LUNDAHL et al.
	Examiner	**Art Unit**
	AHMED M FARAH	3792

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	-	10	9	19										
-	2	-	11	10	20										
-	3	-	12	-	21										
-	4	-	13	-	22										
4	5	-	14	-	23										
2	6	-	15	6	24										
5	7	8	16	7	25										
3	8	-	17												
-	9	-	18												

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	10	
/AHMED M FARAH/ Primary Examiner, Art Unit 3792	13 May 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	Fig. 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Appl. No.:	15/869,164
371(c) Date:	1/12/2018
Examiner:	Ahmed M FARAH
Art Unit:	3792
Conf. No.:	3488

AMENDMENT AND REPLY UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This communication is responsive to the final Office Action dated February 25, 2019, concerning the above-referenced patent application.

Amendments to the Claims begin on page 2 of this document.

Remarks begin on page 5.

Please amend the application as follows:

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L16	96	((Guttadauro near2 Michael) (LUNDAHL near2 Scott)).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:14
L17	17088	((607/88,89,96,100) or (128/898)).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:15
L18	30663	A61N5/06.cpc. A61N5/0616.cpc. A61N5/062.cpc. A61N2005/0662.cpc. A61N2005/0663.cpc. A61N2005/067.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:18
L19	9663	A61K41/0057.cpc. A61K41/0061.cpc. A61K41/0071.cpc. A61K41/0076.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:19
L20	5125	A61K31/74.cpc. A61K31/745.cpc. A61K31/75.cpc. A61K31/756.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:20
L21	57133	17 18 19 20	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:21
L22	90	16 and 21	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:21
L23	12	22 and ((method process technique) with	US-PGPUB;	OR	OFF	2019/05/13

		(treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			22:21
L24	4	23 and ('ALA' "5-aminolevulinic acid")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/05/13 22:23
L25	794	21 and ((method process technique) with (treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:24
L26	187	25 and ('ALA' "5-aminolevulinic acid")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/05/13 22:25
L27	187	26 and ((method process technique) with (treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:26
L28	2	27 and ((enhanc$3 improv$3 assist$3) with (body tissue skin) with (penetration) with topical with (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:27
L29	4	("20050149150" | "20100137950" | "20100179469" | "20100234792").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/13 22:29
L30	0	29 and ('ALA' "5-aminolevulinic acid")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/05/13 22:29
L32	14	27 and ((enhanc$3 improv$3 assist$3) same ((body tissue skin) with (penetration)) same (topical with (composition agent)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2019/05/13 22:30
L34	14	32 and ((treat$5 stimulat$3 activat$3 therap$7 illuminat$3) with (light laser beam radiat$3 irradat$3 pulse))	US-PGPUB; USPAT; USOCR;	OR	ON	2019/05/13 22:45

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S1	95	((Guttadauro near2 Michael) (LUNDAHL near2 Scott)).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:05
S2	16497	((607/88,89,96,100) or (128/898)).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:09
S3	27897	A61N5/06.cpc. A61N5/0616.cpc. A61N5/062.cpc. A61N2005/0662.cpc. A61N2005/0663.cpc. A61N2005/067.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:29
S4	9020	A61K41/0057.cpc. A61K41/0061.cpc. A61K41/0071.cpc. A61K41/0076.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:30
S5	4946	A61K31/74.cpc. A61K31/745.cpc. A61K31/75.cpc. A61K31/756.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:31
S6	53389	S2 S3 S4 S5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:31
S7	88	S1 and S6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:32
S8	12	S1 and ((method process technique) with (treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:35
S9	11	S7 and ((method process technique) with	US-PGPUB;	OR	OFF	2018/08/05

		(treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			19:35
S10	0	S8 and ((enhanc$3 improv$3 assist$3) with (body tissue skin) with (penetration) with topical with (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:37
S11	0	S8 and ((enhanc$3 improv$3 assist$3) same (body tissue skin) same (penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:38
S12	0	S8 and ((enhanc$3 improv$3 assist$3) same (penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:39
S13	0	S8 and ((enhanc$3 improv$3 assist$3) same (penetration) same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:39
S14	0	S8 and ((penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:39
S15	1	S8 not S9	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:40
S16	742	S6 and ((method process technique) with (treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:45
S17	181	S16 and ('ALA' "5-aminolevulinic acid")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT;	OR	ON	2018/08/05 19:46

			IBM_TDB			
S18	0	S17 and (polyethylene near3 barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 19:47
S19	0	S17 and (polyethylene with barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 19:48
S20	4	S17 and (polyethylene same barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 19:48
S21	4	S20 and ((method process technique) with (treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:48
S22	0	S21 and ((enhanc$3 improv$3 assist$3) same (body tissue skin) same (penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:48
S23	0	S21 and ((penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:48
S24	187	S6 and ((enhanc$3 improv$3 assist$3) same (body tissue skin) same (penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 21:07
S25	66	S24 and ('ALA' "5-aminolevulinic acid")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:08
S26	4	S25 and (polyethylene same barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	ON	2018/08/05 21:08

			JPO; DERWENT; IBM_TDB			
S27	23	("0000002" | "20030105163" | "20040157905" | "20090324727" | "20160317831" | "5079262" | "5211938" | "5441531" | "5474528" | "5489279" | "5505726" | "5782895" | "5856566" | "6231593" | "6335465" | "6559183" | "8609073" | "9241957" | "9339540" | "9387341" | "9561276" | "9723991" | "D613872").PN.	US-PGPUB; USPAT	OR	OFF	2018/08/05 21:14
S28	21	S27 and ('ALA' "5-aminolevulinic acid")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:17
S29	0	S28 and (polyethylene same barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:17
S30	0	S28 and (polyethylene same penetration)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:17
S31	2	S28 and (polyethylene same penetrat$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:17

5/13/2019 10:59:57 PM
C:\Users\afarah.USPTO\Documents\EAST\Workspaces\15869164.wsp

EAST Search History

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L35	11030	((607/88,89,96,100) or (128/898)).CCLS.	US-PGPUB; USPAT	OR	OFF	2019/05/13 22:50
L36	7579	A61N5/06.cpc. A61N5/0616.cpc. A61N5/062.cpc. A61N2005/0662.cpc. A61N2005/0663.cpc. A61N2005/067.cpc.	US-PGPUB; USPAT	OR	OFF	2019/05/13 22:51
L37	2106	A61K41/0057.cpc. A61K41/0061.cpc. A61K41/0071.cpc. A61K41/0076.cpc.	US-PGPUB; USPAT	OR	OFF	2019/05/13 22:51
L38	1187	A61K31/74.cpc. A61K31/745.cpc. A61K31/75.cpc. A61K31/756.cpc.	US-PGPUB; USPAT	OR	OFF	2019/05/13 22:51
L39	19286	35 36 37 38	US-PGPUB; USPAT	OR	OFF	2019/05/13 22:51
L40	602	39 and ((method process technique) with (treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	US-PGPUB; USPAT	OR	OFF	2019/05/13 22:52
L41	72	40 and ('ALA' "5-aminolevulinic acid").clm.	US-PGPUB; USPAT	OR	ON	2019/05/13 22:52
L42	43	41 and ((treat$5 stimulat$3 activat$3 therap$7 illuminat$3) with (light laser beam radiat$3 irradat$3 pulse)).clm.	US-PGPUB; USPAT	OR	ON	2019/05/13 22:53
L43	0	42 and ((enhanc$3 improv$3 assist$3) with (body tissue skin) with (penetration) with topical with (composition agent)).clm.	US-PGPUB; USPAT	OR	OFF	2019/05/13 22:54
L44	0	42 and ((enhanc$3 improv$3 assist$3) same ((body tissue skin) with (penetration)) same (topical with (composition agent))).clm.	US-PGPUB; USPAT	OR	OFF	2019/05/13 22:54
L45	2	42 and ((enhanc$3 improv$3 assist$3) same ((body tissue skin) with (penetration)) same (topical with (composition agent)))	US-PGPUB; USPAT	OR	OFF	2019/05/13 22:54
L47	0	42 and (remov$3 with (polyethlynene adj barrier)).clm.	US-PGPUB; USPAT	OR	ON	2019/05/13 22:58
L48	0	42 and (remov$3 with (polyethlynene adj barrier))	US-PGPUB; USPAT	OR	ON	2019/05/13 22:58
L49	0	42 and ((remov$3 cover$3) with (polyethlynene adj barrier))	US-PGPUB; USPAT	OR	ON	2019/05/13 22:59
L50	0	42 and ((remov$3 cover$3) with (polyethlynene adj barrier)).clm.	US-PGPUB; USPAT	OR	ON	2019/05/13 22:59

5/ 13/ 2019 11:00:10 PM
C:\ Users\ afarah.USPTO\ Documents\ EAST\ Workspaces\ 15869164.wsp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Appl. No.:	15/869,164
371(c) Date:	1/12/2018
Examiner:	Ahmed M FARAH
Art Unit:	3792
Conf. No.:	3488

AMENDMENT AND REPLY UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This communication is responsive to the final Office Action dated February 25, 2019, concerning the above-referenced patent application.

Amendments to the Claims begin on page 2 of this document.

Remarks begin on page 5.

Please amend the application as follows:

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Previously Presented) A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

topically applying ALA to a treatment area to be treated with photodynamic therapy;

after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area; and

removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.

2.-4. (Cancelled).

5. (Previously Presented) A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

topically applying ALA to a treatment area to be treated with photodynamic therapy; and

after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area,

wherein the treatment area is located on a hand or a forearm.

6. (Original) A method as set forth in claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours and then blue light is applied to the treatment area for a 10 J/cm^2 light dose.

7. (Original) A method as set forth in claim 5, wherein the low density polyethylene barrier is removed from the treatment area and then red light is applied to the treatment area for a 10 to 75 J/cm^2 light dose.

8. (Previously Presented) The method of claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110ng/mL.

9-15. (Cancelled).

16. (Previously Presented) A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:

contacting a treatment site with a composition comprising the ALA so as to wet the treatment site;

following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier;

removing the low density polyethylene barrier so as to expose the treatment site; and

illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm^2 dose of blue light.

17-18. (Cancelled).

19. (Original) The method of claim 16, wherein the low density polyethylene barrier is removed no later than three hours after the treatment site is covered.

20. (Previously Presented) The method of claim 16, further comprising:

positioning the treatment site between two inches and four inches from a surface of the illuminator.

21-23. (Cancelled).

24. (Previously Presented) The method as set forth in claim 5, wherein the treatment area is a dorsal surface of the hand.

25. (Previously Presented) The method as set forth in claim 5, wherein the treatment area is a dorsal surface of the forearm.

REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and for at least the reasons that follow.

I. Claim Status

Claims 1, 3, 5-8, 16, 19, 20, 24 and 25 were pending. Applicant sincerely appreciates the allowance of claims 1, 5-8, 16, 19, 20, 24 and 25.

To expedite prosecution, claim 3 is cancelled without prejudice or disclaimer. No other claims are cancelled, amended, or added. As the amendments are limited to the cancellation of a rejected claim, entry of the amendments after final rejection is respectfully requested.

Upon entry of the amendments, allowed claims 1, 5-8, 16, 19, 20, 24 and 25 remain pending.

II. Claim Rejection under 35 U.S.C. § 112

Claim 3 was rejected under 35 U.S.C. § 112(d) or pre-AIA 35 U.S.C. § 112, 4th paragraph, as allegedly being of improper dependent form.

Without acquiescing to the propriety of the rejection, claim 3 is cancelled herewith. Favorable reconsideration and withdrawal of the rejection are respectfully requested.

III. Conclusion

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned to advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: April 12, 2019

By /Kiri Lee Sharon/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5426
Facsimile: (202) 672-5399

Glenn Law
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Registration No. 34,371

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Kiri Lee Sharon
Attorney for Applicant
Registration No. 71,828

Electronic Acknowledgement Receipt

EFS ID:	35704412
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Customer Number:	22428
Filer:	Kiri Lee Sharon/Yasmeen Elagha
Filer Authorized By:	Kiri Lee Sharon
Attorney Docket Number:	067286-0399
Receipt Date:	12-APR-2019
Filing Date:	12-JAN-2018
Time Stamp:	11:26:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		067286-0399_Response_FOA.pdf	131861 7f5ca3093b19f1a10ac0bab9b537039daa860dd8	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	6
Warnings:			
Information:			
	Total Files Size (in bytes):	131861	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/869,164	Filing Date 01/12/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $420 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	04/12/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/POLIN ANG/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399	3488

22428 7590 02/25/2019

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
FARAH, AHMED M	

ART UNIT	PAPER NUMBER
3792	

NOTIFICATION DATE	DELIVERY MODE
02/25/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@foley.com

Office Action Summary	Application No. 15/869,164	Applicant(s) LUNDAHL et al.	
	Examiner AHMED M FARAH	Art Unit 3792	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 11/02/2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,3,5-8,16,19-20 and 24-25 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☑ Claim(s) 1,5-8,16,19-20 and 24-25 is/are allowed.

7) ☑ Claim(s) 3 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 09/27/2018.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Rejections - 35 USC § 112

2. The following is a quotation of 35 U.S.C. 112(d):

> (d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of pre-AIA 35 U.S.C. 112, fourth paragraph:

> Subject to the following paragraph [i.e., the fifth paragraph of pre-AIA 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

3. Claim 3 rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Claim 3 recites a step of removing the 'low density polyethylene barrier from the treatment site within 3 hours.' However, such step is positively recited in its parent claim 1 as amended. Thus, claim 3 fails to further limit is parent claim. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

4. Appropriate correction is required.

Allowable Subject Matter

5. Claims 1, 5-8, 16, 19, 20, 24 and 25 are allowed.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to AHMED M FARAH whose telephone number is (571)272-4765. The examiner can normally be reached on Mon - Fri. 9:30AM -10:30 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jackson can be reached on 571-272-4697. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AHMED M FARAH/
Primary Examiner, Art Unit 3792

February 14, 2019

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	15/869,164
Date Submitted: SEP 27 2018				**Filing Date**	1/12/2018
				First Named Inventor	Scott LUNDAHL
(use as many sheets as necessary)				Art Unit	3762
				Examiner Name	Ahmed M FARAH
Sheet	1	of	1	Attorney Docket Number	067286-0399

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	D1	2006/0287696-A1	12-21-2006	WRIGHT ET AL.	
	D2	2014/0067024-A1	03-06-2014	JONES ET AL.	
	D3	2015/0162109-A1	06-11-2015	NAGER, ZACHARY	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	D4	WO-2009/003173-A1	12-31-2008	THE GENERAL HOSPITAL CORPORATION		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D5	Partial International Search, Annex to Form PCT/ISA/206, International Application No. PCT/US2018/027070, July 19, 2018, 10 pages	

Examiner Signature	/Ahmed M Farah/	Date Considered	11/29/2018

4832-8349-2724.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M.F/

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399	3488

22428 7590 12/05/2018

Foley & Lardner LLP
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WASHINGTON, DC 20007-5109

EXAMINER	
FARAH, AHMED M	

ART UNIT	PAPER NUMBER
3792	

NOTIFICATION DATE	DELIVERY MODE
12/05/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@foley.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	15/869,164	LUNDAHL ET AL.	
	Examiner	Art Unit	
	AHMED FARAH	3792	

All participants (applicant, applicant's representative, PTO personnel):

(1) *AHMED FARAH*.

(2) *Glen Law (Reg. No. 34,371)*.

(3) *Kiri Lee Sharon (Reg. No. 71,828)*.

(4) *Scott Lundahl (inventor)*.

Date of Interview: *10 October 2018*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☒ Yes ☐ No.
If Yes, brief description: *Two NPL references submitted prior the interview by the applicant's representatives were discussed*.

Issues Discussed ☐101 ☒112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *claims 1,5,8, and 16*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/AHMED FARAH/ Primary Examiner, Art Unit 3792	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Proposed amendments to independent claims 1 and 16, and dependent claims 5 and 8 were discussed. The allowable subject matter of dependent claim 4 was incorporated into independent claim 1, and the allowable subject matter of dependent claim 17 was incorporated into independent claim 16. Objected but allowable dependent Claim 5 was amended to include all the limitations of its parent claim 1 and presented as an independent form. Insufficient antecedent basis in the claim language of dependent claim 8 was discussed and corrective term was agreed.

With respect to the rejection of claims 1-8 and 16-20 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite, the applicant's representative presented and discussed NPL references in order to obviate the rejection of the claims. Applicant's representatives and the inventor discussed in detail the relevance of the NPL reference to the claimed invention, and particularly to show that the term "low density polyethylene" recited in the independent claims 1 and 16 is well known in the polymer science and packaging industry. The examiner indicated that he will reconsider the indefiniteness rejection of the claims under the 112, 2nd paragraph, and the relevance of the presented NPL references to the claimed invention.

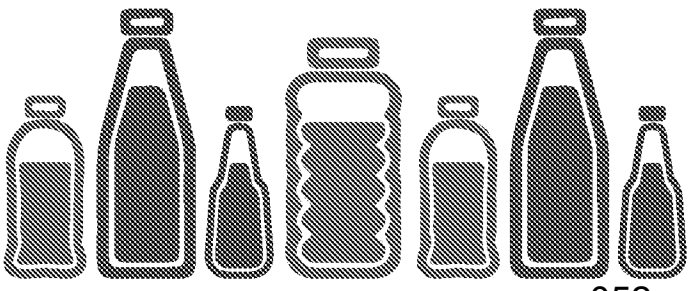
THE DEFINITIVE GUIDE TO

PLASTICS

FOR THE PACKAGING INDUSTRY

NACD

TABLE OF CONTENTS



PLASTICS: A BRIEF HISTORY AND WHERE WE ARE TODAY

Since the early 19th century, plastics have a played a major role in the world's economy. From textiles and building materials, to medical applications and packaging.

Plastics are America's third largest manufacturing industry, employing over 885,000 workers. Add in those employees of companies that supply the plastics industry, and you're looking at over 1.4 million Americans working in plastics today. In the last thirty years, the industry has grown 2.4% annually, continually increasing in volume and value.

The development of plastics began in the 1860's when billiard companies began searching for an alternative to ivory for the production of pool balls. The race was on to develop a strong, lightweight synthetic that would allow the game to continue. Researchers and chemists all over the world began experimenting with plant resins to create a new kind of man-made material.

In 2015, plastic products and packaging are an $800 billion dollar industry with almost 150,000 companies involved and it's common knowledge in the world of container sales and manufacturing that plastics play a key role in the industry.

Because of their diversity and incredibly flexible nature, plastics are often the best solution to a tough packaging problem. They're cost effective, readily available, and reliable enough to be the first and best choice for thousands of companies. They're also generally highly recyclable, with over a billion pounds being recycled into new applications every year.

The purpose of this ebook is to provide professionals with a working knowledge of some of the most common plastics used in the container industry, and to compare and contrast their different uses, values, strengths, and weaknesses. And maybe most important in today's eco-conscious climate, we'll explore the relative sustainability of 6 popular plastics in production today. We'll also cover the best applications for each plastic.

KEY PLASTIC TERMINOLOGY

Here are a few key terms used in plastics and ones you may come across in this ebook:

MONOMER

A monomer is a molecule that can bind chemically to other molecules to form a polymer.

POLYMERS

Polymers are made up multiple monomers (AKA molecules) that are strung together.

THERMOSETTING POLYMER

Thermosetting polymers are also known as plastics. They are materials which become liquid or malleable at low temperatures and become hard and rigid in high temperatures.

SIX PLASTICS THAT DOMINATE THE INDUSTRY

There are many unique varieties of plastic material made from a diverse range of sources, including many made from reclaimed or recycled material. Depending on your business, you may be deeply informed about one type of material, but be seeking out information on others to broaden your knowledge base. In this book we'll cover six major materials:

- HDPE - High-Density Polyethylene
- LDPE - Low-Density Polyethylene
- PET - Polyethylene Terephthalate
- PS - Polystyrene
- PP - Polypropene
- PVC - Polyvinyl Chloride

We'll begin by covering their backgrounds and the basics of the processes by which each material is produced, and then offer insight into the strengths and weaknesses of each in terms of durability, diversity of applications, and finally take a look into their relative sustainability.

This last area will be explored in depth, bringing you up to speed on this hot button issue and giving you an easy reference for key facts about recycling and the relative sustainability of each material.

First let's take a look at two varieties of polyethylene, the most common plastic in the world. Over 88 million tons of polyethylene are produced a year in thousands of different forms for a variety of applications. The two most common types in production today are HDPE and LDPE.

Known for its strength and durability, 26% of all HDPE produced worldwide is used in the production of rigid packaging.

HDPE

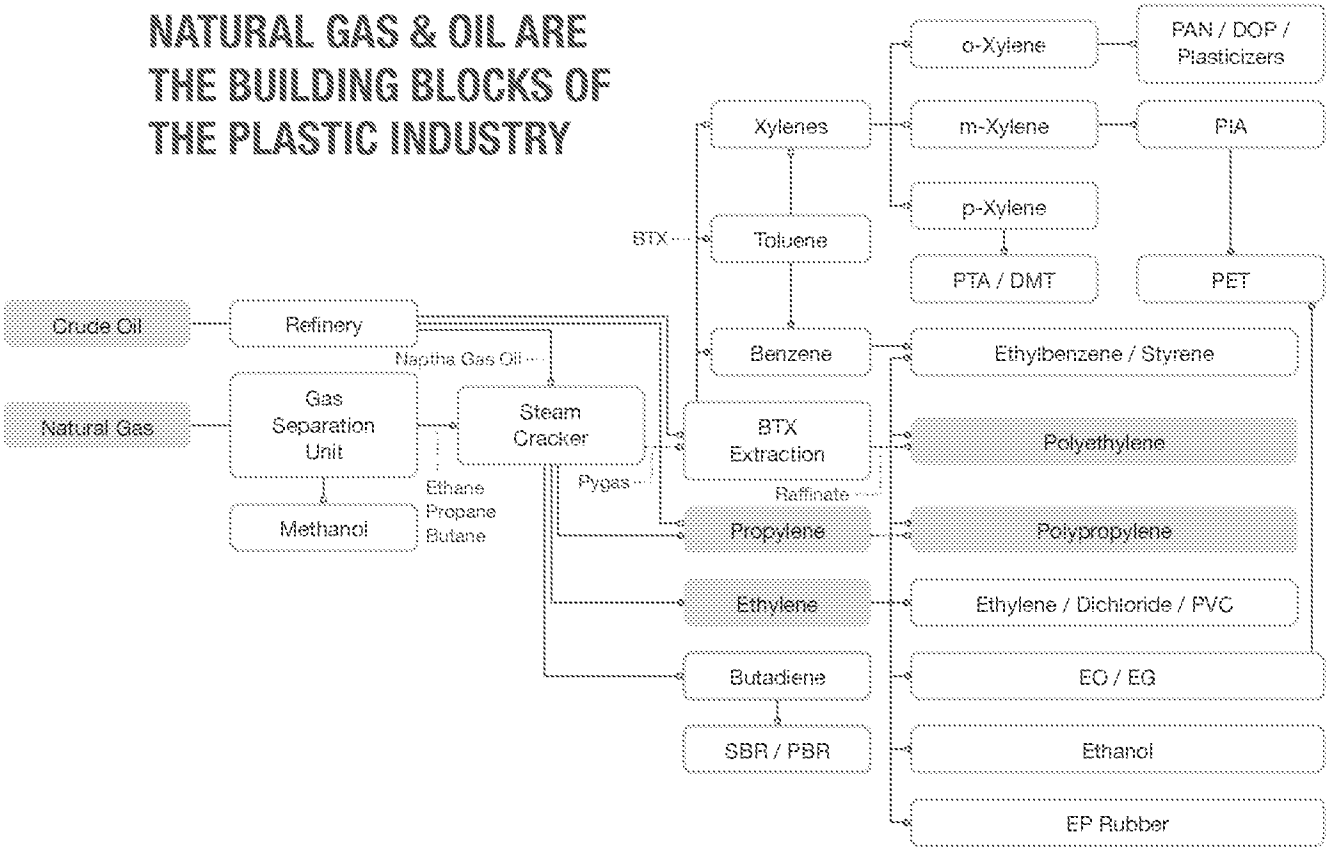
Developed by two researchers in 1953 high-density polyethylene is one of the most common packaging and construction materials in use today. Known for its strength and durability, 26% of all HDPE produced worldwide is used in the production of rigid packaging. In 2014 the global capacity for production, including facilities which can also be used to create other Polyethylene-based materials, was around six hundred million tons.

Growth in production is consistent to meet rising demand, although pricing can fluctuate along with the naphtha and crude oil markets as both are precursors for HDPE production. It's the second most recycled plastic in the United States, with approximately 28% of bottles and jars reclaimed.

HDPE is a great choice for food and beverage applications as many grades of the material are USDA, NSF, and FDA approved for direct contact with food. In addition, it has good impact resistance, is lightweight, and has very low moisture absorption.

HDPE is made from crude oil, but it only takes 4% of the world's annual oil production to produce all the plastic made in the world each year. To produce HDPE, petroleum is heated in a process known as cracking, which produces ethylene gas. These gas molecules link together to form long chains known as polymers — specifically polyethylene. The polyethylene is then pushed through fine holes to form long thin strings that are cut to form small granules.

NATURAL GAS & OIL ARE THE BUILDING BLOCKS OF THE PLASTIC INDUSTRY



Reliability and safety are two of HDPE's strongest value propositions. Unlike some other container materials, HDPE will not degrade due to extreme high or low pH, intense concentrations of salts, or other common chemical corrosives. It is generally extremely inert and as a result makes an ideal material for food and beverage applications.

However, there are some shortcomings to working with HDPE. It has a high instance of thermal expansion, and while it is a strong material it can be subject to some stress cracking. It's also difficult to bond to other materials, and has a relatively low strength/stiffness, making it unsuitable for some of the more rugged applications. Additionally, like many petroleum-based plastics, it can be very flammable and is not suitable for high-temperature applications.

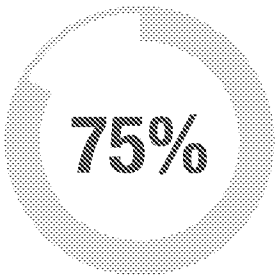
HDPE's SPI Resin Identification Code is 2, and it can be recycled easily throughout the United States. The market for, and production of, post-consumer recycled HDPE products is stable and growing, and the main use for reclaimed HDPE is in creating a new life for the material as a bottle or food and beverage packaging.

If you're looking for a durable, lightweight, food safe, and easy-to-manipulate material for your packaging needs—and one that comes with reasonably good marks for sustainability—HDPE might be right for your project.

LDPE

LDPE stands for low density polyethylene, but you might have guessed that already. It was the first type of polyethylene that was commercially produced. It was developed in 1933 by Imperial Chemical Industries (ICI), which was for many years, the largest manufacturer of LDPE in Great Britain. Of note, ICI is responsible for many other material innovations including the acrylic plastic perspex, an early competitor to plexiglass.

LDPE has slightly less tensile strength than HDPE but is correspondingly more flexible. Its most common application in the modern word is as the material used to make many plastic bags, but there are many other applications for LDPE.



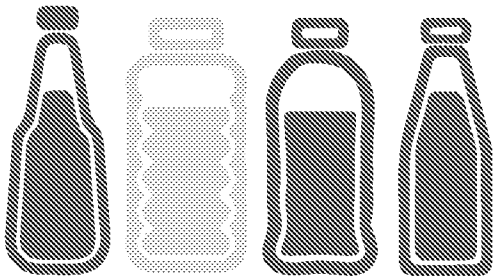
About 75% of all Polyethylene produced globally is LDPE.

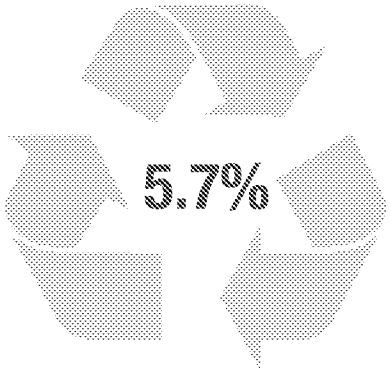
It can be used to make shrink film, overwrap film, food safe packaging film, and strong liquid containers. About 75% of all Polyethylene produced globally is LDPE.

LDPE's low density makes it highly malleable and allows for stretching—one of its chief strengths—and makes it a great choice for lightweight, form fitting film-type packaging. Unlike rigid HDPE, LDPE can be used to create lightweight and flexible packaging. Keep in mind however, that its relatively lower density does make it susceptible to puncture.

Because of its similarity to HDPE, low density polyethylene shares many of HDPE's shortcomings, including low strength/stiffness, high thermal expansion, and poor temperature capability. Like HDPE, it is also subject to stress cracking and is flammable. It is also more difficult to bond than other plastics, limiting its applications slightly.

Another bonus with LDPE is that its high durability allows for packaging (like plastic bags) to be reused by the consumer many times before it has to be recycled or disposed of. Embracing a push towards increased sustainability, some packaging producers are designing LDPE products whose useful life extends past their initial purpose.





Unfortunately, in the United States, LDPE is recycled at a rate of only about 5.7% — lower than its denser sibling.

Unfortunately, in the United States LDPE is recycled at a rate of only about 5.7%—lower than its denser sibling. If sustainability is one of your chief concerns, LDPE may not be the best material choice for your application. Although, recycled LDPE is available and can be combined with a percentage of virgin material to rejuvenate it for a variety of uses. Its resin identification code is 4, and while few curbside programs accept LDPE for recycling many stores and some communities will accept plastic bags.

PET

HDPE and LDPE are both great materials for food and beverage containers, but when it comes to plastic bottles there's one plastic that leads the field—PET.

PET stands for polyethylene terephthalate, and is the most popular polyester produced globally. It is used primarily as a fiber for textile production and as a packaging material for food and beverage products.

PET has an especially good moisture barrier and makes a great material for soft drink bottles. Some kinds of PET can be treated with a thin layer of metal to make it reflective and opaque, while others can be thermoformed into blister packs.

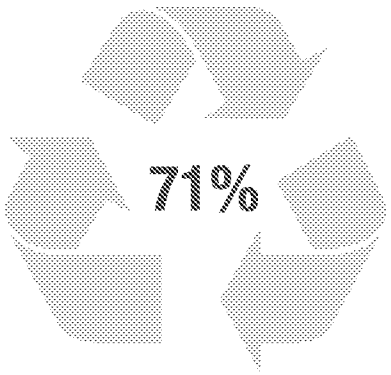
Developed in England in 1941, PET is one of the most common polyesters in the world, and ranks fourth globally in terms of overall polymer production. It also goes by the names PETE and the brand names Dacron, Terylene, and Lavsan.

It's the material responsible for everything from emergency "space blankets" to polar fleece. It's versatility and excellent recyclability make it a great choice for many packaging applications.

The production of PET is a fairly complex process, but there are a few basic points to keep in mind. The precursors for PET production are terephthalic acid and ethylene glycol, both readily available and relatively low-cost materials. After these components are combined they undergo a series of controlled reactions in the presence of specific catalysts and environmental conditions which determine the characteristics of the final product.

PET can be copolymerized with other substances to adjust its internal structure to make it more suitable to certain kinds of extrusion or molding.

On the flip side, one of PET's main shortcomings is its high susceptibility to heat degradation. During the production process temperatures must be carefully maintained to ensure the resulting material is clear, and in many applications high heat will fundamentally compromise packaging and other products made from PET. However, compared to other plastics like HDPE and LDPE, PET is considerably less flammable.



PET is accepted in almost all U.S. recycling programs, and for every pound of recycled material used in place of a new plastic, greenhouse gas emissions are reduced by a whopping 71%!

PET is one of the most easily recycled plastics currently in use today, and consumer packaging made from 100% recycled material is becoming increasingly common in today's sustainability-focused market. In fact, research shows that PET packaging may be more environmentally preferable than many new bioplastic materials due to its healthy closed-loop lifecycle.

It has the resin identification code 1, and most curbside programs accept PET/PETE materials. Thanks to its resilience, PET can be recycled many times very efficiently. It's accepted in almost all U.S. recycling programs, and for every pound of recycled material used in place of new plastic, greenhouse gas emissions are reduced by a whopping 71%!

Let's take a look at another extremely popular and widely used plastic available today—polystyrene.

PS

As one of the oldest plastics still in use, polystyrene was discovered in 1839 by German apothecary Johann Edouard Simon. The original batches of polystyrene were made from the natural resins of the Turkish sweetgum tree. Almost 100 years later, researchers at DOW Chemical developed a process to make a closed-cell, moisture resistant product, and introduced Styrofoam to the world in 1941.

You may know it by the brand name Styrofoam and be surprised to learn about some of its other useful applications.

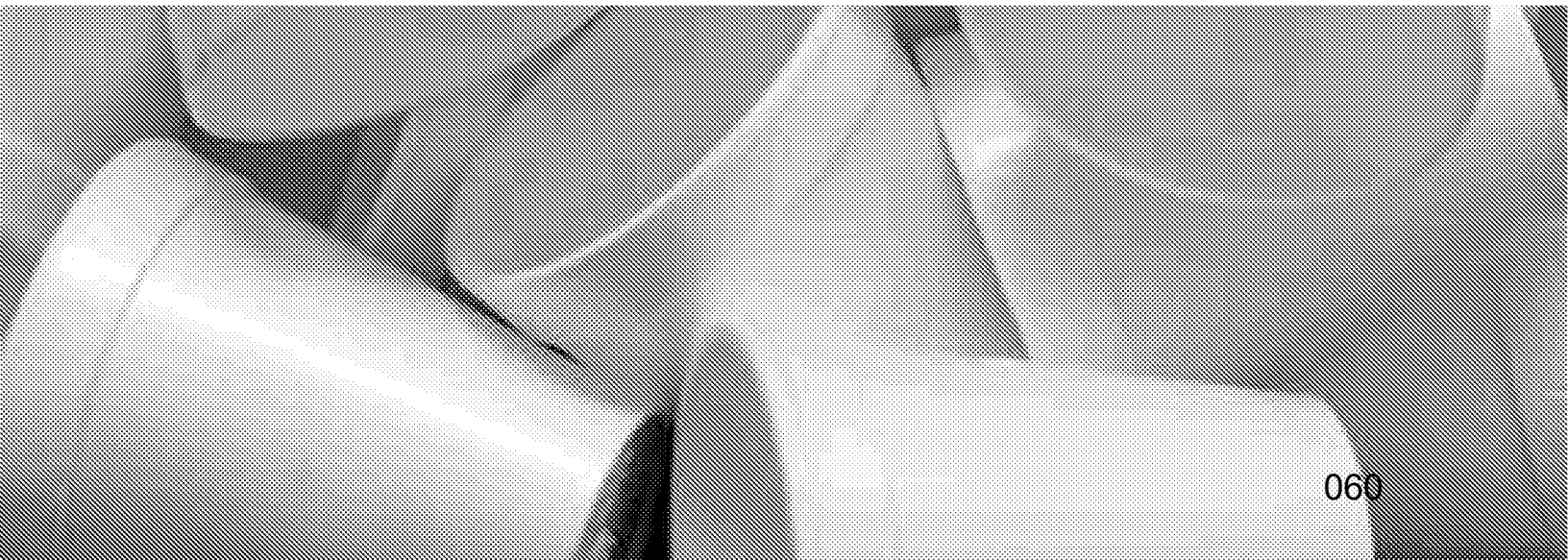
Polystyrene is one of the most commonly used and versatile plastics available today. It can be made both transparent and opaque, with a variety of densities and strengths depending on the application. It can be formed into a solid or a foam, and is a relatively inert and non-reactive material.

Through copolymerization, PS can be combined with other materials to expand its range of properties. For example, so called "high-impact plastic" is a result of one such process. PS can also be stretched into a clear rigid film called Oriented Polystyrene (OPS) that can be used to create comparatively inexpensive transparent packaging, though its durability may suffer greatly.

Polystyrenes disadvantages make it unsuitable for some applications. It is highly flammable (though flame retardant varieties do exist), and low impact varieties can break very easily. It has notoriously poor resistance to most solvents, and is not suitable for containing many types of liquids. It's also worth noting that while the recyclability of polystyrene is on the rise in the U.S., it has a track record as being one of the least sustainable plastic materials, and without special treatment is virtually non-biodegradable.

Applications include rigid plastic packaging for things like computers, as well as food containers, disposable utensils, and even as a building material when used in conjunction with reinforced concrete. Additionally, much of today's conventional protective packaging materials are made from PS. A variety of production techniques and technologies allow polystyrene to be a strong choice for many diverse applications.

It's worth noting that there is a rising trend in American municipalities to ban PS food containers, as they are perceived as a major source of non-biodegradable waste in landfills. Earlier this year, New York City banned single-use expanded polystyrene food containers, citing their belief that these materials could not be recycled effectively. If sustainability is amongst your primary concerns, you may want to consider alternatives to PS for your applications.



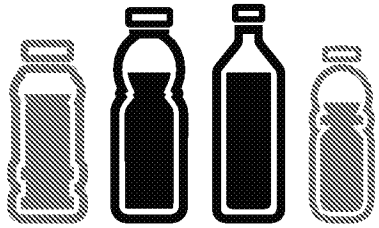
Contrary to what many believe, it is completely possible to recycle polystyrene, including styrofoam food service containers. And while traditionally products made from polystyrene have been considered non-biodegradable, new research with biological agents has led to a process by which PS materials can be converted into more easily broken down substances.

Ongoing research in this area is improving the relative sustainability of PS over time. Polystyrene has the resin identification code 6 and can be picked up by some curbside recycling programs in the U.S.

PP

One of the strongest and most resistant plastics available today, Polypropylene has a wide variety of applications ranging from packaging to textiles. Developed by Phillips Petroleum chemists J. Paul Hogan and Robert L. Banks in 1951, Polypropylene was brought into commercial production within the decade. More than half of all PP produced today is used in flexible packaging, and demand continues to rise for this versatile material.

Polypropylene is produced through a variety of methods, and the resulting materials have various properties such as an anti-static nature to resist dust, or a treated surface designed to improve paintability.



Due to its great physical durability when properly oriented, PP can be used to form strong, long lasting, living hinges in packaging as well. Its strength also allows for very low density production, which reduces its environmental impact.

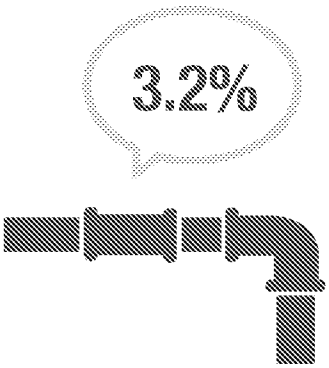
Like Polystyrene, PP can be produced in an "oriented" structure that allows for increased clarity and thinness, without the brittleness of PS. Biaxially Oriented PP is commonly used as packaging for food products due to it being easy to coat, print on, and laminate.

There are many diverse advantages to using polypropylene. Because it's unusually strong, PP is a great choice for producing containers meant to package acid, base, or other highly corrosive substances. Due to its great physical durability when properly oriented, PP can be used to form strong, long lasting, living hinges in packaging as well. Its strength also allows for very low density production, which reduces its environmental impact.

Polypropylene is highly susceptible to some chlorinated solvents and aromatics. Without special treatment it is highly flammable, and difficult to bond or paint. It also oxidizes readily and suffers from UV degradation. While there are special processes available to treat PP to deal with these issues, there are other materials better suited to applications where weathering and UV exposure are likely.

PP recycling is quickly on the rise in the US, more than tripling between 2004 and 2010. Its production results in less solid waste than many alternatives, and it results in much lower CO2 emissions than other similar materials. Many states now have programs to accept polypropylene, with more joining in every year.

Recycled PP has uses across many markets, including packaging, consumer goods, and construction materials. It has the resin identification code 5, and is accepted in many curbside recycling programs.



Demand for PVC is expected to increase by 3.2% per year until 2021.

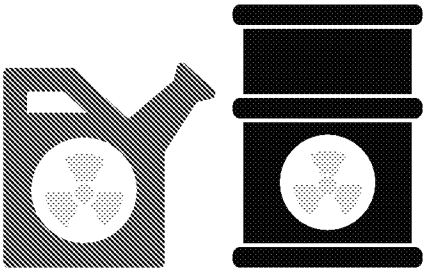
PVC

When most people hear PVC (Polyvinyl Chloride) their first thought might be the ubiquitous white plastic piping used in so many applications, but PVC is more than just pipes. It is the third most widely produced plastic after polypropylene and polyethylene and demand for PVC is expected to increase by 3.2% per year until 2021.

Discovered accidentally in 1872 by German chemist Eugen Baumann, PVC was originally a very rigid and somewhat brittle material that struggled to find widespread use. In 1926 Waldo Semon and B.F. Goodrich developed a way to plasticize PVC, increasing its flexibility and opening it up to a wide range of applications.

Semon, known as the father of the vinyl, is also known for inventing a non-digestible synthetic rubber bubble gum substitute that was so strong it could be used to blow enormous bubbles.

PVC is formed by combining its chemical components (primarily chlorine from industrial salt and carbon) together in a liquid within a pressure-tight container. Stirring and agitation causes the components to polymerize, forming PVC and generating heat which must be drawn off the reaction. Water is continuously added to facilitate the process until it is compete, and individual spheres of PVC have been formed.



PVC is highly durable and non-reactive, making it ideal for applications where contamination or degradation are serious concerns.

Amongst the most visible uses of PVC beyond white pipes are vinyl records, which were once a commonplace item in the days before iPods and streaming music. Other common applications are as a home siding material, a synthetic alternative to leather, and to make plastic bags that are far more durable than those produced from LDPE.

Low cost and lightweight, PVC has many advantages. As a thermoplastic, it can be recycled and reformed as needed. It's highly durable and non-reactive, making it ideal for applications where contamination or degradation are serious concerns. PVC also has low thermal conductivity and a high resistance to chemical stress cracking.

Conversely, there are some drawbacks to using PVC. Because of how it is made, there is the possibility that PVC may release toxins into the environment during production, when it is burned, or as it decomposes. This danger of environmental contamination has given PVC a somewhat bad reputation.

This is a major reason why it is banned in Europe and California presently. In fact, there are only a couple bottle makers left in the United States that still process this resin. Furthermore, due to the many different additives and processes used to produce PVC, recycling it efficiently and economically can often be a major challenge.

That said, PVC can be and is recycled in the U.S. today. With proper care and the right technology, PVC can be reclaimed effectively in two main ways: it can be ground down into small particles to be reformed into new PVC materials, or it can be chemically broken down into its component molecules so those materials can be reused in other applications.

PVC has the resin identification code 3, and is often accepted by manufacturers of plastic lumber for construction.

LOOKING TO THE FUTURE

Scientists and manufacturers working in plastics are always looking to the future to develop new technologies that meet the needs of the consumer market. New "green" materials are being developed every day, replacing older, less sustainable materials. By relying on raw materials rather than petroleum, these new plastics are helping to reduce our reliance on petrochemical energy.

Another big development in the world of plastics is "lightweighting"—finding ways to strengthen materials so less can be used, while reducing the weight of products and packaging. This has major implications in the automotive industry, where lighter weight vehicles can equal higher fuel efficiency.

Lightweighting in packaging also reduces the amount of plastic needed to produce common items like water bottles and reducing the overall amount of waste material.

The versatility and eco-friendly benefits that come with some plastics make them the packaging material of choice for most manufacturers. This is why staying ahead of the latest discoveries and trends in plastics is a top priority for suppliers and distributors who seek to remain on the cutting edge of the ever-shifting packaging industry.

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LEARN MORE

THE DEFINITIVE GUIDE TO

PLASTICS

FOR THE PACKAGING INDUSTRY

NACD

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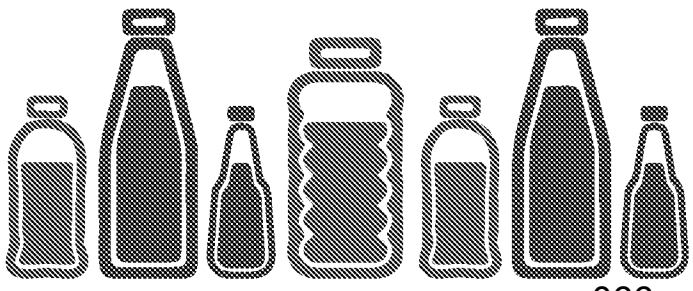


PLASTICS: A BRIEF HISTORY AND WHERE WE ARE TODAY

Since the early 19th century, plastics have a played a major role in the world's economy. From textiles and building materials, to medical applications and packaging.

Plastics are America's third largest manufacturing industry, employing over 885,000 workers. Add in those employees of companies that supply the plastics industry, and you're looking at over 1.4 million Americans working in plastics today. In the last thirty years, the industry has grown 2.4% annually, continually increasing in volume and value.

The development of plastics began in the 1860's when billiard companies began searching for an alternative to ivory for the production of pool balls. The race was on to develop a strong, lightweight synthetic that would allow the game to continue. Researchers and chemists all over the world began experimenting with plant resins to create a new kind of man-made material.

In 2015, plastic products and packaging are an $800 billion dollar industry with almost 150,000 companies involved and it's common knowledge in the world of container sales and manufacturing that plastics play a key role in the industry.

Because of their diversity and incredibly flexible nature, plastics are often the best solution to a tough packaging problem. They're cost effective, readily available, and reliable enough to be the first and best choice for thousands of companies. They're also generally highly recyclable, with over a billion pounds being recycled into new applications every year.

The purpose of this ebook is to provide professionals with a working knowledge of some of the most common plastics used in the container industry, and to compare and contrast their different uses, values, strengths, and weaknesses. And maybe most important in today's eco-conscious climate, we'll explore the relative sustainability of 6 popular plastics in production today. We'll also cover the best applications for each plastic.

KEY PLASTIC TERMINOLOGY

Here are a few key terms used in plastics and ones you may come across in this ebook:

MONOMER

A monomer is a molecule that can bind chemically to other molecules to form a polymer.

POLYMERS

Polymers are made up multiple monomers (AKA molecules) that are strung together.

THERMOSETTING POLYMER

Thermosetting polymers are also known as plastics. They are materials which become liquid or malleable at low temperatures and become hard and rigid in high temperatures.

SIX PLASTICS THAT DOMINATE THE INDUSTRY

There are many unique varieties of plastic material made from a diverse range of sources, including many made from reclaimed or recycled material. Depending on your business, you may be deeply informed about one type of material, but be seeking out information on others to broaden your knowledge base. In this book we'll cover six major materials:

HDPE - High-Density Polyethylene

LDPE - Low-Density Polyethylene

PET - Polyethylene Terephthalate

PS - Polystyrene

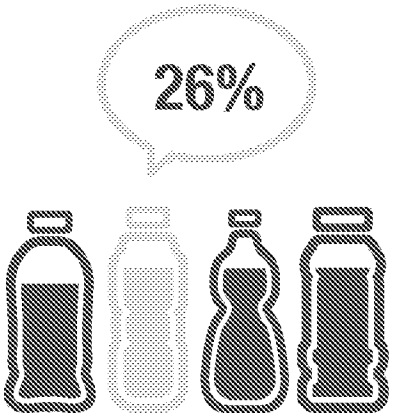
PP - Polypropene

PVC - Polyvinyl Chloride

We'll begin by covering their backgrounds and the basics of the processes by which each material is produced, and then offer insight into the strengths and weaknesses of each in terms of durability, diversity of applications, and finally take a look into their relative sustainability.

This last area will be explored in depth, bringing you up to speed on this hot button issue and giving you an easy reference for key facts about recycling and the relative sustainability of each material.

First let's take a look at two varieties of polyethylene, the most common plastic in the world. Over 88 million tons of polyethylene are produced a year in thousands of different forms for a variety of applications. The two most common types in production today are HDPE and LDPE.



Known for its strength and durability, 26% of all HDPE produced worldwide is used in the production of rigid packaging.

HDPE

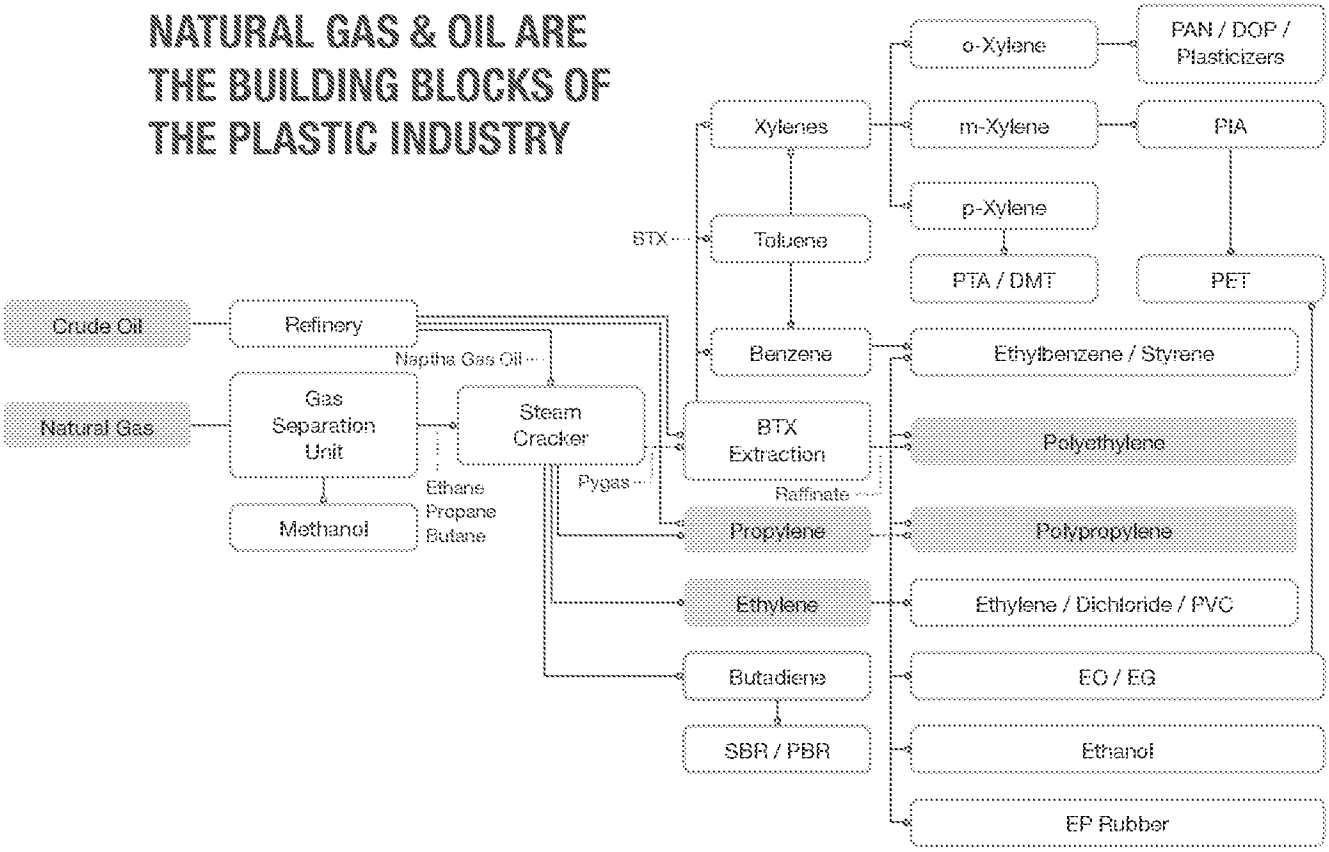
Developed by two researchers in 1953 high-density polyethylene is one of the most common packaging and construction materials in use today. Known for its strength and durability, 26% of all HDPE produced worldwide is used in the production of rigid packaging. In 2014 the global capacity for production, including facilities which can also be used to create other Polyethylene-based materials, was around six hundred million tons.

Growth in production is consistent to meet rising demand, although pricing can fluctuate along with the naphtha and crude oil markets as both are precursors for HDPE production. It's the second most recycled plastic in the United States, with approximately 28% of bottles and jars reclaimed.

HDPE is a great choice for food and beverage applications as many grades of the material are USDA, NSF, and FDA approved for direct contact with food. In addition, it has good impact resistance, is lightweight, and has very low moisture absorption.

HDPE is made from crude oil, but it only takes 4% of the world's annual oil production to produce all the plastic made in the world each year. To produce HDPE, petroleum is heated in a process known as cracking, which produces ethylene gas. These gas molecules link together to form long chains known as polymers — specifically polyethylene. The polyethylene is then pushed through fine holes to form long thin strings that are cut to form small granules.

NATURAL GAS & OIL ARE THE BUILDING BLOCKS OF THE PLASTIC INDUSTRY



Reliability and safety are two of HDPE's strongest value propositions. Unlike some other container materials, HDPE will not degrade due to extreme high or low pH, intense concentrations of salts, or other common chemical corrosives. It is generally extremely inert and as a result makes an ideal material for food and beverage applications.

However, there are some shortcomings to working with HDPE. It has a high instance of thermal expansion, and while it is a strong material it can be subject to some stress cracking. It's also difficult to bond to other materials, and has a relatively low strength/stiffness, making it unsuitable for some of the more rugged applications. Additionally, like many petroleum-based plastics, it can be very flammable and is not suitable for high-temperature applications.

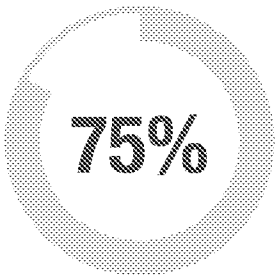
HDPE's SPI Resin Identification Code is 2, and it can be recycled easily throughout the United States. The market for, and production of, post-consumer recycled HDPE products is stable and growing, and the main use for reclaimed HDPE is in creating a new life for the material as a bottle or food and beverage packaging.

If you're looking for a durable, lightweight, food safe, and easy-to-manipulate material for your packaging needs—and one that comes with reasonably good marks for sustainability—HDPE might be right for your project.

LDPE

LDPE stands for low density polyethylene, but you might have guessed that already. It was the first type of polyethylene that was commercially produced. It was developed in 1933 by Imperial Chemical Industries (ICI), which was for many years, the largest manufacturer of LDPE in Great Britain. Of note, ICI is responsible for many other material innovations including the acrylic plastic perspex, an early competitor to plexiglass.

LDPE has slightly less tensile strength than HDPE but is correspondingly more flexible. Its most common application in the modern word is as the material used to make many plastic bags, but there are many other applications for LDPE.



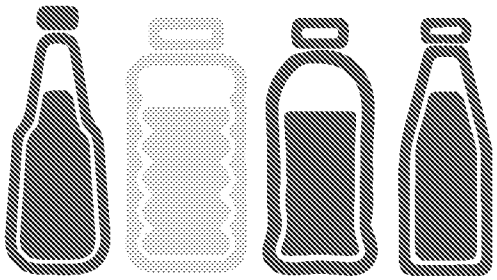
About 75% of all Polyethylene produced globally is LDPE.

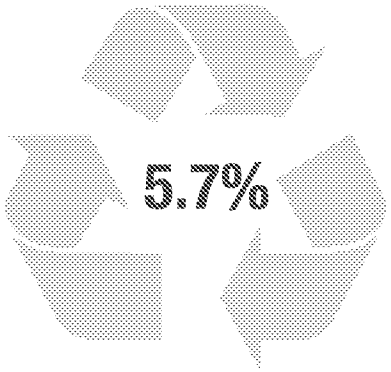
It can be used to make shrink film, overwrap film, food safe packaging film, and strong liquid containers. About 75% of all Polyethylene produced globally is LDPE.

LDPE's low density makes it highly malleable and allows for stretching—one of its chief strengths—and makes it a great choice for lightweight, form fitting film-type packaging. Unlike rigid HDPE, LDPE can be used to create lightweight and flexible packaging. Keep in mind however, that its relatively lower density does make it susceptible to puncture.

Because of its similarity to HDPE, low density polyethylene shares many of HDPE's shortcomings, including low strength/stiffness, high thermal expansion, and poor temperature capability. Like HDPE, it is also subject to stress cracking and is flammable. It is also more difficult to bond than other plastics, limiting its applications slightly.

Another bonus with LDPE is that its high durability allows for packaging (like plastic bags) to be reused by the consumer many times before it has to be recycled or disposed of. Embracing a push towards increased sustainability, some packaging producers are designing LDPE products whose useful life extends past their initial purpose.





Unfortunately, in the United States, LDPE is recycled at a rate of only about 5.7% — lower than its denser sibling.

Unfortunately, in the United States LDPE is recycled at a rate of only about 5.7%—lower than its denser sibling. If sustainability is one of your chief concerns, LDPE may not be the best material choice for your application. Although, recycled LDPE is available and can be combined with a percentage of virgin material to rejuvenate it for a variety of uses. Its resin identification code is 4, and while few curbside programs accept LDPE for recycling many stores and some communities will accept plastic bags.

PET

HDPE and LDPE are both great materials for food and beverage containers, but when it comes to plastic bottles there's one plastic that leads the field—PET.

PET stands for polyethylene terephthalate, and is the most popular polyester produced globally. It is used primarily as a fiber for textile production and as a packaging material for food and beverage products.

PET has an especially good moisture barrier and makes a great material for soft drink bottles. Some kinds of PET can be treated with a thin layer of metal to make it reflective and opaque, while others can be thermoformed into blister packs.

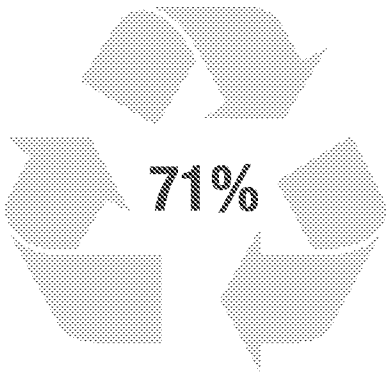
Developed in England in 1941, PET is one of the most common polyesters in the world, and ranks fourth globally in terms of overall polymer production. It also goes by the names PETE and the brand names Dacron, Terylene, and Lavsan.

It's the material responsible for everything from emergency "space blankets" to polar fleece. It's versatility and excellent recyclability make it a great choice for many packaging applications.

The production of PET is a fairly complex process, but there are a few basic points to keep in mind. The precursors for PET production are terephthalic acid and ethylene glycol, both readily available and relatively low-cost materials. After these components are combined they undergo a series of controlled reactions in the presence of specific catalysts and environmental conditions which determine the characteristics of the final product.

PET can be copolymerized with other substances to adjust its internal structure to make it more suitable to certain kinds of extrusion or molding.

On the flip side, one of PET's main shortcomings is its high susceptibility to heat degradation. During the production process temperatures must be carefully maintained to ensure the resulting material is clear, and in many applications high heat will fundamentally compromise packaging and other products made from PET. However, compared to other plastics like HDPE and LDPE, PET is considerably less flammable.



PET is accepted in almost all U.S. recycling programs, and for every pound of recycled material used in place of a new plastic, greenhouse gas emissions are reduced by a whopping 71%!

PET is one of the most easily recycled plastics currently in use today, and consumer packaging made from 100% recycled material is becoming increasingly common in today's sustainability-focused market. In fact, research shows that PET packaging may be more environmentally preferable than many new bioplastic materials due to its healthy closed-loop lifecycle.

It has the resin identification code 1, and most curbside programs accept PET/PETE materials. Thanks to its resilience, PET can be recycled many times very efficiently. It's accepted in almost all U.S. recycling programs, and for every pound of recycled material used in place of new plastic, greenhouse gas emissions are reduced by a whopping 71%!

Let's take a look at another extremely popular and widely used plastic available today—polystyrene.

PS

As one of the oldest plastics still in use, polystyrene was discovered in 1839 by German apothecary Johann Edouard Simon. The original batches of polystyrene were made from the natural resins of the Turkish sweetgum tree. Almost 100 years later, researchers at DOW Chemical developed a process to make a closed-cell, moisture resistant product, and introduced Styrofoam to the world in 1941.

You may know it by the brand name Styrofoam and be surprised to learn about some of its other useful applications.

Polystyrene is one of the most commonly used and versatile plastics available today. It can be made both transparent and opaque, with a variety of densities and strengths depending on the application. It can be formed into a solid or a foam, and is a relatively inert and non-reactive material.

Through copolymerization, PS can be combined with other materials to expand its range of properties. For example, so called "high-impact plastic" is a result of one such process. PS can also be stretched into a clear rigid film called Oriented Polystyrene (OPS) that can be used to create comparatively inexpensive transparent packaging, though its durability may suffer greatly.

Polystyrenes disadvantages make it unsuitable for some applications. It is highly flammable (though flame retardant varieties do exist), and low impact varieties can break very easily. It has notoriously poor resistance to most solvents, and is not suitable for containing many types of liquids. It's also worth noting that while the recyclability of polystyrene is on the rise in the U.S., it has a track record as being one of the least sustainable plastic materials, and without special treatment is virtually non-biodegradable.

Applications include rigid plastic packaging for things like computers, as well as food containers, disposable utensils, and even as a building material when used in conjunction with reinforced concrete. Additionally, much of today's conventional protective packaging materials are made from PS. A variety of production techniques and technologies allow polystyrene to be a strong choice for many diverse applications.

It's worth noting that there is a rising trend in American municipalities to ban PS food containers, as they are perceived as a major source of non-biodegradable waste in landfills. Earlier this year, New York City banned single-use expanded polystyrene food containers, citing their belief that these materials could not be recycled effectively. If sustainability is amongst your primary concerns, you may want to consider alternatives to PS for your applications.

Contrary to what many believe, it is completely possible to recycle polystyrene, including styrofoam food service containers. And while traditionally products made from polystyrene have been considered non-biodegradable, new research with biological agents has led to a process by which PS materials can be converted into more easily broken down substances.

Ongoing research in this area is improving the relative sustainability of PS over time. Polystyrene has the resin identification code 6 and can be picked up by some curbside recycling programs in the U.S.

PP

One of the strongest and most resistant plastics available today, Polypropylene has a wide variety of applications ranging from packaging to textiles. Developed by Phillips Petroleum chemists J. Paul Hogan and Robert L. Banks in 1951, Polypropylene was brought into commercial production within the decade. More than half of all PP produced today is used in flexible packaging, and demand continues to rise for this versatile material.

Polypropylene is produced through a variety of methods, and the resulting materials have various properties such as an anti-static nature to resist dust, or a treated surface designed to improve paintability.

Due to its great physical durability when properly oriented, PP can be used to form strong, long lasting, living hinges in packaging as well. Its strength also allows for very low density production, which reduces its environmental impact.

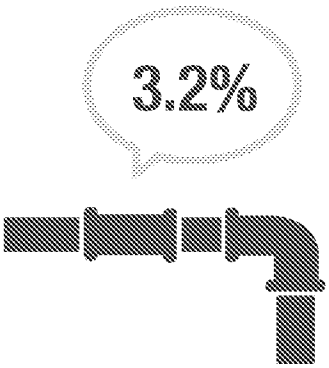
Like Polystyrene, PP can be produced in an "oriented" structure that allows for increased clarity and thinness, without the brittleness of PS. Biaxially Oriented PP is commonly used as packaging for food products due to it being easy to coat, print on, and laminate.

There are many diverse advantages to using polypropylene. Because it's unusually strong, PP is a great choice for producing containers meant to package acid, base, or other highly corrosive substances. Due to its great physical durability when properly oriented, PP can be used to form strong, long lasting, living hinges in packaging as well. Its strength also allows for very low density production, which reduces its environmental impact.

Polypropylene is highly susceptible to some chlorinated solvents and aromatics. Without special treatment it is highly flammable, and difficult to bond or paint. It also oxidizes readily and suffers from UV degradation. While there are special processes available to treat PP to deal with these issues, there are other materials better suited to applications where weathering and UV exposure are likely.

PP recycling is quickly on the rise in the US, more than tripling between 2004 and 2010. Its production results in less solid waste than many alternatives, and it results in much lower CO2 emissions than other similar materials. Many states now have programs to accept polypropylene, with more joining in every year.

Recycled PP has uses across many markets, including packaging, consumer goods, and construction materials. It has the resin identification code 5, and is accepted in many curbside recycling programs.



Demand for PVC is expected to increase by 3.2% per year until 2021.

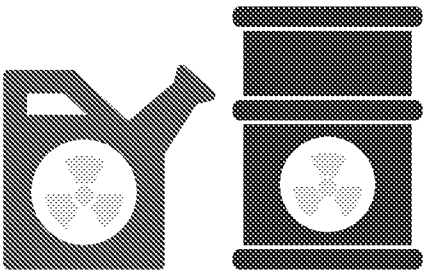
PVC

When most people hear PVC (Polyvinyl Chloride) their first thought might be the ubiquitous white plastic piping used in so many applications, but PVC is more than just pipes. It is the third most widely produced plastic after polypropylene and polyethylene and demand for PVC is expected to increase by 3.2% per year until 2021.

Discovered accidentally in 1872 by German chemist Eugen Baumann, PVC was originally a very rigid and somewhat brittle material that struggled to find widespread use. In 1926 Waldo Semon and B.F. Goodrich developed a way to plasticize PVC, increasing its flexibility and opening it up to a wide range of applications.

Semon, known as the father of the vinyl, is also known for inventing a non-digestible synthetic rubber bubble gum substitute that was so strong it could be used to blow enormous bubbles.

PVC is formed by combining its chemical components (primarily chlorine from industrial salt and carbon) together in a liquid within a pressure-tight container. Stirring and agitation causes the components to polymerize, forming PVC and generating heat which must be drawn off the reaction. Water is continuously added to facilitate the process until it is compete, and individual spheres of PVC have been formed.



PVC is highly durable and non-reactive, making it ideal for applications where contamination or degradation are serious concerns.

Amongst the most visible uses of PVC beyond white pipes are vinyl records, which were once a commonplace item in the days before iPods and streaming music. Other common applications are as a home siding material, a synthetic alternative to leather, and to make plastic bags that are far more durable than those produced from LDPE.

Low cost and lightweight, PVC has many advantages. As a thermoplastic, it can be recycled and reformed as needed. It's highly durable and non-reactive, making it ideal for applications where contamination or degradation are serious concerns. PVC also has low thermal conductivity and a high resistance to chemical stress cracking.

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Food Packaging

Principles and Practice

Gordon L. Robertson

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Excerpt from:

Chapter 2 Structure and Related Properties of Plastic Polymers

Section 2.3 Factors Influencing Polymer Structures and Related Properties

Section 2.3.6 Chemical Structure

Section 2.3.6.1 Polyolefins

even though not excessively large, leads to significant intermolecular bonding forces and relatively high T_ms. For instance, the T_m for PVC is 212°C and for PAN (poly(acrylonitrile)) 317°C.

The temperatures T_m and T_g are governed by the strength of the intermolecular forces (just as in inorganic materials) and by the degree of flexibility and length of the chains. Thus, polar side groups such as chloride and hydroxyl groups favor higher melting and glass transition temperatures because they enhance the strength of the intermolecular bonds.

In some cases, the T_g can be lowered by as much as 100° by the efficient use of plasticizers. For example, pure PVC has a T_g of 87°C and is quite brittle at room temperature. The addition of only 15% plasticizer lowers this to 60°C, and with the addition of further plasticizer, PVC becomes tough and flexible at room temperature.

2.3.6 Chemical Structure

Polymer chains can and do align themselves in ordered structures, and the thermodynamics of this ordered state determines such properties as the melting point, the glass transition temperature, other transition temperatures and the mechanical and electrical properties. However, it is the chemical nature of the polymer that determines its stability to temperature, light, water and solvents.

In the published literature, it is rare to find many details about a particular plastic packaging material apart from its name, sometimes the resin supplier and maybe if it has been oriented. This makes it virtually impossible to replicate the experimental conditions described in the literature since the range of polymers available is vast. For example, the website www.ides.com contains data sheets on over 77,000 commercial polymers from 694 resin manufacturers. Of course, many of these polymers are not approved or suitable for use in food packaging.

2.3.6.1 Polyolefins

Olefin means oil-forming and was originally the name given to ethylene. Today polyolefin is a common term in the plastics industry and refers to the family of plastics based on ethylene and propylene. The term *alkene* is used for hydrocarbons containing a carbon–carbon double bond, for example, ethylene, propylene and octene. The formula, MW, density and boiling point of the alkenes important in food packaging are given in Table 2.3. Polyolefins form an important class of thermoplastics and include low, very low, linear, medium and high density PEs and polypropylene (PP). Industry commonly divides PEs into the following broad categories based on density: HDPE 940–975 kg m^{-3}, MDPE 926–940 kg m^{-3}, LDPE 915–940 kg m^{-3}, LLDPE 915–925 kg m^{-3}, VLDPE 880–915 kg m^{-3}.

2.3.6.1.1 Low Density Polyethylene

This is the largest volume single polymer used in food packaging in both the film and blow molded form. It is a polymer of ethylene, a hydrocarbon gas available in large quantities as a by product of petroleum refining and other processes. Increasing quantities are now also being produced by the catalytic dehydration of ethanol produced by the fermentation of biobased materials, especially sugarcane (Morschbacker, 2009). PE was first produced by Imperial Chemical Industries (ICI) in 1933

TABLE 2.3
Molecular Details and Some Physical Properties of Common Hydrocarbon Monomers

Name	Molecular Formula	Molecular Weight	Density at 15°C (kg m^{-3})	Boiling Point (°C)
Ethylene	C_2H_4	28.05	1.180	−103.7
Propylene	C_3H_6	42.08	1.810	−47.6
Butene-1	C_4H_8	56.11	2.370	−6.3
Hexene-1	C_6H_{12}	84.16	0.678	63
Octene-1	C_8H_{16}	112.24	0.715	121

during a research program devoted to the effects of extremely high pressures on chain reactions, and the basic patent relating to polymerization of ethylene was granted in 1937. It was produced on a pilot plant scale that same year with full commercial-scale production commencing in 1939. For the first few years of its production, it was used in the electrical industry, particularly as an insulating material for underwater cables.

The polymerization of ethylene can occur over a wide range of temperatures and pressures but most commercial high pressure processes utilize pressures between 1000 and 3000 atm and temperatures between 100°C and 350°C (higher temperatures cause degradation of the PE).

The simplest structure for PE is a completely unbranched structure of $-CH_2-$ units as shown in Figure 2.1b. However, the vigorous nature of the high pressure process leads to a great deal of chain branching, with both short and long chains being formed. From Figure 2.3a, it can be seen that the branch contains a terminal methyl ($-CH_3$) group. A convenient way of characterizing branching is by the number of methyl groups per 1000 carbon atoms. Figure 2.5 is a schematic representation of linear and branched polymers of which HDPE short chain branches (SCB) and LDPE with long-chain branches (LCB) are good examples.

The branch chains prevent close packing of the main polymer chains, resulting in the production of PEs of relatively low density (typically 910–940 kg m^{-3}). MWs also tend to be relatively low. The great length of the polymer chains results in a certain amount of entanglement that prevents complete crystallization on cooling. When the polymer melt is cooled slowly, the crystallites may form *spherulites*.

The crystallinity of LDPE usually varies between 55% and 70%. The softening point is also affected by chain branching. The attractive forces between the chains are reduced because they are unable to approach each other closely, and, therefore, less energy (in the form of heat) is necessary to cause them to move relative to each other and thus flow. The softening point of LDPE is just below 100°C, thus precluding the use of steam to sterilize it in certain food packaging applications.

LDPE is a tough, slightly translucent material that can be blow extruded into tubular film, or extruded through a slit die and chill-roll cast, the latter process giving a clearer film. It has good tensile strength, burst strength, impact resistance and tear strength, retaining its strength down to −60°C. While it is an excellent barrier to water and water vapor, it is not a good barrier to gases. One of the great attributes of LDPE is its ability to be fusion welded to itself to give good, tough, liquid-tight seals. It cannot be sealed by high-frequency methods. It has excellent chemical resistance, particularly to acids, alkalis and inorganic solutions, but is sensitive to hydrocarbons, halogenated hydrocarbons, oils and greases. These latter compounds are absorbed by the LDPE, which then swells.

When a polymer is stressed in air to just below its yield point, stress cracking can occur after a certain period of time. However, when simultaneously exposed to both stress and a chemical medium, there is a dramatic reduction in the time to failure. This latter type of failure is termed

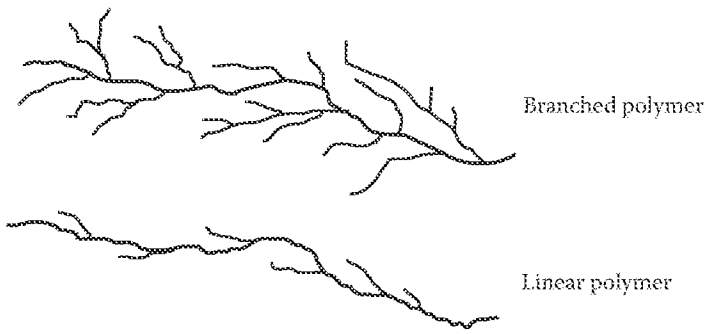

FIGURE 2.5 Schematic representation of branched and linear polymers showing the larger volume swept out by the branched structure, resulting in its lower density. Branches of the main backbone are indicated by narrower lines; they have no direct proportional relationship to cross-sectional dimensions. (From Brown, W.E., *Plastics in Food Packaging: Properties, Design and Fabrication*, Marcel Dekker, New York, p. 106, 1992.)

environmental stress cracking (ESC) and generally manifests itself as surface-initiated cracks or brittle failure (Scheirs, 2000). The stress may be internal (e.g., due to inbuilt molding stress) or external (such as mechanically applied stress). For example, ESC can occur when filled plastic containers are stacked on pallets in a warehouse or during transportation. Although ESC results from the interaction of the polymer with certain chemicals, it is a purely physical mechanism and not a chemical reaction (i.e., not a degradation in the true sense). Interactions between the fluid, the stress and the polymer include local yielding, fluid absorption, plasticization, craze initiation, crack growth and fracture without irreversible chemical change (i.e., without change in MW). The fluid only accelerates the mechanism. ESC is strongly related to the crystallinity of the polymer: the higher the crystallinity, the lower is the ESCR (environmental stress crack resistance). To reduce the crystallinity in polyolefins, comonomers such as butene, hexene, or octene can be used at less than 2%.

Essential oils (a common component of flavorings) and vegetable oils are capable of causing ESC in PEs and PS, and whenever a new flavor is introduced for an existing product, adequate testing must be carried out to ensure that ESC does not result. ASTM D2561 details test methods to measure the ESCR of containers, which is the summation of the influence of container design, resin, blow-molding conditions, posttreatment or other factors that can influence ESC. Three procedures are provided and procedure A can be useful for determining the effect of container design on the ESCR of a blow-molded HDPE package containing a liquid food product. However, any tests have to be correlated with actual field performance to be of practical use. The inability to measure the extent of ESC under controlled laboratory conditions makes it very difficult to understand the role of any one variable, the interaction between variables and the mechanisms of ESC.

PE is one of the most inert polymers and constitutes no hazard in normal handling.

Besides films, LDPE also finds use as a rigid packaging material as it can be easily blow molded into bottles where its flexibility enables the contents to be squeezed out. It is also widely used in the form of snap-on caps, collapsible tubes and a variety of spouts and other dispensers. The surface of PE containers can be treated with fluorine after blow molding to form a very thin, polar, cross-linked surface that decreases the permeability of the PE to nonpolar penetrants. It also eliminates the need for treating the surface by corona-arc discharge or flame techniques (see Section 5.3.1.2) to improve printability properties. The process has been cleared by the U.S. Food and Drug Administration (FDA) for use with food containers.

At the present time, there are many hundreds of grades of LDPE available, most of which differ in their properties in one way or another. Differences arise from the following variables:

1. Variation in the degree of short chain branching in the polymer
2. Variation in the degree of long chain branching
3. Variation in the average MW
4. Variation in the MWD (which may in part depend on the long-chain branching)
5. Presence of small amounts of comonomer residues
6. Presence of impurities or polymerization residues, some of which may be combined with the polymer

2.3.6.1.2 Linear Low Density Polyethylene

The first production of LLDPE was made in a solution process in 1960. Attempts in the 1970s to produce LDPE, either by low pressure gas-phase polymerization or by liquid-phase processes similar to those used for producing HDPE, led to the development of LLDPE and its commercialization in 1977. The term *linear* in LLDPE is used to imply the absence of LCBs. LLDPE has a similar molecular structure to HDPE and although virtually free of LCBs, it does contain numerous short side chains. These arise as a result of copolymerizing ethylene with a small amount of a higher alkene (α-olefin) such as butene. An α-olefin has the chemical formula C_xH_{2x} and a double bond at the primary or alpha (α) position. The general formula for ethylene copolymers with α-olefins is $-CH_2-CHR-$, where R is C_2H_5 in ethylene-1-butene copolymers, n-C_4H_9 in ethylene-1-hexene

copolymers and n-C_6H_{13} in ethylene-1-octene copolymers (Kissin, 2005). An increase in α-olefin content results in a decrease in crystallinity and density and a significant reduction of the polymer mechanical modulus (stiffness). Industry convention is not to indicate the presence of a copolymer such as octene in PE if its concentration is less than 10%.

Due to the linearity of its molecules, LLDPE is more crystalline and, therefore, stiffer but less transparent than LDPE, resulting in an increase of 10°C–15°C in the melting point of LLDPE compared to LDPE. The linearity provides strength, while the branching provides toughness. LLDPEs made with hexene and octene have better puncture resistance, impact strength and tear strength, but are more costly relative to LLDPE made with butene comonomer. The crystallinity and, consequently, the density of PE are controlled by the amount and type of α-olefin incorporated into the backbone. Decreasing α-olefin content leads to higher densities. The concentration of α-olefin in a copolymer varies from 1 mol% in MDPE to 2.5–3.5 mol% in LLDPE and 10–15 mol% in VLDPE (Kissin, 2005).

LLDPE combines the main features of both LDPE and HDPE, a major feature being that its MWD is narrower than that of LDPE. Generally, the advantages of LLDPE over LDPE are improved chemical resistance, improved performance at low and high temperatures, higher surface gloss, higher strength at a given density, better heat sealing properties and a greater resistance to ESC. In film form, LLDPE has higher tensile strength, puncture resistance, tear properties and elongation than LDPE. High-clarity film produced with LLDPE manufactured with metallocene catalysts is widely used for food packaging films and blow molding of bottles. The superior properties of LLDPE have led to its use in new applications for PE as well as the replacement of LDPE and HDPE in some areas; LLDPE is also often blended with LDPE.

2.3.6.1.3 Very Low Density Polyethylene

VLDPE (sometimes referred to as ultralow density polyethylene or ULDPE) is a subclass of LLDPE with a density <915 kg m^{-3}. It has an α-olefin content (normally octene) of >4 mol% and a crystallinity of <25% (Kissin, 2005). In stretch film applications, VLDPE exhibits excellent stretchability as well as good physical and cling properties. VLDPE can also be utilized for the production of blown film requiring a combination of excellent optical properties, outstanding tear and impact strength and very good sealability. VLDPE copolymer is also used as a skin layer in cast film and has excellent low temperature hot tack properties combined with outstanding tear and impact strength. VLDPE can be blended with other PE and PP-based resins to enhance clarity, sealability and toughness of the materials and can be used as a sealant in multilayer film structures. VLDPE also offers greater low temperature flexibility and flex crack resistance. VLDPE is mostly used for the packaging of fresh produce, milk, meat and cheese, as well as for the manufacture of multilayer coextruded film.

2.3.6.1.4 High Density Polyethylene

Prior to 1950, the only commercial polymer of ethylene was the highly branched polymer LDPE. The technique for making a linear polymer was discovered by Nobel laureate Karl Ziegler of Germany in the early 1950s. Ziegler prepared HDPE by polymerizing ethylene at low pressure and ambient temperatures using mixtures of triethylaluminum and titanium tetrachloride. Another Nobel laureate, Giulio Natta of Italy (he shared the Nobel Prize for chemistry with Ziegler in 1963), used these complex coordination catalysts to produce crystalline PP; these are now known as Ziegler–Natta (Z–N) catalysts. However, the credit for first producing stereospecific olefin polymers and HDPE belongs to J. Paul Hogan and Robert Banks of Phillips Petroleum Company, who did so in 1952 using chromium trioxide supported on a silica-alumina catalyst (Carraher, 2010).

HDPE is a nonpolar, linear thermoplastic that possesses a much more linear structure than LDPE. It has up to 90% crystallinity, whereas LDPE exhibits crystallinities as low as 50%. Although some branch chains are formed, these are short and few in number. HDPE film is stiffer and harder than LDPE and densities range from 940 to 975 kg m^{-3}. Because HDPE contains a crystalline phase and

an amorphous phase, the measured density directly reflects the percentage of each. Typical homopolymer is normally 70% crystalline and has a density of 960–965 kg m^{-3}. Higher densities can be achieved by low MW and slow cooling. The MW of typical commercial HDPE grades can vary from 20,000 to >3,000,000, depending on the application. Its softening point is about 121°C, and its low temperature resistance is about the same as LDPE. Tensile and bursting strengths are higher but impact and tear strengths are both lower than LDPE. Of interest is the fact that due to the linear nature of the HDPE molecules, they tend to align themselves in the direction of flow and, thus, the tear strength of the film is much lower in the machine direction (MD) than the transverse direction (TD). This difference can be accentuated by orientation to give a built-in tear tape effect.

The chemical resistance of HDPE is also superior to that of LDPE and, in particular, it has better resistance to oils and greases. The film offers excellent moisture protection, a much decreased gas permeability compared with LDPE film, but is much more opaque. Heat sealing is considerably more difficult compared to LDPE film. The melting point is a function of both MW and branch content. A decrease in MW from ~1,000,000 to 40,000 is accompanied by a decrease in melting point from 137°C to 128°C.

HDPE film has a white, translucent appearance and, therefore, tends to compete more with paper than transparent films. To be competitive with paper on a price-per-unit-area basis, it must be thin, and, consequently, much of the HDPE film used is only 10–12 μm thick.

HDPE is blow molded into bottles for a variety of food packaging applications, although its uses in this area have tended to be taken up by PET bottles that generally have better barrier properties than HDPE.

The basic properties of various PE films are shown in Table 2.4. The melting point of PEs is primarily a function of their densities, the melting point increasing with density, as does the softening temperature.

2.3.6.1.5 Irradiated Polyethylene

Irradiated PE is produced by passing ordinary LDPE film continuously under an electron beam accelerator that produces high-energy ß rays. This converts it to an infusible film, which causes cross-linking between the chains and gives it exceptional strength from the point of view of stretch resistance and shrink tension. Other effects include the evolution of H_2 and a reduction in crystallinity. The process slightly reduces gas and water vapor transmission rates but increases the heat sealing range to make a practical shrink film from PE. The film has good clarity. It is sealed by welding the overlaps together on a hot plate and shrunk by passing through a hot air tunnel at 220°C.

2.3.6.1.6 Polypropylene

Early attempts to polymerize propylene using the high pressure process used to make LDPE gave only oily liquids or rubbery solids of no commercial value. Work by Natta in Italy using Ziegler-type catalysts led to the development in 1954 of a stereospecific catalyst that controlled the position of each monomer unit as it was added to the growing chain, thus giving a polymer of regular structure. Today, typical processes take place at about 100 atm and 60°C. A significant innovation in PP

TABLE 2.4
Basic Properties of Various PE Films

Type of Polyethylene	Water Vapor Transmission	Gas Transmission		Tensile Strength (MPa)	Softening Point (°C)	CH_3 Groups per 1000 C's
		O_2	CO_2			
Low density (920 kg m^{-3})	1.4	500	1350	9–15	120–180	20–33
Medium density (940 kg m^{-3})	0.6	225	500	21	120–180	5–7
High density (960 kg m^{-3})	0.3	125	350	28	135–180	<1.5

production has been the Spherizone process technology, which is based on a multizone circulating reactor (MZCR). In comparison to traditional multistep technologies, the MZCR provides a step change in the polymer homogeneity of the final product by continuously circulating the growing polymeric granules between two interrelated zones where different gas phase compositions are realized (Mei et al., 2009). The Spherizone process can produce all conventional PP grades as well as new and improved products including highly modified random copolymers. In addition to traditional Z–N catalysts, metallocene catalysts are also being introduced in PP manufacture (see next section).

PP is a linear polymer containing little or no unsaturation. Depending on the type of catalyst and polymerization conditions, the molecular structure of the resulting polymer consists of the three different types of stereo configurations: *isotactic*, *syndiotactic* and *atactic*, as shown in Figure 2.6. Industrial processes are designed to minimize the production of atactic PP (where the methyl groups are randomly distributed on either side of the chain), which results when polymerization occurs in the absence of stereospecific catalysts. This noncrystalline material has a density of about 850 kg m^{-3} and is soft, tacky and soluble in many solvents. It is a lower-value product and finds use mainly in hot-melt adhesives.

The most regular crystalline polymer produced by stereospecific catalysts is known as the isotactic form, the name stemming from the original idea that the methyl groups were always above or below the horizontal plane. Isotactic PP, the most common commercial form of PP homopolymer, is never perfectly stereoregular, the degree of isotacticity varying from 88% to 97%. It is a highly crystalline material with good chemical and heat resistance but poor transparency. Two other forms are syndiotactic, where the methyl groups alternate above and below the horizontal plane, and stereoblock, where blocks of methyl groups are alternately above and below the horizontal plane. The regular helices of the isotactic form can pack closely together, whereas the atactic molecules have a more random arrangement.

While atactic PP is an amorphous, rubbery material of little value, isotactic PP is stiff, highly crystalline and has a high melting point. In commercial polymers, the greater the amount of isotactic material, the greater is the crystallinity and, thus, the greater the softening point, tensile strength and hardness, all other structural features being equal (Carraher, 2010). Impact-resistant PP is a mixture of isotactic PP and amorphous ethylene–propylene copolymer.

PP has a lower density (900 kg m^{-3}) and a higher softening point (140°C–150°C) than the PEs, low water vapor transmission, medium gas permeability, good resistance to greases and chemicals, good abrasion resistance, high temperature stability, good gloss and high clarity, with the latter two factors making it ideal for reverse printing.

PP can be blow molded and injection molded, the latter process being widely used to produce closures for HDPE, PET and glass bottles, as well as thin-walled pots and crates. The T_g of PP is placed between 10°C and –20°C with the result that the polymer can become brittle as subzero

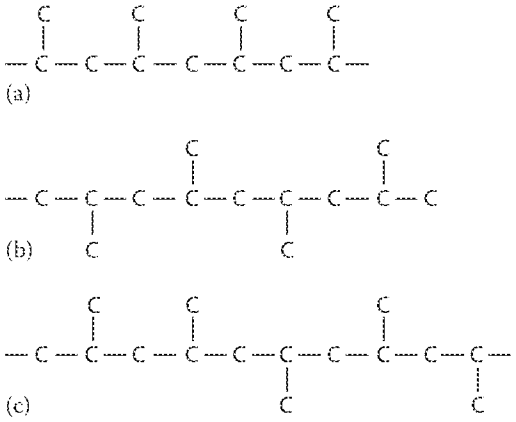

FIGURE 2.6 Types of PP: (a) isotactic, (b) syndiotactic and (c) atactic.

temperatures are approached. The T_m is in the range of 160°C–178°C, enabling foods inside PP containers to be sterilized by heat or reheated in microwave ovens. Copolymerization with 4%–15% ethylene improves the strength and clarity, reduces stiffness, increases impact resistance and lowers the T_m and T_g. For example, homopolymer PP with 3%–4% atactic fraction has a T_m of ~165°C, while a random copolymer with 2% ethylene has a T_m of about 150°C. Such copolymers are often preferred to the homopolymer in injection molding and bottle blowing applications and also find use in shrink wrapping where the lower melting point is an advantage.

Although free from ESC problems, PP is more susceptible to oxidative degradation at elevated temperatures, necessitating the inclusion of antioxidants in all commercial PP compounds. Whereas PE cross-links on oxidation, PP degrades to form lower MW products. A similar effect is observed when PP is irradiated.

Nonoriented PP film is often referred to as cast PP film because it is generally made by the chill-roll cast process, although other methods can be used. PP film is a very versatile material, being used as a thermoformable sheet, in cast form for film and bags, and as thin, strong biaxially oriented films for many applications. Cast and oriented PP are sufficiently different that they do not compete for the same end uses, the cost of cast PP being much lower than that of oriented PP. The cast form has PE-type uses while the oriented form has regenerated cellulose film (RCF)-type uses and has largely replaced RCF in food packaging applications. Cast PP use in food packaging is limited owing to its brittleness at below freezing temperatures, and it is generally not recommended for use with heavy, sharp or dense products unless laminated to stronger, more puncture-resistant materials. The relatively high temperature resistance of PP permits its use as the seal layer in retortable pouches, hot-filled bottles and microwavable packaging.

In recent years there has been a large increase in the use of oriented polypropylene (OPP) for food packaging. Wide variations are possible in the extent of orientation in two directions, leading to a wide range of properties. However, biaxially oriented polypropylene (BOPP) film has a high clarity because layering of the crystalline structures reduces the variations in refractive index across the thickness of the film and this in turn reduces the amount of light scattering. OPP can be produced by the blown tubular or high expansion bubble process, or the tenter frame process.

BOPP film has a tensile strength in each direction roughly equal to four times that of cast PP film. Although tear initiation is difficult, tear resistance after initiation is low. Biaxial orientation also improves the moisture barrier properties of PP film and its low-temperature impact strength. OPP film is not considered to be a gas barrier film but this deficiency can be overcome by coating with PVdC copolymer. OPP films often have a stiff feel and tend to audibly crinkle.

If heating sealing is required, PP is normally coated with a lower melting point polymer because shrinkage tends to occur when highly stretched film is heated. LDPE, PVdC copolymer and acrylic polymers are used as fusible coatings for OPP film. LDPE is cheaper, but PVdC copolymer confers far better resistance to water vapor and O_2 permeability; acrylic polymer adds no barrier properties to OPP film.

Another addition to the family of OPP films is white opaque film, generally made by the tenter frame process and known as cavitated or pearlized film because the diffusion of light gives the film the visual effect of pearlescence. Homopolymer resin is evenly mixed with a small amount of foreign particulate matter such as starch or titanium dioxide. In one product, when the thick filled sheet is oriented, the PP pulls away from each particle creating an air-filled void or closed cell. After heat stabilization, the OPP film is similar to a micropore foamed product. In the second product, the material produced is a filled film without voids, the opacity being a direct result of the amount of particulate material included in the film. The primary opacification is caused by light rays bouncing off the PP cell walls and the air within each cell. White opaque OPP film is widely used for cold seals and finds application in snack food packaging, candy-bar overwraps, ice cream novelties, beverage bottle labels, soup wrappers and other applications that have traditionally used specialty paper-based packaging materials (Mount, 2009).

Another new technology exploits the unique combination of properties, including melt strength, of PP grades for use in foam applications. For example, foamed PP food packaging trays are used for meat, fish, poultry, fruits and cheese where the material overcomes the typical expanded polystyrene (EPS) limitations, that is, aromatics release and susceptibility to cracking (Mei et al., 2009).

2.3.6.1.7 Metallocenes

Metallocenes are a relatively old class of organometallic complexes first discovered in 1951. They are based on a metal atom such as titanium, zirconium or hafnium. As early as 1957 Natta reported the (unsuccessful) polymerization of ethylene with a titanocene catalyst. The current interest in metallocenes originated with a discovery by Kaminsky at the University of Hamburg in the mid-1970s. While studying a homogenous polymerization system, water was accidentally introduced into the reactor, leading to an extremely active ethylene polymerization system. Subsequent studies revealed that the high activity was due to the hydrolysis of the cocatalyst trimethyl aluminum. Because of the discovery of this new cocatalyst, metallocenes are sometimes called "Kaminsky" catalysts (Scheirs and Kaminsky, 2000).

Metallocene-based catalyst technology has revolutionized the polyolefin industry, particularly in the PE and PP markets. Metallocenes have been deemed the single-most important development in catalyst technology since the discovery of Z–N catalysts. Compared to conventional Z–N technology, metallocenes offer some significant process advantages and produce polymers with very favorable properties. The development of metallocene polymers has brought forth the concept of single-site catalysis of which metallocenes are just one example, albeit the first commercial success.

Metallocene catalysts allow the production of consistent, controllable molecular polymer structures that can be designed to improve toughness, provide excellent impact resistance, reduced haze and better clarity (Janiak, 2002). Since 1991, various polyolefins have been produced with the aid of single-site metallocene catalysts. By altering the metallocene structure, the types of polymers produced can be controlled. This characteristic of metallocenes is very important when producing polymers that can have different side branches such as isotactic and syndiotactic PP. These new polymers have features such as lower melting points, better optical characteristics, better heat stability, increased impact strength and toughness, better melt characteristics and improved clarity as films. These advantages are obtained through the control of polymer MW, MWD (elimination of both high- and low-MW fractions), comonomer distribution and content and tacticity.

Metallocenes are important in the production of PE in that they allow the control of side branching due to the single activity site found at the metal center. Traditional Z–N catalysts are hard to control because they have several active sites and polymers are produced by adding monomers to the end of the chain.

Using traditional catalysts, PP is produced as a mixture of the three forms consisting of 95% isotactic, some undesirable atactic and even less of the syndiotactic PP. With metallocene technology, the amount of each type of PP can be controlled through changes in the catalysts' stereochemistry. Isotactic PP made with classical Z–N catalysts still has some atactic fractions. The presence of atactic PP fractions reduces stiffness, heat distortion temperature and cleanliness. The absence of atactic PP in metallocene isotactic PP means higher stiffness, higher use temperature and lower extractable content (Janiak, 2002). New isotactic PP resins can be produced with improved stereoregularity and controlled comonomer content resulting in higher stiffness, clarity and melt strength. Comonomers employed to produce these enhanced PP resins include ethylene, butene and octene. To differentiate polymers produced with metallocenes from polymers manufactured using older, conventional catalysts, a lower case m is placed in front of the polymer abbreviation, for example, mLDPE.

Metallocene-catalyzed resins have expanded beyond PEs and PPs to polystyrenes, ethylene–styrene copolymers and cyclic olefin copolymers, and polymers made using metallocene catalysts have achieved significant market penetration in a wide array of applications including food packaging films and stretch/shrink films.

Electronic Acknowledgement Receipt

EFS ID:	34223873
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	Transmittal.pdf	105505 f8e235d694d7dac43cef2a5a16b3ca4c6ba08ee7	no	1

Warnings:

Information:					
2	Miscellaneous Incoming Letter	Plastics_Exhibit.pdf	491575 17d792223a81bb9ae7ec4e37134b23e24728808c	no	14
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	Food_Packaging_Exhibit.pdf	164118 523ab7648d16d02adca0b38c6ae2e9127afa850a	no	11
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
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Appl. No.:	15/869,164
Filing Date:	1/12/2018
Examiner:	Ahmed M. Farah
Art Unit:	3792
Confirmation No.:	3488

TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Further to the Amendment and Reply submitted on November 2, 2018, Applicant respectfully submits documents referred to on page 7 of the Amendment and Reply that were inadvertently omitted from Applicant's submission of November 2, 2018.

Respectfully submitted,

Date: November 6, 2018

By /Kiri Lee Sharon/

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Appl. No.:	15/869,164
371(c) Date:	1/12/2018
Examiner:	Ahmed M. FARAH
Art Unit:	3762
Conf. No.:	3488

AMENDMENT AND REPLY UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This communication is responsive to the non-final Office Action dated August 9, 2018, concerning the above-referenced patent application.

Amendments to the Claims begin on page 2 of this document.

Remarks begin on page 5.

Please amend the application as follows:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Response.pdf	169586 586c0d496ec316ee57404a6e7d004de499b cf969	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	5	9
	Claims	2	4
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Warnings:			
Information:			
	Total Files Size (in bytes):	169586	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and for at least the reasons that follow.

I. Allowable Subject Matter

Applicant thanks Examiner Farah for indicating in the Office Action that claims 3, 4, 6-8 and 17-20 would be allowable if rewritten to overcome the indefiniteness rejections discussed below and to include all the limitations of their base claim and any intervening claims. As discussed in more detail below, independent claims 1 and 16 are rewritten to include allowable subject matter. Claim 5 is rewritten into independent form, with further revisions as discussed during the interview summarized below. Applicant therefore respectfully submits that the amendments place the application in condition for allowance.

II. Claim Status

Claims 1-23 were pending, with claims 9-15 and 21-23 withdrawn. Claim 1 is amended to include allowable subject matter relating to claim 4. Claims 2, 4, 9-15, 17, 18 and 21-23 are cancelled without prejudice or disclaimer. Claim 5 is rewritten into independent form and revised to include subject matter supported at least by paras. [0022], [0059], [0066] and [0073] of the specification as filed. New claims 24 and 25 include subject matter also supported by at least these portions of the disclosure.

Claim 8 is amended for antecedent basis purposes. Claim 16 is amended to include allowable subject matter relating to claim 17. Claim 20 is amended for consistency with the amendments to claim 16. The amendments are made without acquiescing to the propriety of any rejection and without adding new matter. Upon entry of the amendments, claims 1, 3, 5-8, 16, 19, 20, 24 and 25 will be pending.

III. Record of Interview Substance

Applicant sincerely thanks Examiner Farah for the courtesy of the telephone interview on October 10, 2018 with inventor Mr. Scott Lundahl and Applicant's undersigned representatives. During the interview, the foregoing amendment to claim 8 was discussed and agreed to

overcome the indefiniteness rejection. The inventor and Applicant's representatives explained that the term "low density polyethylene" is a well-known term of art and would not be unclear to those of skill in the art. The appended evidence to that effect was discussed. Examiner Farah indicated that these remarks and evidence would be given further consideration. The status of claim 5 was discussed, in addition to the term "upper extremity," as previously recited in claim 5. Examiner Farah indicated that amendments to claim 5 would overcome the prior art. Applicant sincerely appreciates these indications and thanks Examiner Farah for his time.

IV. Requirements for Restriction and Species Election

Applicant acknowledges the comments in section 4 of the Office Action concerning the species election response filed April 13, 2018. Applicant respectfully disagrees with certain characterizations in this portion of the Office Action, including that the species recite mutually exclusive characteristics.

V. Claim Rejections under 35 U.S.C. § 112

Claims 1-8 and 16-20 are rejected under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as allegedly being indefinite. For at least the following reasons, the rejections should be withdrawn.

The Office Action states that there is insufficient antecedent basis for "the maximum plasma" in claim 8. Claim 8 is amended in a manner agreed during the interview of October 10, 2018 to overcome the rejection.

The Office Action states that the term "low" in claim 1, line 5 and claim 16, line 6 is "a relative term which renders the claim indefinite," and that "the term "low density" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention."

Applicant respectfully disagrees that the term "low density" renders indefinite claims 1 and 16 and their dependents. The term "low density" is found in the recitation "a low density polyethylene barrier" in claims 1 and 16. Per MPEP 2173.02.III.B, in response to an

indefiniteness rejection, an applicant may resolve alleged ambiguity by "showing that a person of ordinary skill in the relevant art would not consider the claim language unclear" (citing *In re Packard*, 751 F.3d 1307, 1311 (Fed. Cir. 2014)). The skilled artisan would not consider the recited "low density polyethylene barrier" unclear for at least the following reasons.

The term "**low density polyethylene**" (LDPE) is a very well-known term in the polymer science and packaging industry. For example, an industry guide (copy attached) discuses types of polyethylene and states that "The two **most common types** in production today are HDPE and LDPE" (see page 5, emphasis added).[1]

The Guide further states that "LDPE stands for low density polyethylene" and that "[i]t was the first type of polyethylene that was commercially produced. It was **developed in 1933** by Imperial Chemical Industries (ICI)" (emphasis added).

Additionally, a food packaging textbook ("Robertson," excerpt attached) states that "Polyolefins form an important class of thermoplastics and include low, very low, linear, medium and high density PEs and polypropylene (PP). **Industry commonly divides** PEs into the following broad categories based on density: HDPE 940–975 kg m^{-3}, MDPE 926–940 kg m^{-3}, **LDPE 915–940 kg m^{-3}**, LLDPE 915–925 kg m^{-3}, VLDPE 880–915 kg m^{-3}" (emphasis added).[2] Robertson further states that LDPE is "the largest volume single polymer used in food packaging in both the film and blow molded form[s]."[3]

In view of the examples from relevant technical literature mentioned above, it is clear that the term "low density polyethylene" is a well-known term of art, and that low density polyethylene itself was developed in the packaging industry over 80 years ago. Also, the specification identifies trade names for various brands of low density polyethylene products in Tables 1 and 2. The skilled artisan would therefore be familiar with this term and would understand what is meant by "a low density polyethylene barrier" as recited in claims 1 and 16.

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[1] National Association of Container Distributors, "The Definitive Guide to Plastics for the Packaging Industry," available at https://www.nacd.net/pdf/07102015_NACD_Guide ToPlastics_1-1.pdf (pdf creation date July 15, 2015, last accessed September 8, 2018) (attached).

[2] Section 2.3.6.1, Chapter 2, G. Robertson, FOOD PACKAGING PRINCIPLES AND PRACTICE, 3rd Ed., CRC Press: Boca Raton, FL (2013). Applicant is submitting an excerpt of the textbook but would be pleased to provide additional portions or the entirety of this reference upon request.

[3] *See* the Robertson textbook cited above at Section 2.3.6.1.1.

For at least these reasons, claims 1 and 16 and their dependents are not unclear. For similar reasons, independent claim 5 is also not unclear. Applicant respectfully solicits favorable consideration and withdrawal of the rejection.

VI. Claim Rejections under 35 U.S.C. § 102

Claims 1, 2, 5 and 16 are rejected under 35 U.S.C. § 102(a)(1) as allegedly anticipated by U.S. Patent Publication No. 2009/0324727 ("Foguet Roca"). Claims 1 and 16 are rejected under 35 U.S.C. § 102(a)(1) as allegedly anticipated by U.S. Patent Publication No. 2011/0053965 ("Trigiante"). For at least the following reasons, the rejections should be withdrawn.

Without conceding to the propriety of the rejections, independent claims 1 and 16 are amended to include indicated allowable subject matter, and claim 2 is cancelled without prejudice or disclaimer. Claim 1, as amended, includes indicated allowable subject matter relating to claim 4. Claim 16, as amended, includes indicated allowable subject matter relating to claim 17.

Claim 5 is amended so as to recite "*[a] method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising topically applying ALA to a treatment area to be treated with photodynamic therapy; and after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area, wherein the treatment area is located on a hand or a forearm*."

Neither of the cited references discloses or teaches a method including the combination of features recited in amended claim 5. As noted above, during the interview of October 10, 2018, Examiner Farah indicated that such amendments would overcome the prior art. Accordingly, Applicant respectfully submits that amended claim 5 is allowable, and that new claims 24 and 25 are allowable by virtue of their dependence from claim 5, in addition to their respective recitations.

In view of the foregoing, favorable reconsideration and withdrawal of the rejections are respectfully requested.

VII. Conclusion

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned to advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: November 2, 2018

By /Kiri Lee Sharon/

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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently Amended) A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

topically applying ALA to a treatment area to be treated with photodynamic therapy; [[and]]

after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area; and

removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.

2. (Cancelled).

3. (Original) A method as set forth in claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours to avoid excessive irritation while maintaining therapeutic efficacy.

4. (Cancelled).

5. (Currently Amended) A method ~~as set forth in claim 1,~~ of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

topically applying ALA to a treatment area to be treated with photodynamic therapy; and

after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area,

wherein the treatment area is located on a hand or a forearm ~~an upper extremity~~.

6. (Original) A method as set forth in claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours and then blue light is applied to the treatment area for a 10 J/cm^2 light dose.

7. (Original) A method as set forth in claim 5, wherein the low density polyethylene barrier is removed from the treatment area and then red light is applied to the treatment area for a 10 to 75 J/cm^2 light dose.

8. (Currently Amended). The method of claim 1, wherein [[the]] a maximum plasma concentration of ALA following application of the ALA is less than about 110ng/mL.

9.-15. (Cancelled).

16. (Currently Amended) A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:

contacting a treatment site with a composition comprising the ALA so as to wet the treatment site; [[and]]

following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier;

removing the low density polyethylene barrier so as to expose the treatment site; and

illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm^2 dose of blue light.

17.-18. (Cancelled).

19. (Original) The method of claim 16, wherein the low density polyethylene barrier is removed no later than three hours after the treatment site is covered.

20. (Currently Amended) The method of claim 16, further comprising:

~~removing the low density polyethylene barrier; and~~

positioning the treatment site between two inches and four inches from a surface of [[an]] the illuminator.

21.-23. (Cancelled).

24. (New) The method as set forth in claim 5, wherein the treatment area is a dorsal surface of the hand.

25. (New) The method as set forth in claim 5, wherein the treatment area is a dorsal surface of the forearm.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/869,164	Filing Date 01/12/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $420 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	11/02/2018	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 11	Minus	** 23	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 4	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	KIMBERLY D WILLIAMS
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	15/869,164
Date Submitted: SEP 27 2018				**Filing Date**	1/12/2018
(use as many sheets as necessary)				**First Named Inventor**	Scott LUNDAHL
Sheet	1	of	1	Art Unit	3762
				Examiner Name	Ahmed M FARAH
				Attorney Docket Number	067286-0399

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	D1	2006/0287696-A1	12-21-2006	WRIGHT ET AL.	
	D2	2014/0067024-A1	03-06-2014	JONES ET AL.	
	D3	2015/0162109-A1	06-11-2015	NAGER, ZACHARY	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	D4	WO-2009/003173-A1	12-31-2008	THE GENERAL HOSPITAL CORPORATION		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D5	Partial International Search, Annex to Form PCT/ISA/206, International Application No. PCT/US2018/027070, July 19, 2018, 10 pages	

Examiner Signature		Date Considered	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Application No.:	15/869,164
Filing Date:	1/12/2018
Examiner:	Ahmed M FARAH
Art Unit:	3762
Confirmation No.:	3488

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicant does not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(c), before the mailing date of any of a final action under 37 CFR §1.113, a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application.

CONCISE EXPLANATION OF RELEVANCE

Documents D1-D4 listed on the attached PTO/SB/08 are documents cited in a Partial International Search, dated July 19, 2018, issued in International application PCT/US2018/027070 (document D5).

The cited documents are in English.

FEE

Fees in the amount of $240.00 to cover the fee associated with an information disclosure statement are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required for this application to Deposit Account Number 19-0741.

Respectfully submitted,

Date SEP 27 2018

By 

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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, BR, BW, BY, BZ, CA, CH, 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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

[Continued on next page]

(54) Title: METHOD AND APPARATUS FOR OPTICAL INHIBITION OF PHOTODYMANIC THERAPY

(57) Abstract: A system and method are provided for preventing damage to the epidermis or other epithelial or non-target tissue during photodynamic therapy treatment. For example, an inhibiting radiation can be used to control formation of a photosensitizer from a precursor photosensitizer in the epidermis or epithelial tissue. Subsequent application of a treatment radiation can activate the photosensitizer to damage or destroy target sites while the non-target tissue remains substantially unaffected.

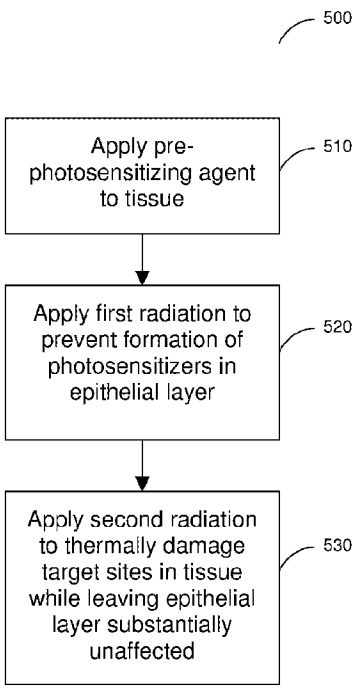

Fig. 5

WO 2009/003173 A1

FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

METHOD AND APPARATUS FOR OPTICAL INHIBITION OF PHOTODYNAMIC THERAPY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to and the benefit of U.S. provisional patent application number 60/946,536, filed June 27, 2007. The disclosure of which is incorporated by reference herein in it's entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to methods and apparatus for protecting non-target tissue (e.g., epithelial tissue) during photodynamic therapy using optical inhibition.

BACKGROUND

[0003] Photodynamic therapy ("PDT") generally involves a local or systemic application of a light-absorbing photosensitive agent, or photosensitizer, which may accumulate selectively in certain target tissues. Upon irradiation with electromagnetic radiation, such as visible light of an appropriate wavelength, reactive oxygen species (e.g., singlet oxygen and/or free radicals) may be produced in cells or other tissue containing the photosensitizer, which promotes cell damage or death. The oxidative damage from these reactive intermediates is generally localized to the cells or structures at which the photosensitizer is present. PDT treatments therefore may be capable of 'targeting' specific cells and lesions, for example, if the photosensitizer is present in significant quantity only at desired target sites and/or light activation is performed only at such target sites.

[0004] A precursor photosensitizer, such as aminolevulinic acid ("ALA") or ALA-ester, which converts into a photosensitizer (e.g., a porphyrin) when it metabolizes, can also be used in PDT treatments. ALA is an FDA-approved topical PDT agent. ALA can be the first committed precursor of heme synthesis, and occurs naturally in mammalian cells. When supplied in excess, ALA can overdrive the heme synthesis pathway until intracellular iron stores are depleted, after which photosensitizing porphyrins (e.g., protoporphyrin IX) may accumulate in tissues as described, e.g., in Kennedy et al., "Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience," J Photochem Photobiol B (1990), 6:143-148; Kennedy et al., "Endogenous protoporphyrin IX, a clinically

useful photosensitizer for photodynamic therapy," J Photochem Photobiol B: Biol (1992), 14:275-92; and Kennedy et al., "Photodynamic therapy (PDT) and photodiagnosis (PD) using endogenous photosensitization induced by 5-aminolevulinic acid (ALA): mechanisms and clinical results," J Clin Laser Med Surg (1996), 14:289-304.

[0005] PDT has been used to treat various medical conditions, including infectious diseases, malignant diseases (such as skin cancers, lymphomas, etc), premalignant conditions (as actinic keratosis), viral warts, hair removal, etc. in many different medical fields, including dermatology, ophthalmology, oncology, and others.

[0006] For example, ALA-PDT is a potent, long-lasting treatment for severe and scarring acne vulgaris, a common skin disease caused by abnormalities of sebaceous follicles in skin that can lead to permanent scars and disfigurement. PDT is observed to have about the same potency as oral isotretinoin (Accutane®), a very effective treatment. However, isotretinoin, which suppresses sebaceous (oil) gland function in the skin, is dangerous because it may cause birth defects if a woman becomes pregnant during or after taking the drug. PDT treatment can pose a far lower risk than application of oral isotretinoin, is less expensive and has fewer side effects, does not require blood tests, can be used in women of childbearing potential, and can efficiently control severe acne. A course of 1-4 PDT treatments given over 3 months typically inhibits acne for a period varying between several months to permanently. Retreatment can be performed as needed. However, PDT treatment of acne vulgaris using ALA and/or methyl-ALA can have undesirable side effects such as epidermal photosensitization, which causes pain during light exposure, sunburn-like reactions, and/or post-treatment pigmentation as described, e.g., in Hongcharu et al, "Topical ALA-photodynamic therapy for the treatment of acne vulgaris," J Invest Dermatol, 115, 183-192 (2000).

[0007] Although PDT techniques using a photosensitizer or precursor photosensitizer can be effective for certain applications, it is often difficult to control application to the treatment area. For example, the photosensitizer or precursor photosensitizer can be absorbed and/or accumulate in healthy tissues as well as the target tissue. In hair removal, for example, a photosensitizer or precursor photosensitizer that is applied to the skin topically may be absorbed by both the epidermal and dermal layers of the skin. As a result, application of light can cause phototoxicity to the epidermis, which can lead to long-lasting hyperpigmentation or

epidermal necrosis. In general, PDT treatments of subepithelial tissue using topically-applied photosensitizers often leads to unwanted damage to the epithelial tissue.

[0008] Thermal or chemical inhibition of photosensitizer formation in epithelial tissue from precursors can be used to reduce unwanted damage to such tissue. However, it may be difficult to accurately control the formation and accumulation of photosensitizers in particular tissues and/or tissue layers using thermal or chemical techniques. Also, such techniques can further interfere with the PDT process when using photosensitizers such as ALA.

[0009] Accordingly, there is a need for an improved method and apparatus for photodynamic therapy that can reduce or eliminate damage to epithelial tissue in a controllable manner while allowing treatment of underlying targeted tissue.

OBJECTS AND SUMMARY OF THE INVENTION

[0010] Although various photosensitizer and ALA-induced PDT techniques provide an effective treatment for many conditions, accumulation of precursor photosensitizers and/or photosensitizers may generally not be selective. Thus, the precursor photosensitizer can metabolize into a photosensitizer in both surface tissue and underlying targeted tissue, thereby potentially causing unintended damage to non-targeted, healthy surface tissue during subsequent PDT treatment. Exemplary embodiments of the present invention provide methods and devices for preventing or reducing the extent or likelihood of unwanted damage to epithelial tissue, or other non-targeted tissues, during PDT.

[0011] In one aspect of the present invention, a method is provided for applying a precursor photosensitizer to an anatomical structure, and then applying a first inhibiting radiation to the anatomical structure. The first inhibiting radiation is configured to substantially reduce or eliminate the presence of a photosensitizer within a first region of the anatomical structure, such as a surface or epithelial region, by inhibiting or preventing formation of the photosensitizer from the precursor photosensitizer. A second radiation is then applied to the anatomical structure to produce a phototoxic species from the photosensitizer located in a second region of the anatomical structure. The first region may be substantially unaffected by the second radiation, and the second region can contain particular target sites which are to be damaged by the phototoxic species. Preferably, the first radiation is applied at a lower level (e.g., lower fluence and/or irradiance) than the second radiation. The first and second radiation

can be applied at different wavelengths or wavelength bands (e.g., a first wavelength of the first inhibiting radiation can be shorter than a second wavelength of the second radiation).

[0012] In embodiments of the present invention, the first inhibiting radiation has a wavelength that is between about 320 nm and about 850 nm, or preferably between about 320 nm and about 450 nm, and the second radiation has a wavelength that is between about 470 nm and about 700 nm, or more preferably between about 625 nm and about 645 nm if, e.g., ALA, ALA derivatives, or porphyrins are used. Other wavelengths may be used as appropriate with different precursor photosensitizers.

[0013] In further embodiments of the present invention, the first inhibiting radiation is applied with an irradiance that is between about 0.01 mW/cm^2 and about 30 mW/cm^2 and a total fluence that is between about 1 and about 100 J/cm^2. The inhibiting radiation is preferably applied within 30 minutes of application of the precursor photosensitizer (e.g., an ALA solution) to the tissue, or more preferably less than about 15 minutes after applying the precursor photosensitizer.

[0014] For example, exemplary embodiments of the present invention may be used for controlling the application of PDT induced using a precursor photosensitizer, and in particular for preventing damage to epithelial tissue, such as the epidermis, during PDT. A precursor photosensitizer, such as a porphyrin precursor, is administered to a targeted treatment site by topical application or injection. The precursor photosensitizer is absorbed through the surrounding tissue and into tissue at the targeted site, where it is generally metabolized and converted into a photosensitizer, such as a porphyin. Formation of the photosensitizer is inhibited or prevented in epithelial tissue surrounding the targeted treatment site by application of an inhibiting radiation. The targeted site is then irradiated with a treatment radiation to activate the photosensitizer and damage tissue at the targeted treatment site, while epithelial tissue surrounding the targeted treatment site remains substantially unaffected. The treatment radiation is preferably applied within 30 minutes after exposure to the inhibiting radiation is stopped, or more preferably less than about 15 minutes after ending the application of the inhibiting radiation.

[0015] In further embodiments, metabolism of the precursor photosensitizer in non-targeted epithelial tissue surrounding the targeted treatment site is inhibited by exposing the tissue to electromagnetic radiation. For example, electromagnetic radiation that is highly absorbed

and/or scattered by the epithelial tissue can be applied, such that a sufficient exposure dose of the radiation does not penetrate to the targeted site to any significant degree. Inhibition of the metabolism of the precursor photosensitizer is thereby confined to regions above a particular depth of the epithelial tissue, and the photosensitizer may still form and accumulate within the targeted site. Subsequent PDT treatment with application of a treatment radiation can lead to cellular damage or death within the targeted site, while leaving the epithelial tissue relatively undamaged because of a relative lack of photosensitizers therein.

[0016] In another embodiment, a method is provided for treating a disorder of the skin in a subject by administering 5-aminolevulinic acid to the subject and applying a first inhibiting radiation to the skin of the subject in an amount and duration sufficient to reduce protoporphyrin IX accumulation within the epidermis of the skin. A second radiation is then applied to the skin of the subject an amount and duration sufficient to produce a phototoxic species from the protoporphyrin IX located in dermis of the skin. The epidermis may be substantially unaffected by the second radiation, thereby treating the disorder of the skin in the subject. The first inhibiting radiation can, if desired, be applied continuously during the period of metabolism which occurs after administration of the 5-aminolevulinic acid or similar precursor photosensitizer.

[0017] In still further embodiments, a photobleachable compound such as, e.g., a porphyrin, is used as a photosensitizer. Such photosensitizers can be photobleached in non-targeted tissue by exposing the non-targeted tissue to electromagnetic radiation having an appropriate irradiance, fluence and wavelength to photobleach the agent without forming sufficient reactive oxygen species or otherwise causing cellular damage or death. The photosensitizer is thus "deactivated" in certain tissue regions and can still accumulate within the targeted site. Again, subsequent PDT treatment leads to cellular damage or death within the targeted site, while leaving the epithelial tissue relatively undamaged because of the relative lack of photosensitizers therein. The radiation used to photobleach a compound is preferably provided at a lower fluence and/or irradiance than the radiation subsequently applied during PDT treatment. The wavelength of the photobleaching radiation may also be different than that of the PDT treatment radiation. For example, the photobleaching radiation may have a shorter wavelength than the PDT treatment radiation, such that it does not penetrate as deeply into the tissue, allowing unbleached compounds to remain in higher concentrations at deeper levels

within the tissue. The delay time between applying the photosensitizer and applying the photobleaching light can be optimized to allow accumulation of photosensitizer in the target tissue as compared with the non-target tissue, as described in more detail below.

[0018] Photobleachable photosensitizers that may be used in embodiments of the present invention include, but are not limited to, a porphyrin, chlorin, porphycene, purpurin, phthalocyanine, naphthalocyanine, bacteriochlorin, benzophenothiazine, tetracycline, methylene blue, and/or hypericin.

[0019] In certain embodiments, the first inhibiting radiation has a wavelength between about 320 nm and about 800 nm, or preferably between about 380 nm and about 420 nm. In other embodiments, the first inhibiting radiation is applied at an irradiance that is between about 0.1 mW/cm^2 and about 30 mW/cm^2, and a fluence that is between about 1 J/cm^2 and about 100 J/cm^2. In further embodiments, the second radiation has a wavelength between about 400 nm and about 900 nm, preferably between about 600 nm and about 800 nm, or even more preferably between about 625 nm and about 720 nm.

[0020] In a further aspect, embodiments of the present invention provide an apparatus for performing PDT treatment that avoids significant damage to epithelial tissue. The apparatus includes an inhibiting radiation source, which can be configured to prevent or reduce the formation of photosensitizers in the epithelial tissue above a targeted treatment site or, alternatively, to photobleach photosensitizers in certain regions of tissue near the targeted site. A treatment radiation source is provided, where the treatment radiation is configured to activate the photosensitizers located at the target site while leaving the epithelial tissue essentially unaffected because of the lack of photosensitizers in that tissue. A controller and delivery arrangement are also provided to control parameters associated with the inhibiting and treatment radiation sources, and to direct the radiations toward the tissue being treated. The apparatus may also include an arrangement configured to cool the surface of the tissue being treated. Optionally, a sensing device is provided to detect one or more characteristics of the tissue being treated, and to communicate with the controller such that the controller may vary one or more parameters of the inhibiting and/or treatment radiations based on the detected characteristics.

[0021] The inhibiting radiation can have a wavelength that is shorter than that of the treatment radiation, e.g., it may be green, blue or near-UV light. The inhibiting radiation may thus be scattered and absorbed more than the treatment radiation, such that the treatment radiation penetrates more deeply into the tissue than the inhibiting radiation. This difference in the radiation characteristics allows formation and accumulation of photosensitizers at target sites deeper within the tissue. For example, the inhibiting radiation can have a wavelength between about 320 nm and about 450 nm, or between about 380 and about 430 nm. In certain embodiments, the inhibiting radiation has a longer wavelength, and may include green, yellow, orange or even red light at wavelengths, fluences and/or irradiances capable of suppressing accumulation of photosensitizer during metabolism of the precursor photosensitizer used. For example, the inhibiting radiation may have a wavelength between about 320 nm and about 850 nm.

[0022] Characteristics of the treatment radiation are generally selected such that it can penetrate the tissue to a sufficient depth to reach the target sites. The treatment radiation can thus have, for example, a wavelength between about 630 nm and about 640 nm. The treatment radiation generally has a higher fluence and/or irradiance than the inhibiting radiation.

[0023] In further embodiments, cooling and/or radiative heating of the tissue being treated is provided. Cooling can be performed before, during and/or after application of the inhibiting radiation and/or treatment radiation. Such cooling can reduce discomfort during the PDT procedure, and may also further inhibit metabolism of pre-photosynthesizers in epithelial tissue. Radiative heating provided prior to application of the treatment radiation can enhance accumulation of photosensitizers at target sites to promote more effective treatment.

[0024] Embodiments of the present invention can be used to treat various conditions, including hair removal, acne, tumors, cysts, malformed blood vessels, cutaneous nevi, adnexal tumors, syringomas, cutaneous T cell lymphomas, squamous carcinomas, basal cell carcinomas, or cutaneous warts.

[0025] These and other objects, features and advantages of the present invention will become apparent upon reading the following detailed description of embodiments of the invention, when taken in conjunction with the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Further objects, features and advantages of the invention will become apparent from the following detailed description taken in conjunction with the accompanying figures showing illustrative embodiments of the invention, in which:

[0027] Fig. 1 is an exemplary cross-section of a portion of an anatomical structure showing several features of skin tissue;

[0028] Fig. 2 is a schematic diagram of an exemplary procedure in accordance with exemplary embodiments of the present invention on the portion of an anatomical structure;

[0029] Fig. 3 is a block diagram of an exemplary apparatus/system which may be used in accordance with exemplary embodiments of the present invention;

[0030] Fig. 4 is a schematic diagram of a further exemplary system which may be used in accordance with exemplary embodiments of the present invention;

[0031] Fig. 5 is a flowchart of an exemplary method in accordance with exemplary embodiments of the present invention;

[0032] Fig. 6 depicts blue light inhibiting ALA-PDT;

[0033] Fig. 7 depicts exemplary clinical photographs taken after 24 hours demonstrating temperature modulating PDT reaction under two different incubation times (180 minutes and 30 minutes), for 0.1% injected ALA and 20% topical ALA, with 632 nm LED irradiation (Omnilux®) applied to all sites (200 J/cm^2) after incubation;

[0034] Fig. 8 is an exemplary graph of incubation times observed for metabolization of precursors photosensitizer;

[0035] Fig. 9a is a schematic illustration of exemplary absorption behavior of a radiation beam that is approximately normal to a tissue surface; and

[0036] Fig. 9b is a schematic illustration of exemplary absorption behavior of a radiation beam that is provided at an acute incident angle to the tissue surface shown in Fig. 9a.

[0037] While the present invention will now be described in detail with reference to the figures, it is done so in connection with the illustrative embodiments.

DETAILED DESCRIPTION

I. DEFINITIONS

[0038] As used herein, the phrase "anatomical structure" refers to, but is not limited to, a complex structure or system of the body having multiple layers and/or regions.

[0039] As used herein, the phrase "inhibiting radiation" refers to, but is not limited to, radiation provided at a suitable wavelength and in an amount and duration sufficient to: 1) reduce conversion of a precursor photosensitizer into a photosensitizer, or 2) photobleach a photosensitizer. The effects of such radiation may be more easily controlled by administering the radiation at a low level of irradiance and fluence.

[0040] As used herein, the term "photobleach" refers to, but is not limited to, treatment of a photosensitizer with an optical radiation in a spectrum that can be absorbed by the photosensitizer, but may not be of a sufficient excitation wavelength (e.g., the optical radiation causes little or no phototoxic species to be produced).

[0041] As used herein, the term "photosensitizer" refers to, but is not limited to, a photoactivatable compound that can produce a reactive species (e.g., singlet oxygen, free radicals, reactive excited state or cleavage products of the photosensitizer) which may have a toxic effect on a cell, cellular component or biomolecule.

[0042] As used herein, the phrase "precursor photosensitizer" refers to, but is not limited to, any agent or prodrug that can be converted in vivo (e.g., metabolically) into a photosensitizer.

[0043] As used herein, the phrase "phototoxic species" refers to, but is not limited to, a reactive species (e.g., singlet oxygen, free radicals, reactive excited state or cleavage products of the photosensitizer) which is produced from a photosensitizer in the presence of light administered at an excitation wavelength, where the reactive species can have a toxic effect on a cell, cellular component or biomolecule.

[0044] As used herein, to "reduce" as it refers to a photosensitizer, can indicate an at least about 1-fold (for example 1-, 2-, 3-, 4-, 5-, 10-, 20-, 30-, 40-, 50-, 60-, 70-, 80-, 90-, 100-, 1000-, 10,000-fold or more) less formation or accumulation of a photosensitizer in a subject upon treatment with inhibiting radiation as compared to without treatment. "Reduce" as it refers to a photosensitizer can also mean, e.g., at least about 5% (for example 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 99 or 100%) less formation or

accumulation of a photosensitizer in a subject upon treatment with inhibiting radiation than without treatment.

[0045] As used herein, the phrase "substantially unaffected" refers to, but is not limited to, a reduction or absence of damage (e.g., a visually undetectable amount), or non-lethal damage (e.g., oxidative damage) in a region or layer of an anatomical structure receiving inhibiting radiation prior to photodynamic therapy.

[0046] As used herein, the phrase "target tissue" refers to, but is not limited to, abnormal or unhealthy tissue, or a particular tissue structure such as, e.g., sebaceous glands in the skin, which may be selected for photodynamic therapy.

[0047] As used herein, the phrase "non-target tissue" refers to, but is not limited to, normal or healthy tissue or tissue structures or any other tissue in which photodynamic therapy is undesirable.

[0048] In this disclosure, "comprises," "comprising," "containing," "having," and the like have the meaning ascribed to them in U.S. Patent law and can mean " includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

[0049] Other definitions may appear in context throughout this disclosure.

II. EXEMPLARY EMBODIMENTS

[0050] The methods and apparatus according to embodiments of the present invention utilize electromagnetic radiation to control and/or inhibit formation of a photosensitizer from a precursor photosensitizer administered to certain tissues for PDT procedures.

[0051] Fig. 1 shows an exemplary cross-section of a skin tissue 100 which can be treated using exemplary embodiments according to the present invention. The skin tissue 100 includes a superficial (e.g., epidermal) layer 110, which further includes a stratum corneum 120 — a thin, nonliving outer layer of skin — and an epidermis 130, which is a superficial epithelial layer about 0.1 mm thick. The epidermis 130 is often the location of much of the perceived

pain and undesirable side-effects that can accompany conventional PDT treatment. The dermal layer of skin 180 can be about 1-4 mm thick, and is located beneath the epidermis 130. The dermal layer (or dermis) 180 often contains certain targets which may be treated using PDT.

[0052] For example, a sebaceous gland 140 can be a primary target structure for treating acne using PDT. The sebaceous glands 140 are approximately 0.1-0.5 mm in diameter and are generally located about 1-3 mm below the epidermal layer 110. A hair-producing portion of a hair follicle 150 can be another target for the exemplary PDT treatment which can achieve hair removal. This portion of a hair follicle 150 can extend about 1-5 mm below the epidermal layer 110. A cellular structure 160 located within the dermis 180 can also be targeted and treated using PDT. Such structure 160 can include, e.g., a cutaneous tumor, a cyst, a nevus, a blood vessel or another biological feature. Cellular infiltrates 170 can represent still further targets, such as cutaneous T cell lymphoma cancer cells, which may also be treated using PDT. A fatty layer 190, located below the dermal layer 180, can also be targeted for PDT treatment in certain applications.

[0053] Fig. 2 is a schematic illustration of an exemplary technique applied to the tissue 100 according to exemplary embodiments of the present invention. A precursor photosensitizer is applied topically to a region of the tissue 100 to be treated, such that it is absorbed into the volume of a tissue portion 210 which includes target sites 220 to be treated. The tissue portion 210 containing the precursor photosensitizer generally includes a portion of both epiphelial tissue (e.g., the epidermal layer 110) and the dermal layer 180 (and, optionally, a portion of the fatty layer 190).

[0054] For example, a precursor photosensitizer such as the porphyrin precursor ALA, can be topically applied to the tissue surface, e.g., epidermal tissue 110, above a targeted treatment site 220. The precursor photosensitizer is absorbed through such epidermal tissue 110 and into tissue 210 located at and around the targeted treatment site. ALA or other precursor photosensitizers can also be administered orally or by intravascular injection or by direct injection into tissue, e.g., by intradermal injection of an ALA solution.

[0055] An inhibiting radiation 250 is then directed onto the tissue portion 210. This inhibiting radiation 250 can have a relatively short wavelength (e.g., blue light) such that it is mostly absorbed in the superficial layer 110 and does not penetrate into the volume of tissue containing the target sites 220. The inhibiting radiation 250 can be applied during the time that

the precursor photosensitizer is being metabolized to form a photosensitizer. Thus, it may selectively reduce or prevent formation of a photosensitizer in the superficial layer 110, while not significantly affecting formation of such photosensitizer in the target sites 220 and adjacent tissue. The photosensitizer can be selected such that, once formed, it preferentially accumulates at or around the target sites 220. Although only a single local beam of the inhibiting radiation 250 is shown in Fig. 2, the inhibiting radiation 250 is preferably applied over most or all of the area where the precursor photosensitizer was applied.

[0056] Parameters associated with the inhibiting radiation 250 (e.g., wavelength, total fluence, etc.) can be selected to inhibit formation of the photosensitizer to a particular depth within the tissue. The precursor photosensitizer located in the target sites 220, which is preferably exposed to a lower irradiance of the inhibiting radiation that does not substantially inhibit formation of the photosensitizer in the target sites 220, can metabolize into a photosensitizer, such as the protoporphyrin IX (PpIX).

[0057] A treatment radiation 260 is then directed onto the tissue portion 210. This treatment radiation 260 is preferably capable of penetrating the tissue to a depth containing the target sites 220, interacting with the photosensitizer and generating a reaction that can damage or destroy cells associated with the target sites 220. Upon the application of the treatment radiation 260 (e.g., light having an appropriate wavelength, fluence and irradiance), the photosensitizer absorbs such radiation and becomes phototoxic, releasing singlet oxygen or other intermediates that alter, damage or destroy cells within the target site. Although only a single local beam of the treatment radiation 260 is shown in Fig. 2, the treatment radiation 260 is preferably applied over most or all of the area where the precursor photosensitizer was applied. Because the formation of photosensitizers in the superficial layer 110 can be suppressed by the inhibiting radiation 250, the treatment radiation 260 may have little effect on the superficial layer 110, and cellular damage or death may be confined primarily to the target sites 220, and possibly to a lesser degree in other tissue regions below the superficial layer 110.

[0058] Using this exemplary technique, target sites 220 may be treated using PDT treatments, and damage to tissue in the superficial layer 110 can be avoided or reduced. This exemplary technique can also reduce pain experienced by a subject and/or post-treatment sensitivity of the superficial layer 110 to general exposure to light.

[0059] Exemplary embodiments of the present invention can be used for various applications such as, e.g., protection of the epidermis 110 during PDT treatment for removal of hair. For example, a precursor photosensitizer can be topically applied to the epidermal tissue surface 110 above a targeted treatment site 220, and an inhibiting radiation 250 is then directed to the targeted site 220. This radiation 250 may inhibit metabolism of the precursor photosensitizer within the epidermal tissue 110, while allowing the precursor photosensitizer to metabolize into a photosensitizer at hair follicles located in the target site 220. A treatment radiation 260 is then applied to the targeted treatment site 220 to destroy the hair follicles without damaging the epidermis 110. Surface cooling (e.g., contact or spray cooling) may optionally be provided before or during application of the treatment radiation. Such cooling can have an analgesic or anesthetic effect on the tissue being treated.

[0060] Parameters associated with the inhibiting radiation 250 and the treatment radiation 260 may be selected based on the precursor photosensitizer and photosensitizer used, the depth and type of the target sites 220, and other relevant factors. Such parameters can include, for example, irradiance, frequency, total fluence, pulse or continuous wave duration, and/or pulse repetition rate (frequency) of the applied radiation. The inhibiting radiation 250, e.g., may be a green or red light, and/or it can have a lower fluence and irradiance than the treatment radiation 260.

[0061] A flowchart of an exemplary method 500 in accordance with embodiments of the present invention is shown in Fig. 5. A precursor photosensitizer, such as a porphyrin precursor, is administered to a targeted treatment site (step 510). This can be achieved, for example, by topically applying the precursor photosensitizer to epithelial tissue surrounding the targeted site. The precursor photosensitizer is then absorbed through the surrounding tissue and into tissue at the targeted site, where it can be metabolized and converted into a photosensitizer, such as a porphyin. Such metabolism of the photosensitizer is inhibited or prevented in epithelial tissue surrounding the targeted treatment site by application of an inhibiting radiation (step 520). The targeted site is then irradiated with a treatment radiation to activate the photosensitizer, e.g., to cause phototoxicity, at the targeted treatment site such that the epithelial tissue surrounding the targeted treatment site is substantially unaffected (step 530) because of a lack of photosensitizers there. The treatment radiation is preferably applied within

30 minutes after exposure to the inhibiting radiation is stopped, or more preferably less than about 15 minutes after ending the application of the inhibiting radiation.

[0062] Two significant time intervals relate to embodiments of the present invention. The first interval (the "inhibiting interval") is the time between application of the precursor photosensitizer to the tissue being treated and the initial exposure of the tissue to the inhibiting radiation. The second interval (the "treatment interval") is the time between when the inhibiting radiation exposure is stopped and the exposure of the tissue to the treatment radiation begins. These time intervals should be selected appropriately to allow the precursor photosensitizer to reach the target regions and metabolize there, while not allowing significant formation of photosensitizers in the tissue regions to be protected.

[0063] Studies of ALA metabolism and porphyrin accumulation rates have been performed in anterior ear skin of swine. Such tissue bears many similarities to facial skin tissue in humans with respect to size and location of relevant tissue layers and target regions such as hair follicles and sebaceous glands. Topical 20% ALA in a water/alcohol solution was applied to the skin tissue, and formation of photosensitizers was analyzed based on quantitative fluorescence analysis of porphyrins formed from the ALA.

[0064] Overall porphyrin fluorescence was not observed until about 30-45 minutes after application of the ALA solution, although epidermis fluorescence measurement was statistically significant after only 15 minutes following the ALA application. Between about 30 and 120 minutes following application of the ALA solution, epidermis, hair follicles, and sebaceous glands became progressively more fluorescent. Eccrine gland fluorescence was detected starting at about 30 minutes, and sebaceous glands showed fluorescence starting at about 45-75 minutes. Fluorescence in all sites reached a maximum intensity between about 75 and 180 minutes after application of the ALA solution. There was a trend for hair follicles and sebaceous glands to express stronger fluorescence compared with epidermis and eccrine glands. A summary of these results is presented in Fig. 8.

[0065] Based on these observations, it is generally preferable to apply the inhibiting radiation to tissue within about 30 minutes after topical application of ALA in accordance with certain embodiments of the present invention. An inhibition interval longer than about 30 minutes may allow undesirably significant formation of photosensitizers in the epithelial tissue. Preferably the inhibition interval is less than about 15 minutes to further prevent formation of

significant amounts of photosensitizers in the epithelial layer. Shorter inhibition intervals may also be used.

[0066] The treatment interval corresponds to the delay between cessation of exposure of tissue to the inhibiting radiation and application of the treatment radiation. Based on the ALA metabolism observations described above and shown in Fig. 8, it is also generally preferable to apply the treatment radiation to tissue within about 30 minutes after the inhibiting radiation is stopped. A treatment interval longer than about 30 minutes may allow undesirable formation of photosensitizers in the epithelial layer from ALA still present in the tissue. Preferably the treatment interval is less than about 15 minutes to further prevent formation of significant amounts of photosensitizers in the epithelial layer. Even more preferably, the treatment radiation may be applied within a few minutes after exposure to inhibiting radiation is stopped, or even immediately thereafter.

[0067] In certain embodiments of the present invention, a photobleachable photosensitizer such as, e.g., Photofrin may be used instead of (or in addition to) a precursor photosensitizer. For example, the inhibiting radiation 250 can be applied to bleach a portion of the photobleachable photosensitizer. Subsequent application of the treatment radiation 260 can then induce damage or death in cells and tissue containing the unbleached photosensitizer. Application of the inhibiting radiation 250 can reduce or eliminate prolonged skin photosensitivity which can often be a side effect of PDT treatments.

[0068] In further embodiments, superficial porphyrin accumulation resulting from topical application of ALA may be suppressed by blue light exposure during ALA metabolism. For example, a topical solution of 20% ALA can be applied to a region of skin. The region of skin can then be exposed to low level irradiance 410 nm blue light to inhibit accumulation of porphyrins. This light can be applied during the period of ALA metabolism, e.g., immediately after the application of the topical ALA solution or later in time. It has been observed that exposure of skin to such low-intensity blue light (e.g., light having a wavelength of 415 nm) at an irradiance between about 10 mW/cm^2 and 30 mW/cm^2 during the period of ALA metabolism can provide almost complete clinical suppression of epidermal and/or superficial porphyrin synthesis, and does not itself induce a PDT reaction. Some suppression of photosensitizer formation was observed for irradiances between about 60 $\mu W/cm^2$ and 3 mW/cm^2. No clinical suppresion was observed at less than about 30 $\mu W/cm^2$. Here, clinical

suppression refers to a diminished response of the tissue to treatment radiation in subsequent PDT procedures.

[0069] Red light inhibiting radiation at a wavelength of 633 nm was observed to be less effective for clinical suppression of photosensitizer formation. Although such red light did not provide complete clinical suppression of superficial porphyrin synthesis, some clinical suppression was observed at irradiances between about 14 mW/cm^2 and about 40 mW/cm^2.

[0070] Other types of light, including but not limited to UV-A, blue, green, yellow and red light, may also be applied during the metabolism period to suppress porphyrin formation and/or accumulation. The suppression efficiency may depend in part on the absorption characteristics of the applied light. Such techniques can also be used with similar porphyrin precursor drugs, e.g., methyl-ester of ALA, that may also be suitable for photodynamic treatment of skin.

[0071] Several types of radiation or light sources may be used to provide the inhibiting radiation. Such sources include, for example, a fluorescent narrow-band light source, light emitting diodes ("LEDs"), lasers, arc lamps, or fluorescent and incandescent filtered lamps. In addition, pulsed or continuous sources can be used. In addition, the inhibiting radiation can be applied in various patterns, such that photosensitization is inhibited in only some parts of the non-target tissue. In some applications, the target tissue may be a fraction of a tissue region, while adjacent fractions are to be spared. Spatially "fractional" treatments using photothermal methods have been described, e.g., in Khan, M.H. et al, Lasers Surg Med 2005; 9999:1-11, and Manstein, D. et al, Lasers Surg Med 2004;34:426-438-. Using inhibiting radiation in a pattern of exposure can create fractional photodynamic therapy.

[0072] Exemplary embodiments of the present invention may also be used to treat organs other than skin for which optical suppression of porphyrin synthesis in epithelial tissues may be useful. For example, when treating internal cancers with PDT, vital organs can be damaged because of insufficient selectively of the PDT reaction. Thus, the use of an inhibitng radiation or light during the incubation time can selectively suppress PDT reactions in certain areas, which may protect vital organs and reduce the generation of undesirable side-effects. The deeper tissue layer may contain the preferred targets for treatment such as hair follicles, sebaceous glands, eccrine glands, fat, cancer, blood vessels, nerves or other structures, whereas the superficial protected layer may be an epithelium such as the epidermis, oral or other mucosa, gastrointestinal or bladder epithelium, etc.

[0073] The treatment radiation is preferably selected such that it penetrates the tissue to a sufficient depth to reach the target sites. The rate of oxidative damage that occurs at target sites should be sufficient during application of the treatment radiation to cause at least the desired amount of damage to the target sites. In general, the rate of oxidative damage increases with the local concentration of photosensitizer in the targets, the local concentration of oxygen in the targets, and the rate of treatment radiation absorption by photosensitizer in the target sites. The inhibiting radiation can be administered in an amount and duration such that the concentration of the photosensitizer in the target sites is sufficient for at least a desired amount of damage to be produced at the target sites, while damage to the non-target sites should be substantially inhibited.

[0074] Embodiments of the present invention can be used with a variety of precursor photosensitizers including, e.g., enzyme-activated pre-photosensitizer constructs such as protease-sensitive oligopeptide conjugates, caged photosensitizers which are un-caged by an enzyme action, and porphyrin precursors. For example, ALA and similar compounds may be used as described in U.S. Patent Publication No. 2002/0099094. ALA can be used in a variety of forms, including in a pharmacologically equivalent form, such as an amide or ester, or as a salt, such as hydrochloride salt, and it can be topically applied to a tissue (e.g., skin) surface surrounding a targeted treatment site which may underlie epithelial tissue at the skin surface. ALA (e.g., 5-aminolevulinic acid) is converted in vivo to a photoactivatable compound, protoporphyrin IX (PpIX).

[0075] The wavelength of photoactivating light for protoporphyrin IX is generally in the range of between about 625 and 670 nm, or more preferably between about 625 and 640 nm. The fluence and irradiance range appropriate for treatment radiation can depend on the concentration of the photosensitizer in the target tissue, depth of the targets, and/or sensitivity of the particular type of targets involved. Fluence generally refers to a delivered optical energy per unit area, and can represent energy density delivered by an optical exposure. Irradiance generally refers to optical radiant power incident per unit area upon a surface, and may be expressed in watts per square meter. Preferred treatment wavelengths for some other photosensitizers can include, for example: chlorins (about 650 nm); porphycenes (about 635 nm); purpurins (about 630 to about 715 nm); phthalocyanines (about 680 nm), naphthalocyanines (about 780 to about 810 nm); and bacteriochlorins (about 650 to 800 nm).

[0076] Clinically, after topical application of 20% ALA to skin, followed by a period of metabolism between about 10 minutes and 24 hours, the range of 635 nm treatment radiation fluence is preferably between about 20 and about 200 J/cm^2, and the range of treatment radiation irradiance is preferably between about 20 and about 200 mW/cm^2.

[0077] In general, longer metabolism times are associated with lower fluence and irradiance requirements to achieve a therapeutic effect. After local injection of ALA, the local concentration can greatly exceed the local concentration achieved after topical application of ALA. Therefore, treatment fluence and irradiance ranges may generally be lower after administration of ALA or other pre-photosensitizers or photosensitizers by parenteral or local injection.

[0078] In other exemplary embodiments, the photosensitizer is photobleached upon exposure to selected inhibition radiation. For example, many photosensitizers used for PDT can also be destroyed by the reactive oxygen species produced during light exposure, a process which may be referred to as photobleaching. Cells may be able to tolerate a certain low dose of oxidative damage, because cells possess antioxidant and repair mechanisms. For cellular target sites to be irreversibly damaged during PDT, the rate of oxidative damage should exceed the rate of oxidative repair in target cells and achieve an amount of damage needed for cell killing by, for example, necrosis or apoptosis. In contrast, photobleaching is often irreversible. A low rate of photobleaching can therefore be used to prevent accumulation or reduce the concentration of the photosensitizer in the non-target sites, by administration of the inhibiting (photobleaching) radiation at a rate low enough that allows the non-target cells to repair.

[0079] Photobleachable photosensitizers include, for example, porphyrins, chlorins, some porphycenes, purpurins, phthalocyanines, naphthalocyanines, bacteriochlorins, benzophenothiazines, tetracyclines, methylene blue, hypericin, flavines, and derivatives thereof, either as free agents or in combination with specific delivery agents such as in liposomes or as photosensitizer conjugates with targeting molecules, such as peptides, receptor ligands or antibodies.

[0080] Accordingly, in one exemplary embodiment, relatively low-level light exposure is used for photobleaching of a photosensitizer in a non-target tissue, while allowing a sufficient amount of photosensitizer to remain in the target cells. This can be done, for example, in a superficial non-target epithelial layer by prolonged exposure to low-level short wavelength

light, which harmlessly photobleaches in the non-target upper tissue layer but not in a deeper target layer.

[0081] Across the optical spectrum from about 320 nm to about 1200 nm, shorter wavelengths tend to penetrate less deeply than longer wavelengths due to optical scattering and absorption as described, e.g., in Anderson, R.R. et al., J Invest Dermatol 1981;77:13-19. For example, the penetration of radiation having wavelengths between about 380 to 420 nm (e.g., UVA and deep blue light) into human skin is less than the penetration at wavelengths between about 620 to 700 nm (e.g., red light), due to relatively stronger scattering by dermal collagen, stronger absorption by epidermal melanin, and stronger absorption by hemoglobins in blood vessels. Attenuation by scattering and absorption within tissue can lead to an approximately exponential overall loss of irradiance with depth. Near the tissue surface, a maximum of irradiance may be present within the tissue at a depth of approximately $1/\mu s$, where μs is an effective scattering coefficient. For example, using ALA or ALA derivatives as a pre-photosensitizer, and/or using porphyrins and chlorins as photobleachable photosensitizers, a wave length of about 380 to about 420 nm may be a preferred wavelength for the inhibiting radiation. These agents involve a photosensitizer with strong Soret absorption band in this wavelength region.

[0082] In an exemplary embodiment of the present invention, an irradiance of about 1 mW/cm^2 at a wavelength between about 380 nm to about 420 nm can be used to inhibit porphyrin accumulation in epidermis (e.g., a superficial epithelium of skin) following topical application of 20% ALA in both animal and human skin. An irradiance less than about 1 mW/cm^2 of this wavelength region can also photobleach porphyrin and chlorin photosensitizers, at a rate which may be tolerable to the epidermis. The 1/e (37%) penetration depth of 380 to 420 nm radiation in caucasian human skin is about 0.06–0.15 mm, which corresponds to an approximate thickness of human epidermis. For applications such as acne therapy, the epidermis is often a non-targeted tissue that is preferably spared from damage, whereas the target structures include sebaceous glands and sebaceous follicles in the underlying dermis. Sebaceous glands associated with acne are cellular target structures located about 1 mm below the surface. For example, with a target gland located about 1 mm deep, using an inhibiting radiation with a wavelength between about 380 to about 420 nm that has a 1/e penetration depth of about 0.1 mm, the target is about 10 times the 1/e penetration depth. The

inhibiting radiation in this example is therefore attenuated by a factor of up to e^{10} (e.g., about 0.00005 times the original intensity) by the time it reaches the target gland. The inhibiting radiation therefore can produce an irradiance in the epidermis (e.g., non-target tissue) which may be thousands of times greater than the irradiance in the sebaceous gland (e.g., target tissue). The inhibiting radiation can inhibit accumulation and/or photobleach a photosensitizer in the epidermis at a rate which may be tolerable for the non-target epidermal tissue, while having a very small effect on accumulation of photosensitizer in the deeper target tissue. In contrast, the 1/e penetration depth of the treatment radiation having a wavelength between about 620 to 700 nm is about 0.5 to 0.75 mm in human skin. This depth corresponds roughly to the depth of the target tissue. Such treatment radiation may be attenuated by a factor of only about 5 (and not, e.g., by orders of magnitude) before reaching the target. Because the inhibiting radiation step is used to greatly reduce or eliminate photosensitizer in the epidermis, the epidermis can be spared from significant damage during application of the treatment radiation.

[0083] Fig. 9a shows an application of a beam of radiation 900 that is approximately normal to the tissue surface 910. This corresponds to an incident angle θ of about 90°. The penetration depth D_o 920 associated with the beam 900 can refer to, e.g., a maximum depth at which at least a pre-defined amount of energy is locally absorbed by tissue. As described herein above, the depth D_o 920 can depend on the wavelength of the radiation beam 900. For example, a desired depth D_o 920 can be specified for a particular treatment by appropriate selection of a wavelength for the inhibiting and/or treatment radiation.

[0084] An effective penetration depth can also be controlled by varying the incident angle of applied radiation beam relative to the tissue surface. For example, Fig. 9b shows an exemplary application of an angled beam of radiation 950 that is provided at an incident angle θ of about 60° relative to the direction 980 normal to the tissue surface 910. The penetration depth D_θ 960 corresponding to the angled beam 950 will generally be smaller than the depth D_o 920 associated with a normally incident beam 900 as shown in Fig. 9a. The depth D_θ can be expressed approximately as $D_\theta \sim D_o n \sin(\theta)$ based on Snell's law, where n is the index of refraction of skin tissue relative to air. In skin, the value of n is approximately 1.3, which is similar to the value for water. Thus, the absorption path 970 within the tissue is generally not parallel to the incident angled beam 950, and can project at a slightly steeper angle into the

tissue due to refraction. The approximate relationship $D_\theta \sim D_o n \sin(\theta)$ also assumes that the local absorption behavior within the tissue along the path 970 is similar to the local absorption behavior along the path 940 in Fig. 9a, e.g., the tissue along each path has similar absorption characteristics.

[0085] When applying an incident radiation at some angle incident angle θ with respect to a tissue surface, the fluence and/or irradiance of the applied radiation may be reduced appropriately to provide a volumetric density of absorbed energy that is comparable to that of a beam that is normal to the tissue surface. For example, if the beams 900, 950 shown in Figs. 9a and 9b have the same fluence, then the amount of energy absorbed by the tissue within a depth D_o 920 in Fig. 9a would be absorbed within a shallower depth D_θ shown in Fig. 9b. To provide a comparable local density of energy absorption within the tissue, the fluence and irradiation of the incident angled beam 950 may be reduced by a factor of approximately $n\sin(\theta)$. Although depth variations of tissue composition and/or presence of target structures within the tissue may affect local absorption characteristics, the factor of $n\sin(\theta)$ provides a basis for predicting effective penetration depth D_θ 960 and for maintaining a relatively constant density of energy absorption when applying a radiation beam 950 at an incident angle θ, as shown in Fig. 9b. Other factors such as, e.g., focusing of the radiation beam 950 can also affect the penetration depth D_θ 960.

[0086] Photosensitizers and precursor photosensitizers can be administered in a pharmaceutically acceptable excipient, such as water, saline, aqueous dextrose, glycerol, or ethanol. The compositions may also contain other medicinal agents, pharmaceutical agents, carriers, and/or auxiliary substances such as wetting or emulsifying agents, and/or pH buffering agents. The photosensitizer or pre-photosensitizer can also be delivered by nanoparticles, microsponges, or other drug carriers.

[0087] Standard texts, such as Remington: The Science and Practice of Pharmacy, 17th edition, Mack Publishing Company, incorporated herein by reference, can be consulted to prepare suitable compositions and formulations for administration, without undue experimentation. Suitable dosages can also be based upon the text and documents cited herein. A determination of the appropriate dosages can be provided by one of ordinary skill in the art based on the parameters and criteria described herein.

[0088] A "therapeutically effective amount" refers to, but is not limited to, an amount sufficient to effect a beneficial or desired clinical result. In terms of treatment, an effective amount generally refers to an amount that may be sufficient to palliate, ameliorate, stabilize, reverse or slow the progression of a disorder (e.g., a skin disorder). A therapeutically effective amount can be provided in one or a series of administrations or doses. The effective amount may generally be determined by a physician on a case-by-case basis.

[0089] Several factors are typically taken into account when determining an appropriate dosage for *in vivo* therapeutics or diagnostics. These factors can include, for example, age, sex and weight of the patient, the condition being treated, the severity of the condition and/or the form of the antibody being administered.

[0090] The dosage of photosensitizer compositions for systemic administration typically range from about 0.1 to about 10 mg/kg. Methods for administering photosensitizer compositions are described, for example, in U.S. Patent Nos. 5,952,329, 5,807,881, 5,798,349, 5,776,966, 5,789,433, 5,736,563, 5,484,803, 5,234,940 and by Sperduto et al. (1991) Int. J. Radiat. Oncol. Biol. Phys. 21:441-6; and Walther et al. (1997) Urology 50:199-206. Such dosages may vary, for example, depending on whether multiple administrations are given, tissue type and route of administration, the condition of the individual, the desired objective and other factors. Administrations can be conducted infrequently, or on a regular (e.g., weekly) basis until a desired, measurable parameter is detected, such as diminution of disease symptoms. Administration can then be diminished, such as to a biweekly or monthly basis, as appropriate.

[0091] Photosensitizers used in accordance with embodiments of the present invention can be administered by a mode appropriate for the form of the composition. Available routes of administration include, e.g., subcutaneous, intramuscular, intraperitoneal, intradermal, oral, intranasal, intrapulmonary (e.g., by aerosol), intravenously, intramuscularly, subcutaneously, intracavity, intrathecally or transdermally, alone or in combination with other pharmaceutical agents. Therapeutic compositions of photosensitizers can be administered by injection or by gradual perfusion. Compositions for oral, intranasal, or topical administration can be supplied in solid, semisolid or liquid forms, including tablets, capsules, powders, liquids, and suspensions. Compositions for injection can be supplied as liquid solutions or suspensions, as emulsions, or as solid forms suitable for dissolution or suspension in liquid prior to injection.

For administration via the respiratory tract, a preferred composition can be one that provides a solid, powder, or liquid aerosol when used with an appropriate aerosolizer device. Although not required, compositions may preferably be supplied in unit dosage form suitable for administration of a precise amount. Slow release or sustained release forms of such compositions may also be used, whereby a relatively consistent level of the active compound can be provided over an extended period.

[0092] Cooling of the epithelial tissue can also be applied in certain embodiments of the present invention. For example, the skin surface can be cooled after application of a precursor photosensitizer such that the epidermis has a temperature that is less than the temperature of the underlying targeted tissue. Cooling can be performed using conventional techniques and arrangements such as, e.g., cryogen spray cooling or conductive contact cooling. A lower surface temperature can further inhibit the precursor photosensitizer from metabolizing into a photosensitizer in the epithelial tissue as described, e.g., in U.S. Patent Publication No. 2004/0259855. Epithelial cooling can greatly reduce the metabolism rate in the epithelial tissue (e.g., in non-targeted tissue).

[0093] In further exemplary embodiments of the present invention, the inhibiting radiation may be applied in patterns to reduce or prevent formation of photosensitizers in certain regions of tissue. Such patterns may be provided across a portion of the epithelial tissue and/or can include different exposure depths within the tissue to be treated, e.g., by varying the wavelength and/or intensity or fluence of the inhibiting radiation. In this manner, certain regions of tissue can be spared from the effects of a subsequent PDT procedure which involves application of a treatment radiation.

[0094] In yet further embodiments of the present invention, formation and/or accumulation of porphyrin or other photosensitizing metabolite accumulation are optically suppressed prior to photodynamic therapy light exposure, e.g., during conversion of ALA, ALA-esters or other pre-photosensitizer drugs which may be applied topically, orally or systemically to tissue. A light source is used to provide inhibiting radiation at one or more wavelengths between, e.g., about 320 nm and 850 nm. Over this spectral range, shorter wavelengths tend to penetrate tissue to a lesser extent than longer wavelengths. Thus, wavelength can be one factor which may be varied to control the depth of a superficial tissue layer to be limited or protected from damage during PDT treatment. For epidermal protection, wavelengths from about 320 to 450

nm may be preferred. Sources of radiation providing such wavelengths can include, for example, LEDs, lamps, filtered lamps, or lasers.

[0095] The depth of a superficial layer or other tissue region in which photosensitizers are to be suppressed can also depend on the fluence of the inhibiting radiation applied. A very low irradiance and fluence of blue light, for example, may be sufficient to suppress prophyrin accumulation during metabolism of topically applied 20% aminolevulinic acid, ALA. An irradiance of about 0.1 mW/cm^2 of blue light (e.g., 400-430 nm) can provide a suppressing effect. Typical irradiance values for inhibiting radiation procedures using blue light are between about 1 mW/cm^2 and about 30 mW/cm^2. Typical fluence values which may be used for inhibiting radiation procedures are between about 1 J/cm^2 and about 100 J/cm^2. Such irradiance and fluence values chosen for a particular PDT procedure can vary with wavelength and the precursor photosensitizer used.

[0096] In a further aspect, embodiments of the present invention provide a PDT treatment apparatus/system 300 which can be used to treat a tissue 380, as shown in Fig. 3. The PDT system 300 includes a control system 310 which is provided in communication with an inhibiting energy source 320 and a treatment energy source 330. The control system 310 can include a user interface for selecting and reviewing parameters of a treatment procedure, such as activation times, pulse rate and duration, radiation wavelength and/or fluence associated with the inhibiting and treatment energy sources 320, 330. Further control parameters may include timing and extent of cooling which may be provided by optional cooling device 350, positioning (including translational speed) of delivery device 340, and activation and/or feedback characteristics of optional sensing device 360.

[0097] The inhibiting energy source 320 is configured to generate an appropriate inhibiting radiation, as described herein. Such radiation can be provided, e.g., by a laser, one or more LEDs (such as an array of near-UV or blue LEDs), etc. The treatment energy source 330 is configured to generate an appropriate treatment radiation, as described herein. Such radiation can be provided, e.g., by a laser, one or more LEDs (such as an array of red or near-IR LEDs), etc. The inhibiting and treatment energy sources 320, 330 can be the same source, which may be configured with different parameters such as fluence, pulse frequency and duration, etc., and optionally with different wavelengths if the radiation source has a variable wavelength or

filterable energy output. Alternatively, the inhibiting and treatment energy sources 320, 330 can be different sources as described above and may also be provided in separate enclosures.

[0098] The delivery device 340 may include optical components such as, e.g., optical fibers and/or mirrors which are configured to direct radiation from the inhibiting and treatment energy sources 320, 330 towards the tissue 380 to be treated. The delivery device 340 is optionally provided in a housing together with the inhibiting and treatment energy sources 320, 330 or otherwise integrated with one or both of them. For example, the delivery device 340 can include a reflective surface located behind or adjacent to one or more LEDs which may be provided as part of the energy sources 320, 330.

[0099] An optional cooling device 350 can also be provided with the exemplary PDT system 300. Such cooling device 350 can be integrated with the delivery device 340, or it may be a separate component. The cooling device 350 effectuates cooling of the tissue 380 to be treated using conventional cooling techniques including, for example, contact or conductive cooling, spray cooling (e.g., cryogenic spray) or convective cooling (e.g., a fan).

[0100] The exemplary PDT system 300 optionally includes a sensing device 360 that is configured to detect, for example, temperature and/or fluorescence of the tissue 380 being treated. The sensing device 360 can also be configured to detect a relative translational speed of the delivery device 340 with respect to the tissue surface 380, if the delivery device 340 is scanned or otherwise translated over the tissue 380 during the PDT procedure. The sensing device 360 is provided in communication with the control system 310, such that adjustment of various parameters (e.g., duration and timing intervals, pulse rate and/or fluence of the inhibiting and/or treatment radiation) can be affected by one or more conditions sensed by the sensing device 360.

[0101] In further embodiments, the exemplary PDT system 300 is powered by a portable electrical source such as a battery pack, which allows the entire PDT treatment to be performed at various locations within or outside of a clinical setting.

[0102] In a further embodiment, an exemplary apparatus/system 400 configured to provide PDT treatment of facial skin 410 with optical photosensitizer inhibition is shown in Fig. 4. A topical solution of ALA, methyl ester of ALA, a similar photosensitizing precursor drug, or any photobleachable PDT agent is first applied to the skin 410 to be treated. The apparatus/system 400 includes a support structure 420 which partially or completely surrounds the skin 410 to be

treated. Several treatment energy sources 430 may be located on the supporting structure 420. These treatment sources 430 can include, for example, an array of LEDs (e.g., LEDs having a wavelength between about 630 and 640 nm) or similar radiation sources. The apparatus/system 400 also includes one or more photoinhibition sources 450 affixed to the support structure 420, which may include an array of near-UV or blue LEDs (e.g., LEDs having a wavelength between about 380 and 430 nm).

[0103] The apparatus/system 400 optionally includes one or more cooling and/or warming devices 440 such as, e.g., a fan, a cooling spray, a filtered incandescent lamp and/or an infrared LED. Such cooling and/or warming devices 440 may be mounted onto support structure 420 above and/or below the level of the sources 430, 450. Warming devices 440 may be used, e.g., to enhance absorption and accumulation of photosensitizers at targeted treatment sites (e.g., hair follicles or sebaceous glands).

[0104] The exemplary apparatus/system 400 can also include vision portals 460, which can allow a patient to view content displayed on entertainment panel 480 during treatment. One or more sensors 470 are optionally provided to detect skin temperature and/or fluorescence during PDT treatment. Such sensors 470 can include, for example, discrete detectors or camera detectors. The PDT apparatus/system 400 may further include other subunits 490 such as, e.g., a user interface for selecting and displaying treatment parameters, a control arrangement for controlling the parameters of the various components, etc. The physical layout of the various components in the exemplary apparatus/system 400 can be modified for treatment of other body sites, by providing certain components in separate housings and/or by articulation and/or placement of such components as needed.

[0105] In an exemplary PDT treatment procedure in accordance with certain embodiments of the present invention, the superficial layer to be protected is the epidermis, which may be about 0.1 mm thick. The target sebaceous glands to be treated (e.g., thermally damaged) are located on a patient's face, between about 1 to 3 mm deep in the underlying dermis layer of skin. First, the face is washed to remove oil and dirt. Various cleansers may be used including, e.g., abrasive cleansers that can increase uptake of topical medications by degreasing and scratching the skin surface.

[0106] A topical form of aminolevulinic acid (e.g., Levulan Kerastick®), a methyl ester of aminolevulinic acid (e.g. Metvx®), or another analog and/or PDT drug is then applied to at least one affected skin area. An occlusive, transparent plastic mask or covering such as, e.g., Saran® wrap or a transparent occlusive ointment may optionally be placed, sprayed or spread on the skin to further enhance penetration and uptake of the drug(s) to the intended target sites, e.g., sebaceous follicles. The occlusive ointment may contain volatile components such as water that can cool the skin surface.

[0107] The patient is positioned in front of (e.g., while sitting) or beneath (while lying down) an integrated exemplary treatment apparatus, such as those shown in Figs. 3 and 4. The treatment apparatus can be programmed for "phase I" (e.g., pre-phototreatment) parameters. Such phase I parameters can include, for example, uptake and incubation time for the precursor photosensitizer, energy source settings for photoinhibition of epidermal porphyrin accumulation, surface cooling settings for temperature-based suppression of epidermal porphyrin accumulation, radiant tissue heating settings to enhance porphryin accumulation in the targeted sites, monitoring characteristics of skin temperature to control the cooling/heating devices for achieving a desired skin surface temperature, and/or monitoring of porphyrin fluorescence during or after it accumulates, etc.

[0108] The inhibiting radiation applied during phase I is preferably provided after an interval of less than about 30 minutes following application of the ALA or other PDT drug, or more preferably less than about 15 minutes following application of the precursor photosensitizer. Still shorter intervals may be even more preferable. As described above, longer intervals may allow initial metabolizing of the precursor photosensitizer to form photosensitizers in epithelial tissue regions where protection from PDT effects is desired.

[0109] "Phase II" (e.g., phototreatment) parameters may also be selected for a particular PDT treatment. Such phase II parameters can include, for example, fluences, irradiances, exposure times and/or wavelengths of the treatment energy to be delivered. Wavelength variation, if desired, may be achieved by using, for example, a mixed LED array, by filtering of a single broadband source, or by using multiple light sources including sources that can be delivered by fiber optics or fiber optic bundles. The treatment energy may be delivered with or without skin cooling; such exemplary cooling (e.g., by flowing air) can provide added comfort.

[0110] "Phase III" (e.g., post-phototreatment) parameters and conditions may also be selected. For example, during phase III, skin cooling may be continued for comfort and to reduce swelling, and post-treatment porphyrin fluorescence may be monitored to assess epidermal or target viability.

[0111] In accordance with certain exemplary embodiments, phase I is typically configured to be activated for about 30-240 minutes, or preferably about 90-180 minutes, but the duration may range from about 0-300 minutes or more. Radiation sources which may be used for photoinhibition of photosensitizer formation/accumulation in phase I include, for example, one or more near-UV or blue (e.g., 320-450 nm) LEDs, a filtered lamp or array, one or more diode lasers, etc. The photoinhibition radiation source may optionally be the same source used to generate radiation for PDT treatment during phase II, but with a lower fluence or irradiance being provided during Phase I as compared to phase II. For example, irradiance during Phase I using an array of 635 nm LEDs can be between about 0.01 and 1 mW/cm^2, whereas during phase II the irradiance using the same LEDs can be between about 50 and 100 mW/cm^2. However, it may be preferable to use different radiation sources for phase I and phase II.

[0112] A variety of techniques in addition to photoinhibition may be used during phase I to control or optimize the PDT treatment. For example, skin surface cooling may also be provided to increase comfort and/or to further suppress formation and/or accumulation of photosensitizers such as porphyrins near the skin surface, by partial inhibition of enzymes that convert ALA or methyl ALA to porphyrins. Such cooling can be provided, e.g., by a cooling fan with or without a heat exchanger, and/or by evaporative techniques. Skin warming may also be provided during phase I using, e.g., a near infrared source such as filtered incandescent lamps or LEDs, or warmed air. Such warming during phase I may increase metabolism of ALA or methyl ALA to porphyrins in the targeted tissue sites, e.g., in sebaceous glands. Skin surface cooling, radiant skin warming, and photoinhibition may be used simultaneously or sequentially during phase I.

[0113] The treatment energy sources activated during phase II are preferably applied after an interval of less than about 30 minutes following application of the inhibiting radiation, or more preferably less than about 15 minutes following completion of the inhibiting radiation. Still shorter intervals may be even more preferable. As described above, longer intervals may allow

further spreading and metabolizing of the precursor photosensitizer to form photosensitizers in tissue regions where protection from PDT effects is desired.

[0114] The radiation sources used to provide treatment radiation can include LED arrays, which may be preferable because of their simplicity, power, lifetime, and electrical and optical safety. The exemplary PDT system can also provide audio and/or visual indicators for procedure progress and/or warning signals such as speech indicating time, progress during each phase, and events that are about to occur. These indicators can also be used to request information such as degree of discomfort being experienced, and responses can be provided using manual inputs, voice-activated inputs or both. An entertainment device may also be provided to reduce patient boredom and/or to query the patient for information about treatment progress, sensations, preferences, etc.

[0115] During phase II, treatment exposure can often generate a tingling, burning, or painful sensation after a brief delay. An interface can be provided which includes the ability to reduce the treatment source irradiance, pause the treatment, increase skin cooling and/or air circulation on the skin, or distract the patient, based on input provided by a patient and/or operator. Treatment exposure time during phase II is typically in the range of about 10-45 minutes, but it may range from about 1 minute to about 120 minutes.

[0116] Other types of apparatus for PDT can be provided in accordance with embodiments of the present invention. For example, a portable treatment "patch" which includes a programmable photoinhibition device with or without cooling or warming (phase I), followed by a treatment light source activation device (phase II) with or without cooling can be constructed. Such a patch-based system can allow a patient complete mobility after application, injection or ingestion of the ALA, methyl-ALA, or other precursor photosensitizer. The patch-based system includes an energy supply, one or more radiation sources (such as LEDs), a processor or other device to control timing and application of the inhibition and treatment radiations, etc. These components can be provided in a small housing which can be affixed to the body over the area to be treated after application of the precursor photosensitizer.

[0117] For example, PDT procedures to treat acne can be provided by apparatus, systems and methods according to embodiments of the present invention in a physician's office, a treatment center, as a prescription home-use device, or as a non-prescription home use device. PDT treatment can be a labor-intensive office procedure. The embodiments of the present

invention as described herein can allow a simpler and more flexible way to provide PDT treatment.

[0118] Optimized PDT techniques according to embodiments of the present invention can be practiced for skin diseases including acne, skin cancer, hair removal, nevus sebaceous, cutaneous nevi, adnexal tumors including syringomas, cutaneous T cell lymphoma, squamous and basal cell carcinomas, abnormal blood vessels, melanocytic and other cutaneous nevi, dysfunctional nerves, unwanted subcutaneous fat, and infections including fungal disease such as onychomycosis and viral disease such as cutaneous warts. For non-cutaneous applications, the methods and systems can be modified to fit the anatomical features involved. For example, the exemplary methods and apparatus/systems according to exemplary embodiments of the present invention may be used in gynecology for cervical and vaginal diseases, to treat oral and airway diseases, or gastrointestinal and internal diseases including neural tissues, cardiovascular, heart, endocrine, and muscle.

[0119] Embodiments of the present invention may also be used to treat skin cancer. For example, a precursor photosensitizer can applied to the skin and an inhibiting radiation can be applied to epidermal tissue above the targeted tumor site. The photoinhibition technique can allow the precursor photosensitizer to metabolize into a photosensitizer at the tumor site, thereby allowing the PDT to destroy the tumor cells while preventing damage to healthy non-cancerous epidermal tissue.

EXAMPLES

Example 1

[0120] Suppression of epidermal porphyrin accumulation by blue light exposure during ALA metabolism, in accordance with exemplary embodiments of the present invention, was tested in humans. A 20% topical ALA solution was applied to human skin, covered with aluminum foil, while only some uncovered areas received 410-nm blue light (1.47mW/cm^2) during the incubation time (See Figs. 6A-C). A fluorescent photo was taken after 2 hours of incubation, as shown in Fig. 6D, and 632-nm light (100J/cm^2) was then applied to all areas as shown in Fig. 6E. A clinical photograph, shown in Fig. 6F, was taken after PDT treatment.

[0121] Blue light exposure during the period of ALA metabolism was observed to suppressed porphyrin accumulation and subsequent PDT reactions. Inactivation of porphyrin synthetic enzymes or the pre-porphyrin metabolites, concurrent repair of oxidative damage during blue light exposure, and/or changes in cell signaling may contribute to this observed effect. Such findings indicate that exemplary embodiments of the present invention can provide a method to suppress porphyrin accumulation as a technique for controlling ALA-PDT. Low intensity blue light exposure during the period of ALA metabolism can suppress epidermal porphyrin synthesis, thus allowing for PDT of acne with less pain and/or fewer side effects.

[0122] When a skin surface is cooled, there can be a gradient of temperature such that ALA metabolism might favor the warm dermis. To examine this effect, cooling and heating plates were applied to skin after topical and injected ALA administration, and porphryin synthesis and skin photosensitization were then determined. Skin cooling to a temperature less than about 20°C was observed to significantly suppress conversion of epidermal ALA to porphyrins, thereby limiting the phototoxicity reaction of epidermis. Dermal porphyrin synthesis was observed to be partially suppressed when the skin surface temperature was 20°C, as shown, e.g., in Fig. 7. These results indicate that a device that cools the epidermis while simultaneously warming the dermis can selectively suppress unwanted epidermal porphyrins and could be used together with other porphyrin suppression methods in accordance with exemplary embodiments of the invention.

Example 2

[0123] In accordance with embodiments of the present invention, 20% topical ALA was applied to the skin of a pig. Nine different areas were divided and different attenuating films were placed over the skin during the entire incubation time (or the metabolism period). The attenuating films reduced the light transmittance allowing a range of irradiance varying from 100%, 56%, 44%, 35%, 26%, 21%, 19% to 17% of light during the incubation period.

[0124] Immediately after the drug application, a 410 nm blue light was irradiated through all the experiment sites at an irradiance of 2.6 mW/cm^2 for 3 hours. During this period, porphyrin accumulation was measured in each test area by digital fluorescence photography (~410 nm excitation, >600 nm emission), and microscopically determined by fluorescence microscopy of skin biopsies (8 mm diameter) obtained prior to light exposure. After the 3 hours of incubation, red light at 635 nm exposure with 200 J/cm^2 fluence was delivered at 100 mW/cm^2 irradiance,

provided by an LED array source (Omnilux, PhotoTherapeutics LTD, Cheshire UK). Measurements and biopsies were repeated after 24 hours, prior to euthanasia.

[0125] The results show inhibition of porphyrin accumulation in all sites down to 17% light transmittance (0.4 mW/cm^2), but for the site that was covered during the blue light exposure.

Example 3

[0126] Embodiments of the present invention were used to treat a 23 year old female Asian patient exhibiting moderate to severe inflammatory acne (acne III-IV). The patient's recalcitrant acne was resistant to conventional treatments (oral and topical antibiotics, topic retinoids and benzoyl peroxide), and failed to respond to Accutane treatment (2 cycles). A 20% ALA solution (Dusa Pharmaceutics) was applied topically to the patient's face. The right side of the patient's face was covered with saran wrap and aluminum foil for 3 hours of incubation (to provide a conventional PDT treatment), while blue light at very low intensity (an inhibiting radiation) was applied to the left side of the patient's face for 3 hours (using a Clearlight at 90W/cm^2, provided about 2 meters from the patient).

[0127] After the incubation period, both sides of the face were irradiated with red light treatment radiation (635 nm wavelength, at about 180 J/cm^2, using an Aktilite). During the red light irradiation, the patient indicated a subjective pain score of about 9-10 (on a 0-10 scale, with 0 being no pain, 5 being moderate pain, and 10 being maximum pain) on the right side of her face receiving conventional PDT treatment. On the optically inhibited (left) side, the patient indicated subjective pain scores of 3-4 during application of the same treatment radiation.

[0128] Immediately after the treatment, the patient exhibited a significant inflammatory reaction and persistent pain on the conventionally-treated (right) side, while the optically inhibited (left) side only exhibited mild inflammation and no pain. The conventionally-treated side evolved with areas of exudative and exulcerated lesions, especially near the nose, and crusting was observed. In contrast, the optically inhibited (left) side only exhibited mild hyperpigmentation.

[0129] After four weeks, both sides of the patient's face showed no new inflammatory acne, with subjective reduction of sebum noticed by the patient. Hyperpigmentation was observed on

the right side treated with the conventional PDT technique, while no negative side effects were observed on the left side of the face, which was treated with an inhibiting radiation prior to application of the treatment radiation, in accordance with embodiments of the present invention.

[0130] The reduction in perceived pain during PDT treatment, and reduction or elimination of short-term and long-term adverse side effects which were observed by application of the inhibiting radiation prior to PDT treatment clearly suggest the advantages of such methods and apparatus for PDT techniques.

[0131] The foregoing merely illustrates the principles of the invention. Various modifications and alterations to the described embodiments will be apparent to those skilled in the art in view of the teachings herein. It will thus be appreciated that those skilled in the art will be able to devise numerous systems, arrangements and methods which, although not explicitly shown or described herein, embody the principles of the invention and are thus within the spirit and scope of the present invention. In addition, all publications, patents and patent applications referenced herein are incorporated herein by reference in their entireties.

[0132] What is claimed is:

1. An apparatus for applying radiation to an anatomical structure, comprising:

a first radiation source configured to provide a first radiation to the anatomical structure, wherein the first radiation is configured to at least one of reduce or eliminate formation of a photosensitizer from a precursor photosensitizer within a first region of the anatomical structure; and

a second radiation source configured to provide a second radiation to the anatomical structure, wherein the second radiation is configured to interact with the photosensitizer to damage at least a portion of the second region, and wherein the first region is substantially unaffected by the second radiation.

2. The apparatus of claim 1, further comprising a controller arrangement configured to control at least one parameter associated with at least one of the first radiation source or the second radiation source, wherein the at least one parameter includes at least one of a wavelength, a fluence, an irradiance, a pulse rate, an angle of incidence, or a duration of application.

3. The apparatus of claim 1, wherein the anatomical structure comprises skin.

4. The apparatus of claim 1, wherein the precursor photosensitizer comprises at least one of ALA or a methyl-ester of ALA.

5. The apparatus of claim 1, wherein the photosensitizer comprises a porphyrin.

6. The apparatus of claim 1, wherein the first region comprises an epithelial layer of tissue.

7. The apparatus of claim 1, wherein the first radiation is provided by at least one of an LED, a laser or a filtered light source.

8. The apparatus of claim 1, wherein the first radiation has a wavelength that is between about 320 nm and about 850 nm.

9. The apparatus of claim 1, wherein the first radiation has a wavelength that is between about 320 nm and about 450 nm.

10. The apparatus of claim 1, wherein the second radiation is provided by at least one of an LED, a laser or a filtered light source.

11. The apparatus of claim 1, wherein the second radiation has a wavelength that is between about 470 nm and about 700 nm.

12. The apparatus of claim 1, wherein the second radiation has a wavelength that is between about 625 nm and about 645 nm.

13. The apparatus of claim 1, wherein the first radiation is applied at an irradiance that is between about 0.01 mW/cm^2 and about 30 mW/cm^2.

14. The apparatus of claim 1, wherein the first radiation is applied at a fluence that is between about 1 J/cm^2 and about 100 J/cm^2.

15. The apparatus of claim 1, wherein a first wavelength of the first radiation is shorter than a second wavelength of the second radiation.

16. The apparatus of claim 1, further comprising a cooling arrangement configured to cool at least a portion of the first region.

17. The apparatus of claim 1, wherein the portion of the second region comprises at least one sebaceous gland.

18. The apparatus of claim 1, wherein the portion of the second region comprises at least a portion of a hair follicle.

19. The apparatus of claim 1, further comprising a detecting arrangement configured to detect at least one characteristic of at least a portion of the anatomical structure, and selecting at least one parameter associated with at least one of the first radiation or the second radiation based on the at least one characteristic.

20. An apparatus for applying radiation to an anatomical structure, comprising:

a first radiation source configured to provide a first radiation to the anatomical structure, wherein the first radiation is configured to photobleach a photosensitizer within a first region of the anatomical structure; and

a second radiation source configured to provide a second radiation to the anatomical structure, wherein the second radiation is configured to interact with the photosensitizer located in a second region of the anatomical structure to produce a phototoxic species so as to damage at least a portion of the second region, and wherein the first region is substantially unaffected by the second radiation.

21. The apparatus of claim 20, further comprising a controller arrangement configured to control at least one parameter associated with at least one of the first radiation source or the second radiation source, wherein the at least one parameter includes at least one of a wavelength, a fluence, an irradiance, a pulse rate, an angle of incidence, or a duration of application.

22. The apparatus of claim 20, wherein the photobleachable photosensitizer includes at least one of a porphyrin, chlorin, porphycene, purpurin, phthalocyanine, naphthalocyanine, bacteriochlorin, benzophenothiazine, tetracycline, methylene blue, or hypericin.

23. The apparatus of claim 20, wherein the first radiation has a wavelength between about 320 nm and about 800 nm.

24. The apparatus of claim 20, wherein the first radiation has a wavelength between about 380 nm and 420 nm.

25. The apparatus of claim 20, wherein the first radiation is applied at an irradiance that is between about 0.1 mW/cm^2 and about 100 mW/cm^2.

26. The apparatus of claim 20, wherein the first radiation is applied at a fluence that is between about 1 J/cm^2 and about 100 J/cm^2.

27. The apparatus of claim 20, wherein the second radiation has a wavelength between about 400 nm and about 900 nm.

28. The apparatus of claim 20, wherein the second radiation has a wavelength between about 600 and about 800 nm.

29. The apparatus of claim 20, wherein the second radiation has a wavelength between about 625 and about 720 nm.

30. A method for applying radiation to an anatomical structure, comprising:

providing at least one precursor photosensitizer to an anatomical structure;

applying a first radiation to the anatomical structure, wherein the first radiation is configured to at least one of reduce or eliminate formation of a photosensitizer from the precursor photosensitizer within a first region of the anatomical structure; and

applying a second radiation to the anatomical structure which is configured to interact with the photosensitizer located in a second region of the anatomical structure to damage at least a portion of the second region, wherein at least a portion of the first region is substantially unaffected by the second radiation.

31. The method of claim 30, wherein a time interval between providing the at least one precursor photosensitizer and applying the first radiation is less than about 30 minutes, and wherein a time interval between applying the first radiation and applying the second radiation is less than about 30 minutes.

32. A method for applying radiation to an anatomical structure, comprising:

providing at least one photobleachable photosensitizer to an anatomical structure;

applying a first radiation to the anatomical structure, wherein the first radiation is configured to photobleach the photosensitizer within a first region of the anatomical structure; and

applying a second radiation to the anatomical structure which is configured to interact with the photosensitizer located in a second region of the anatomical structure to produce a phototoxic species, wherein at least a portion of the second region is damaged and at least a portion of the first region is substantially unaffected by the second radiation.

33. A method for treating a disorder of the skin in a subject, comprising:

administering a therapeutically effective amount of 5-aminolevulinic acid to the subject;

applying a first radiation to the skin of the subject in an amount and duration sufficient to reduce protoporphyrin IX accumulation within the epidermis of the skin; and

applying a second radiation to the skin of the subject to produce a phototoxic species from the protoporphyrin IX located in dermis of the skin, wherein the epidermis is substantially unaffected by the second radiation, thereby treating the disorder of the skin in the subject.

34. The method of claim 33, wherein the first inhibiting radiation has a wavelength between about 320 nm and about 450 nm.

35. The method of claim 33, wherein the first inhibiting radiation is applied at an irradiance that is between about 0.01 mW/cm^2 and about 30 mW/cm^2.

36. The method of claim 33, wherein the first inhibiting radiation is applied at a fluence that is between about 1 100 J/cm^2 and about 100 J/cm^2.

37. The method of claim 33, wherein the second radiation has a wavelength between about 625 nm and about 670 nm.

38. A computer-readable medium, comprising:

a first set of executable instructions which, when executed by a processing arrangement, configure the processing arrangement to control a first radiation source to provide a first radiation to the anatomical structure, wherein the first radiation is configured to at least one of reduce or eliminate a formation of a photosensitizer from a precursor photosensitizer within a first region of the anatomical structure; and

a second set of executable instructions which, when executed by a processing arrangement, configure the processing arrangement to control a second radiation source to provide a second radiation to the anatomical structure, wherein the second radiation is configured to interact with the photosensitizer to produce a phototoxic species located in a second region of the anatomical structure so as to damage at least a portion of the second region, and wherein the first region is substantially unaffected by the second radiation.

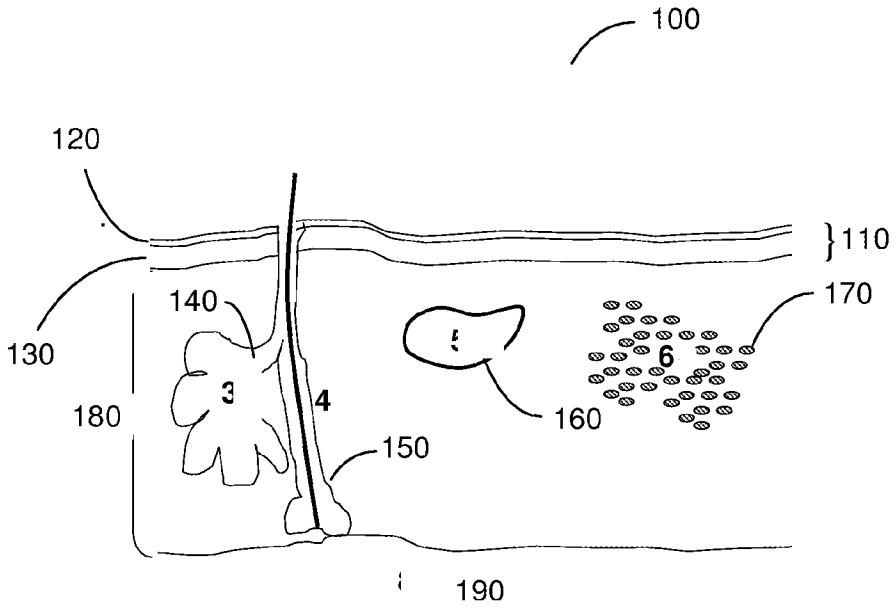

Fig. 1

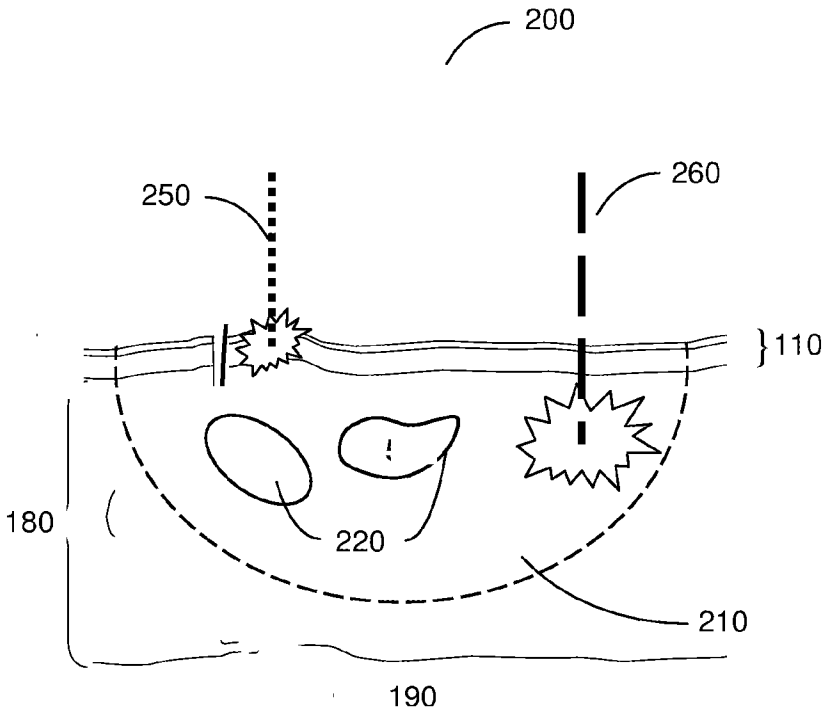

Fig. 2

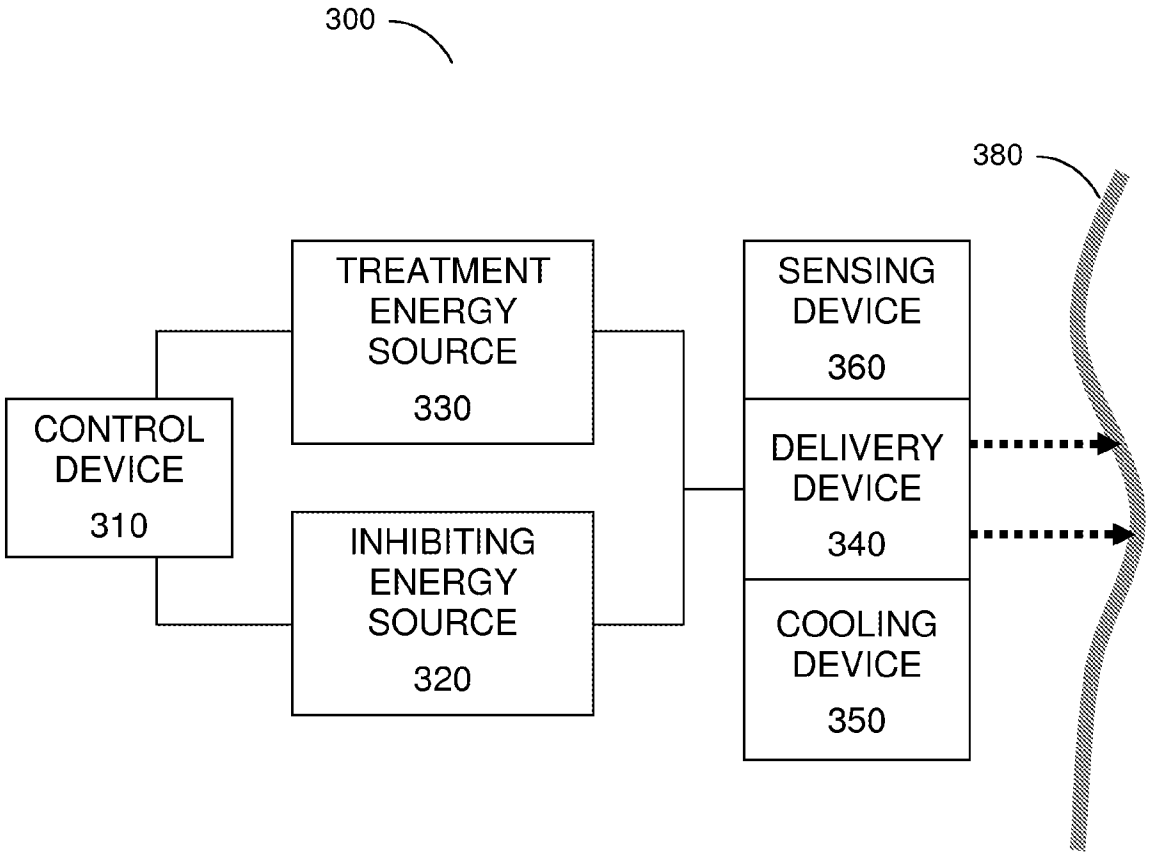
300
380
TREATMENT ENERGY SOURCE 330
CONTROL DEVICE 310
INHIBITING ENERGY SOURCE 320
SENSING DEVICE 360
DELIVERY DEVICE 340
COOLING DEVICE 350

Fig. 3

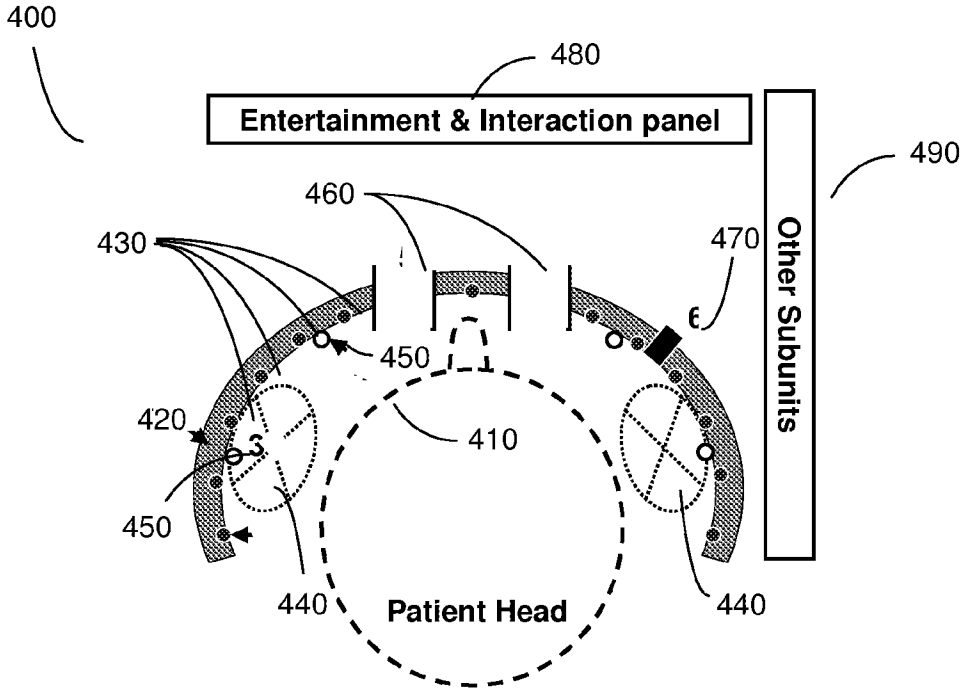
400
480
Entertainment & Interaction panel
490
460
430
470
Other Subunits
450
420
410
450
440
Patient Head
440

Fig. 4

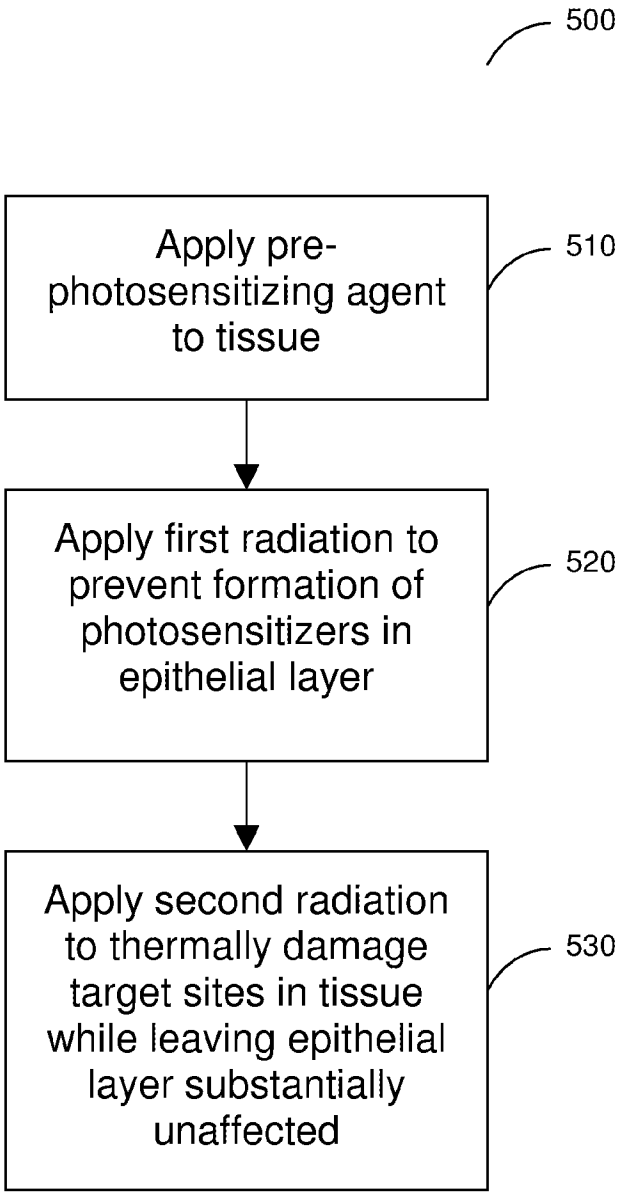
500
Apply pre-photosensitizing agent to tissue
510
Apply first radiation to prevent formation of photosensitizers in epithelial layer
520
Apply second radiation to thermally damage target sites in tissue while leaving epithelial layer substantially unaffected
530

Fig. 5

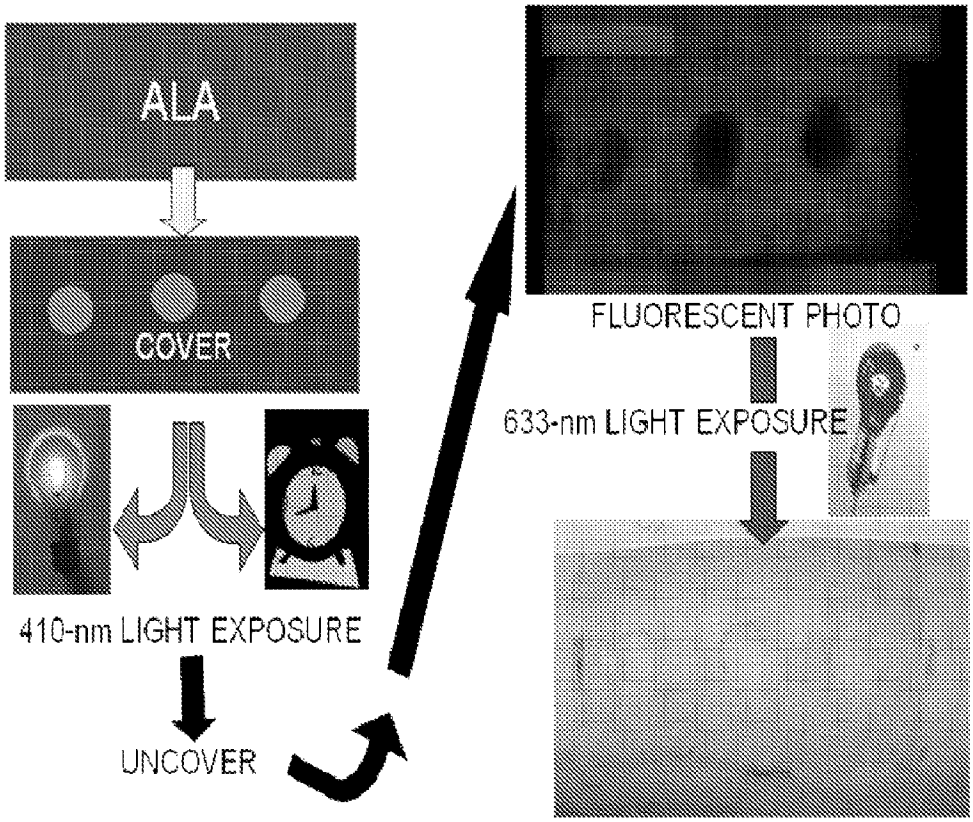
ALA
COVER
410-nm LIGHT EXPOSURE
UNCOVER
FLUORESCENT PHOTO
633-nm LIGHT EXPOSURE

Fig. 6

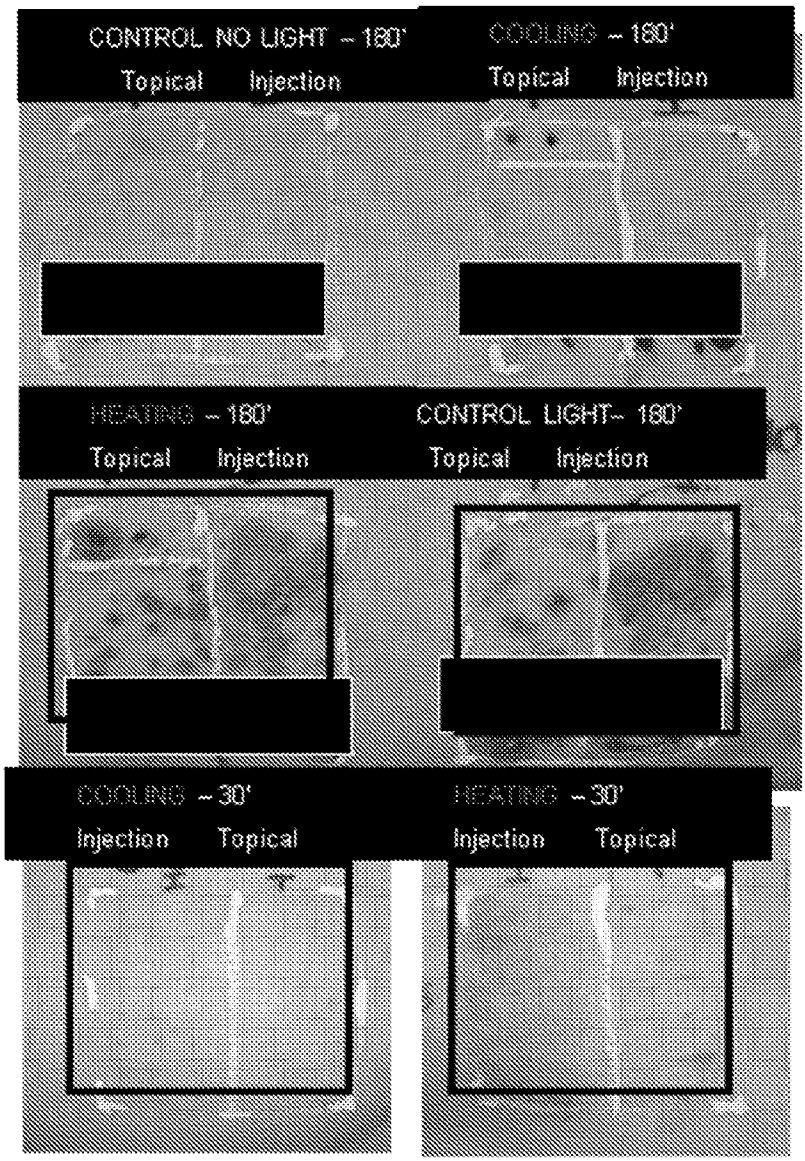
CONTROL NO LIGHT – 180'
Topical Injection
COOLING – 180'
Topical Injection
HEATING – 180'
Topical Injection
CONTROL LIGHT– 180'
Topical Injection
COOLING – 30'
Injection Topical
HEATING – 30'
Injection Topical

Fig. 7

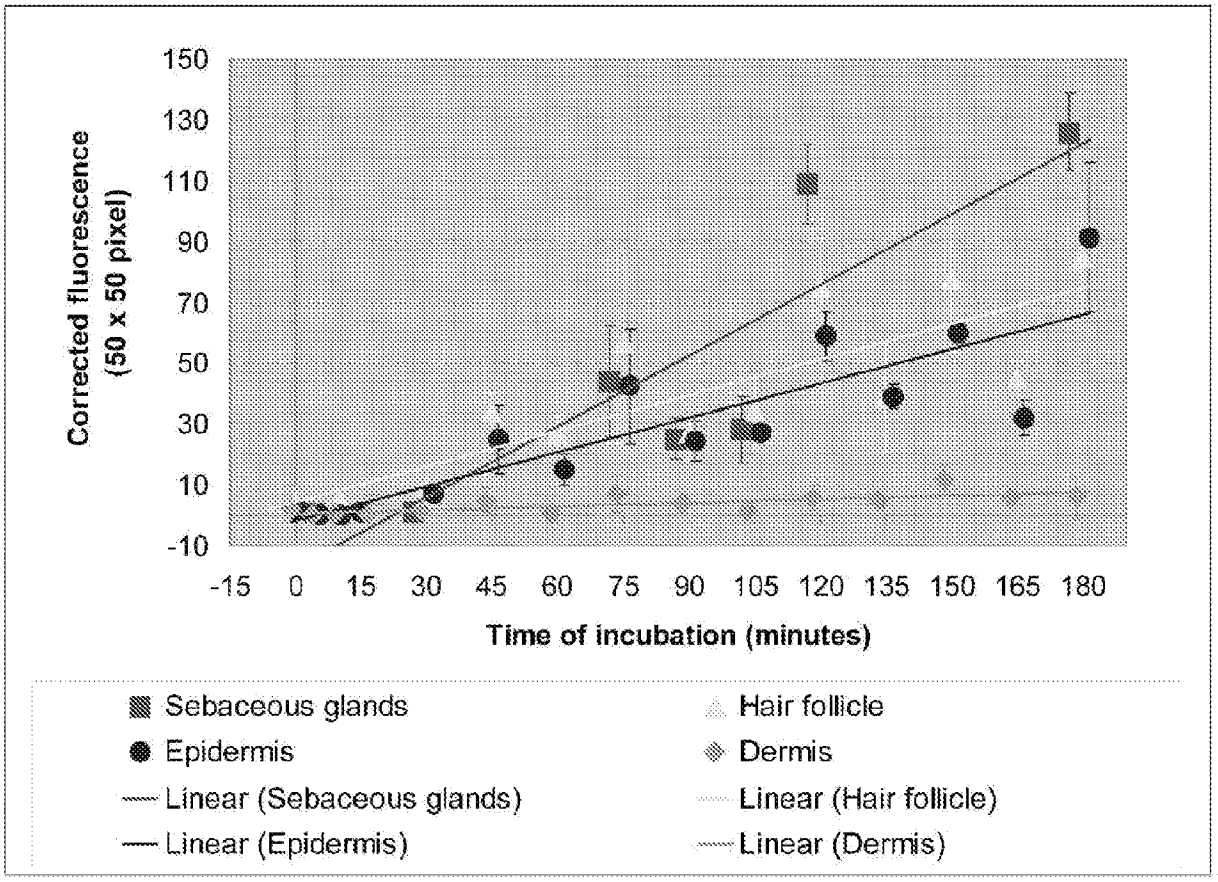
Corrected fluorescence (50 x 50 pixel)
150
130
110
90
70
50
30
10
-10
-15 0 15 30 45 60 75 90 105 120 135 150 165 180
Time of incubation (minutes)
Sebaceous glands
Hair follicle
Epidermis
Dermis
Linear (Sebaceous glands)
Linear (Hair follicle)
Linear (Epidermis)
Linear (Dermis)

Fig. 8

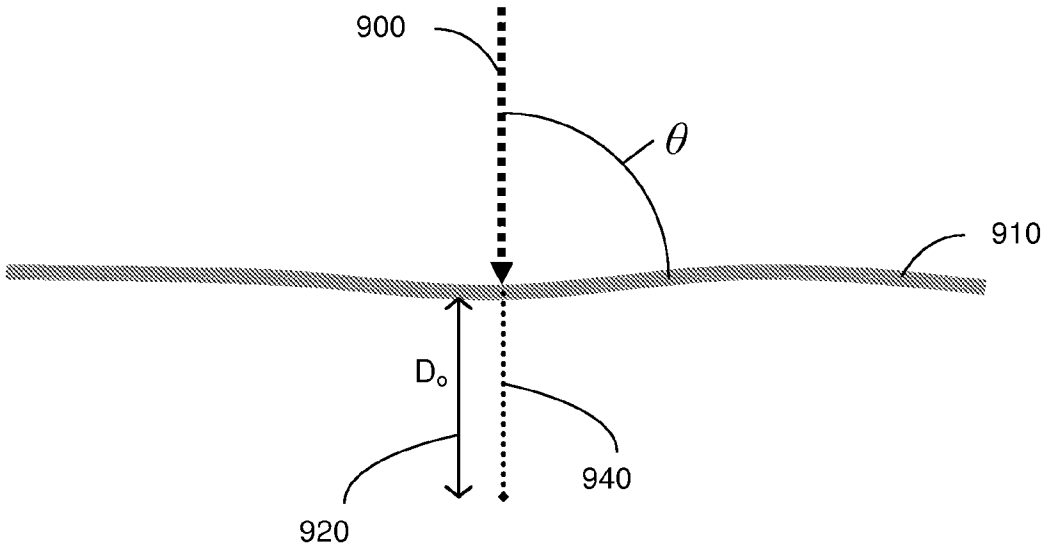

Fig. 9a

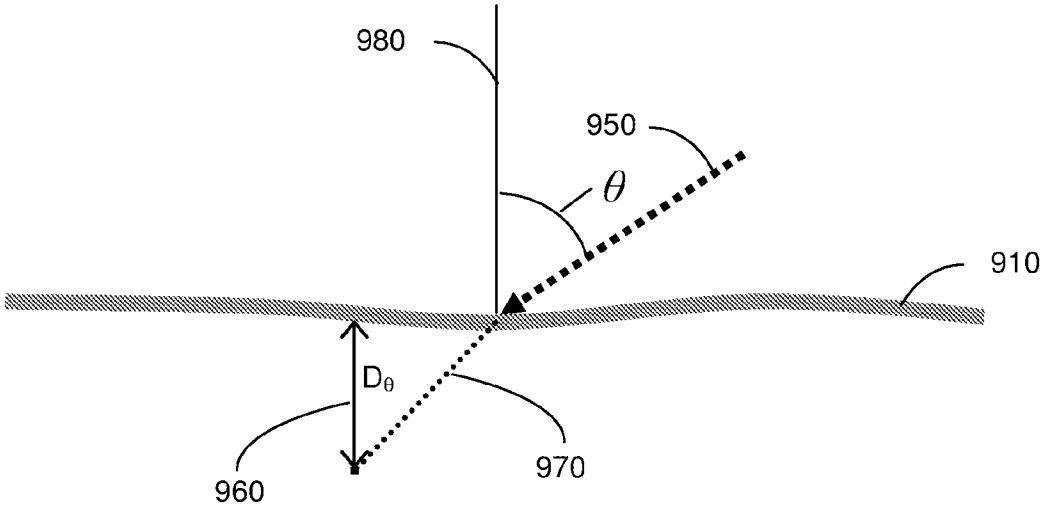

Fig. 9b

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/68593

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 18/18 (2008.04)
USPC - 606/9
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: A61B 18/18 (2008.04)
USPC: 606/9

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC: A61B 18/18 (2008.04)
USPC: 606/1, 2, 9, 10, 11, 13, 22; 607/88, 90, 94, 95

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Pubwest: PGPB, USPT, USOC, EPAB, and JPAB
Searched Terms: photodynamic therapy, photodynamic treatment, PDT, photosensitizer, prevent$3, inhibit$3, stop$3, eliminat$3, decreas$3, terminat$3, reduc$3, damag$3, destroy$3, $2affect$3, healthy, $3target, normal, control$3, processor, computer, hair, cooling, light, laser, led$

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 2003/0083649 A1 (MARGARAN et al.) 01 May 2003 (01.05.2003), entire patent, more specifically, para[0010]-[0015], para[0023], para[0024], para[0033]-[0040], para[0048], para[0094], para[0095], para[0099], para[0102], para[0103], para[0147], and para[0163]).	1, 3-12, 14, 15, 17, 18, 20, 22-24, 26-34, 36, and 37 --- 2, 13, 16, 19, 21, 25, 35, and 38
Y	US 2005/0045189 A1 (JAY) 03 March 2005 (03.03.2005), Fig 1, Fig 2, para[0096]-[0099], and para[0118]-[0119]	2, 16, 19, 21, and 38
Y	US 2006/0269580 A1 (COLE et al.) 30 November 2006 (30.11.2006), para[0014]	13, 25, and 35

☐ 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

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2008 (15.09.2008)	22 SEP 2008
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. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
Law, Glenn
FOLEY & LARDNER LLP
3000 K Street, N.W. Suite 600
Washington, DC 20007
ETATS-UNIS D'AMERIQUE

INVITATION TO PAY ADDITIONAL FEES AND, WHERE APPLICABLE, PROTEST FEE

(PCT Article 17(3)(a) and Rule 40.1 and 40.2(e))

	Date of mailing *(day/month/year)* 19 July 2018 (19-07-2018)
Applicant's or agent's file reference 067286-0400	**PAYMENT DUE** within **ONE MONTH** from the above date of mailing
International application No. PCT/US2018/027070	International filing date *(day/month/year)* 11 April 2018 (11-04-2018)
Applicant DUSA PHARMACEUTICALS, INC.	

1. This International Searching Authority

(i) considers that there are 2 *(number of)* inventions claimed in the international application covered by the claims indicated on an extra sheet:

(ii) therefore considers that **the international application does not comply with the requirements of unity of invention** (Rules 13.1, 13.2 and 13.3) for the reasons indicated on an extra sheet:

(iii) [X] has carried out a partial international search (see Annex) [ ] will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:

see extra sheet

(iv) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid.

2. Consequently, the applicant is hereby **invited to pay,** within the time limit indicated above, the amount indicated below:

EUR 1.775,00	x	1	=	EUR 1.775,00
Fee per additional invention		number of additional inventions		currency/total amount of additional fees

3. The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest,** i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive, where applicable, subject to the payment of a protest fee.

Where the applicant pays additional fees under protest, the applicant is hereby invited, within the time limit indicated above, to pay a protest fee (Rule 40.2(e)) in the amount of EUR 875,00 *(currency/amount)*

Where the applicant has not, within the time limit indicated above, paid the required protest fee, the protest will be considered not to have been made and the International Searching Authority will so declare.

4 [X] Claim(s) Nos. see extra sheet have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	ULLRICH, Josef Tel: +49 (0)89 2399-8048

Form PCT/ISA/206 (April 2005)
Registered Mail

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 4.

Claim(s) completely searchable:
1-12, 23-25

Claim(s) not searched:
13-22

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US2018/027070

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-12

An illuminator for photodynamically diagnosing or treating a surface, comprising a plurality of panels, a plurality of light sources, each mounted to one of the plurality of panels, the plurality of light sources configured to irradiate the surface with visible light, and a heat source configured to emit heat to a patient between outer panels of the plurality of panels.

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2. claims: 23-25

An illuminator for photodynamically diagnosing or treating a surface, comprising a plurality of panels, a plurality of light sources, each mounted to one of the plurality of panels, the plurality of light sources configured to irradiate the surface with visible light, and at least one sensor configured to detect an orientation of at least one of the plurality of panels.

An illuminator for photodynamically diagnosing or treating a surface, comprising a plurality of panels, a plurality of light sources, each mounted to one of the plurality of panels, the plurality of light sources configured to irradiate the surface with visible light, is known from several documents, such as US 2014/0067024 A1.
The heat source according to group 1 solves the problem of enhancing a photodynamic sensitizer's efficiency.
The at least one sensor according to group 2 allow for adaptation of the treatment protocol according to the panels' orientation.
Since the problems solved by the distinct features are not technically interlinked, the inventions (or groups of inventions) as defined above therefore do not share a single general inventive concept. Therefore, the application does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.
According to Article 17(3) PCT, the International Search Report has been established on those parts of the application which relate to the invention first mentioned in the claims ('main invention'), i.e. the subject-matter of the claims mentioned under group 1.

Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/US2018/027070

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.

3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.

4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/067024 A1 (JONES ROSS PETER [GB] ET AL) 6 March 2014 (2014-03-06) paragraphs [0070] - [0074]	1-12
X	WO 2009/003173 A1 (GEN HOSPITAL CORP [US]; SAKAMOTO FERNANDA HIDEMI [US]; ANDERSON RICHAR) 31 December 2008 (2008-12-31)	1,2,4-7, 9-12
Y	paragraphs [0102] - [0107] figure 4	8
X	US 2015/162109 A1 (NAGER ZACHARY [US]) 11 June 2015 (2015-06-11) paragraphs [0021], [0040] - [0049] figure 2	1-7,9-12
Y	US 2006/287696 A1 (WRIGHT DAVID W [US] ET AL) 21 December 2006 (2006-12-21) paragraphs [0050], [0051]	8

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

☒ Patent family members are listed in 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 document 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

2

Patent Family Annex

Information on patent family members

International Application No
PCT/US2018/027070

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014067024 A1	06-03-2014	BR 112015004114 A2	04-07-2017
		CA 2881614 A1	06-03-2014
		EA 201590362 A1	30-11-2015
		EP 2890458 A1	08-07-2015
		JP 2015528338 A	28-09-2015
		US 2014067024 A1	06-03-2014
		US 2016008623 A1	14-01-2016
		US 2016367832 A1	22-12-2016
		WO 2014033254 A1	06-03-2014
WO 2009003173 A1	31-12-2008	CA 2724949 A1	31-12-2008
		EP 2164418 A1	24-03-2010
		EP 2644228 A1	02-10-2013
		ES 2454974 T3	14-04-2014
		US 2010174223 A1	08-07-2010
		US 2015238776 A1	27-08-2015
		WO 2009003173 A1	31-12-2008
US 2015162109 A1	11-06-2015	NONE	
US 2006287696 A1	21-12-2006	US 2006287696 A1	21-12-2006
		WO 2007002073 A1	04-01-2007

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/US2018/027070

TITLE: ADJUSTABLE ILLUMINATORS AND METHODS FOR PHOTODYNAMIC THERAPY AND DIAGNOSIS

APPLICANT: DUSA PHARMACEUTICALS, INC.

IPC CLASSIFICATION: A61N5/06

EXAMINER: Lohmann, Stefan

CONSULTED DATABASES: EPODOC, WPI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61N5/062, A61N2005/0652, A61N5/0625, A61N2005/0642

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
Illuminator for PDD or PDT with LED-panels and heat source

EPO FORM F04A02

Application no:
Demande n°:
Anmelde-Nr: PCT/US2018/027070

DISCLAIMER

The attached provisional opinion on the patentability of the first invention searched serves only as information.
A reply addressing the points raised in the opinion is **not** required and will **not** be taken into account when issuing the final search report and opinion on patentability.

AVERTISSEMENT

L'avis provisoire ci-joint sur la brevetabilité de la première invention recherchée ne sert qu'à titre d'information.
Une réponse abordant les points soulevés dans l'avis n'est **pas** nécessaire et ne sera **pas** prise en compte lors de l'établissement du rapport final de la recherche et de l'avis sur la brevetabilité.

DISCLAIMER

Die beigefügte vorläufige Stellungnahme zur Patentierbarkeit der ersten geprüften Erfindung dient lediglich zur Information.
Eine Antwort auf die erhobenen Punkte in der Stellungnahme ist **nicht** erforderlich und bleibt bei der Erstellung des endgültigen Recherchenberichts und der Stellungnahme zur Patentierbarkeit **unberücksichtigt**.

Re Item III:

1 The methods defined in claims 13-22 relate to therapeutic treatment of the human or animal body, thus being considered to be covered by the provisions of Article 17(2)(a)(i) PCT and Rule 39.1(iv) PCT.

Moreover, according to Article 34(4)(a)(i) PCT and Rule 67.1(iv) PCT, no examination is required to be carried out on these claims.

Re Item IV:

This Authority considers that the application does not meet the requirements of unity of invention:

2 There are two inventions covered by the claims indicated as follows:

Group 1: claims 1-12

An illuminator for photodynamically diagnosing or treating a surface, comprising a plurality of panels, a plurality of light sources, each mounted to one of the plurality of panels, the plurality of light sources configured to irradiate the surface with visible light, and a heat source configured to emit heat to a patient between outer panels of the plurality of panels.

Group 2: claims 23-25

An illuminator for photodynamically diagnosing or treating a surface, comprising a plurality of panels, a plurality of light sources, each mounted to one of the plurality of panels, the plurality of light sources configured to irradiate the surface with visible light, and at least one sensor configured to detect an orientation of at least one of the plurality of panels.

3 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

An illuminator for photodynamically diagnosing or treating a surface, comprising a plurality of panels, a plurality of light sources, each mounted to one of the plurality of panels, the plurality of light sources configured to irradiate the surface with visible light, is known from several documents, such as US 2014/0067024 A1 (cited as D1 below; see e.g. par. [0070]-[0074]).

The heat source according to group 1 solves the problem of enhancing a photodynamic sensitizer's efficiency.

The at least one sensor according to group 2 allow for adaptation of the treatment protocol according to the panels' orientation.

Since the problems solved by the distinct features are not technically interlinked, the inventions (or groups of inventions) as defined above therefore do not share a single general inventive concept. Therefore, the application does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

Re Item V:

4 Reference is made to the following documents:

D1 US 2014/067024 A1 (JONES R P ET AL) 6 March 2014 (2014-03-06)

D2 WO 2009/003173 A1 (GEN HOSPITAL CORP) 31 December 2008 (2008-12-31)

D3 US 2015/162109 A1 (NAGER Z) 11 June 2015 (2015-06-11)

D4 US 2006/287696 A1 (WRIGHT D W ET AL) 21 December 2006 (2006-12-21).

5 INDEPENDENT CLAIM 1

5.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D2 discloses an illuminator for photodynamically diagnosing or treating a surface (see par. [0102]) having the following features:

- a plurality of panels (par. [0102] and Fig. 4)
- a plurality of light sources, each mounted to one of the plurality of panels, the plurality of light sources configured to irradiate the surface with substantially uniform intensity visible light (par. [0102] and Fig. 4)
- a heat source configured to emit heat to a patient between outer panels of the plurality of panels (par. [0103], [0112] and Fig. 4).

5.2 It is indicated, that the subject-matter of claim 1 is also anticipated by document D3 (see the passages cited in the Search Report).

6 DEPENDENT CLAIMS 2-12

Dependent claims 2-12 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT):

- re. cl. 2: see e.g. par. [0104]-[0107] in D2
- re. cl. 3: see par. [0044] in D3
- re. cl. 4: see e.g. par. [0102] in D2
- re. cl. 5, 6: see par. [0068] and [0102] in D2
- re. cl. 7, 9, 10: tailoring of an appropriate light field, including determination of an appropriate number of LEDs, comes within the standard knowledge of a skilled person
- re. cl. 8: see par. [0050], [0051] in D4
- re. cl. 11, 12: dose based on area and time amount to standard control parameters; also see e.g. par. [0111] and [0112] in D2.

Electronic Patent Application Fee Transmittal

Application Number:	15869164
Filing Date:	12-Jan-2018
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Filer:	Glenn Law/Effie Hale
Attorney Docket Number:	067286-0399

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	33843907
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Customer Number:	22428
Filer:	Glenn Law/Effie Hale
Filer Authorized By:	Glenn Law
Attorney Docket Number:	067286-0399
Receipt Date:	27-SEP-2018
Filing Date:	12-JAN-2018
Time Stamp:	10:43:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	092718INTEFSW10445600
Deposit Account	190741
Authorized User	Effie Hale

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		IDSTrans_SB08.pdf	290509 1569ff5472f088cfd655b2b1d28d0e327d49bd13	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Information Disclosure Statement (IDS) Form (SB08)		3	3	
	Transmittal Letter		1	2	
Warnings:					
Information:					
2	Foreign Reference	WO2009_003173.pdf	5346780 a1bdea8d8c4173f5b6093f4e89ce57879bccacdb	no	51
Warnings:					
Information:					
3	Non Patent Literature	Partial_ISR.pdf	2214304 19561c8e82fd92274b83927025ffd4566c2fcdbd	no	10
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30455 c0060815e314b4cb80f4284aef77d1d6e12aa003	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	7882048		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Sep 17 2018

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Kiri Lee Sharon

S-signature:
/Kiri Lee Sharon/

Registration Number:
71828

U.S. Application Number:
15869164

Confirmation Number:
3488

E-mail Address:
ksharon@foley.com

Phone Number:
2022954092

Proposed Time of Interview:
10-8-2018 2:00 PM ET

Alternative Proposed Time(s) of Interview:
10-10-2018 11:00 AM ET

Prefered Interview Type:
Telephonic

I am the applicant or applicant's representative for this application.

Topic for Discussion:

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399	3488

22428 7590 08/09/2018

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
FARAH, AHMED M	

ART UNIT	PAPER NUMBER
3762	

NOTIFICATION DATE	DELIVERY MODE
08/09/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@foley.com

Office Action Summary	Application No. 15/869,164	Applicant(s) LUNDAHL ET AL.	
	Examiner AHMED FARAH	Art Unit 3762	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/13/2018*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-23* is/are pending in the application.

5a) Of the above claim(s) *9-15 and 21-23* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-8 and 16-20* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *01/12/18, 04/12/18, 05/10/18*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Election/Restrictions

2. Applicant's election without traverse of the invention of Group I, claims 1-8 and 16-23 in the reply filed on 04/13/2018 is acknowledged.

3. Claims 9-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/13/2018.

4. With respect to the requirement for election of one of species A and species B, the applicant elected species A with traverse. Claims 1-8 and 16-20 encompass the elected species (**note**: the applicant erroneously or inadvertently lists claims 9-12 of the non-elected invention as part of the elected species). The applicant traverses the election of species requirement and argues that there is no serious examination burden. Applicant further argues that "a search for 5-aminolevulinic acid would yield results including 5-aminolevulinic acid hydrochloride." In response to the applicant's argument, the claims in species A require for patentability application of 5-aminolevulinic acid (molecular formula $C_5H_9NO_3$) composition to the body, whereas the claims of species B require for patentability application of composition characterized by a combination of 5-aminolevulinic acid mixed with hydrochloric acid as described in paragraphs 0011 and 0050 -0051 of the specification. The species recite mutually exclusive characteristics of the chemical compositions used for the different embodiments. A search (e.g., searching different

classes /subclasses or electronic resources, or employing different search strategies or search queries) required for a single chemical composition is different than a search required for a combination of mixed chemical compositions. Hence, the examiner maintains the election requirement between species A and B.

5. **Note**: if and when the claims of the elected species A become allowable, any claim of the withdrawn species that requires all the limitations of an allowable generic claim will be considered for rejoinder.

Claim Rejections - 35 USC § 112

6. The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-8 and 16-20 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

- The term "low" in claim 1 line 5 is a relative term which renders the claim indefinite. The term "low density" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Hence, this term renders claims 1-8 indefinite.

- The term "low" in claim 16 line 6 is a relative term which renders the claim indefinite. The term "low density" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Hence, this term renders indefinite claims 16-20.
- Claim 8 recites the limitation "the maximum plasma" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Appropriate corrections are required.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.
>
> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

9. Claims 1, 2, 5 and 16 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Foguet Roca, Pub. No. U.S. 2009/0324727.

Foguet Roca discloses compositions for photodynamic treatment (see Pars. 0027 -0028 and 0065) and methods of use, the method comprising: the step of topically apply a composition of 5-aminolevulinic acid (ALA) to a treatment area to be treated with photodynamic therapy (see Example 5 and claims 1, 64 and 76). Foguet Roca teaches that, according to the invention, the "composition preferably comprises an

active agent which is selected from 5-aminolevulinic acid, or a derivative, a precursor and/or a metabolite thereof," see Par. 0045. Foguet Roca further teach the step of applying/covering polyethylene barrier to the treatment area after the ALA composition is applied to the treatment area as claimed (see Par. 0053).

10. With respect to claim 2, Foguet Roca discloses that the treatment area includes actinic keratosis (see Par. 00140).

Note: in the Background section of the instant application, the applicant describes the use of ALA composition for photodynamic therapy is well known in the art. The applicant further indicates that the inventors found 'coving polyethylene for a period of time over a treatment area is effective to minimize trans-epidermal water loss from the treatment area (see Par. 006 of the specification). The examiner further notes that the use of surfactants such as polyethylene for coating on a surface to minimize water loss for a period of time, or on a surface of a medical capsule to minimize water absorption is well known in the art (see Pars. 0004 and 0208 of Parent et al., Pub. No. U.S. 2014/0010761; and Pars. 0090 and 0106 of Bonasera et al., Pub. No. U.S> 2005/0090429).

11. Claims 1 and 16 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Trigiante, Pub. No. U.S. 2011/0053965.

Trigiante discloses pharmaceutical compositions and methods for photodynamic treatment of skin, comprising: topically applying 5-aminolevuline acid (ALA) to a treatment area (see Pars. 0009; and covering the treatment area with polyethylene barrier to the treatment area in combination with the ALA or after the application of the

ALA to the treatment area to enhance penetration of the topical application (see Pars. 0036 – 0037).

Allowable Subject Matter

12. Claims 3-8 and 17-20 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AHMED FARAH whose telephone number is (571)272-4765. The examiner can normally be reached on Mon - Fri between 9:30 AM 10:30 PM, multi-flex.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jackson can be reached on (571) 272-4697. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AHMED FARAH/
Primary Examiner, Art Unit 3762

August 5, 2018

Notice of References Cited	Application/Control No. 15/869,164	Applicant(s)/Patent Under Reexamination LUNDAHL ET AL.	
	Examiner AHMED FARAH	Art Unit 3762	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2009/0324727 A1	12-2009	Foguet Roca; Montserrat	A61K8/06	424/489
*	B	US-2011/0053965 A1	03-2011	Trigiante; Giuseppe	A61K31/513	514/274
*	C	US-2014/0010761 A1	01-2014	Parent; Stephan D.	C07C229/22	424/9.6
*	D	US-2005/0090429 A1	04-2005	Bonasera, Thomas A.	A61K41/0057	514/11.1
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	95	((Guttadauro near2 Michael) (LUNDAHL near2 Scott)).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:05
L2	16497	((607/88,89,96,100) or (128/898)).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:09
L3	27897	A61N5/06.cpc. A61N5/0616.cpc. A61N5/062.cpc. A61N2005/0662.cpc. A61N2005/0663.cpc. A61N2005/067.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:29
L4	9020	A61K41/0057.cpc. A61K41/0061.cpc. A61K41/0071.cpc. A61K41/0076.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:30
L5	4946	A61K31/74.cpc. A61K31/745.cpc. A61K31/75.cpc. A61K31/756.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:31
L6	53389	2 3 4 5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:31
L7	88	1 and 6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:32
L8	12	1 and ((method process technique) with	US-PGPUB;	OR	OFF	2018/08/05

		(treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			19:35
L9	11	7 and ((method process technique) with (treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:35
L10	0	8 and ((enhanc$3 improv$3 assist$3) with (body tissue skin) with (penetration) with topical with (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:37
L11	0	8 and ((enhanc$3 improv$3 assist$3) same (body tissue skin) same (penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:38
L12	0	8 and ((enhanc$3 improv$3 assist$3) same (penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:39
L13	0	8 and ((enhanc$3 improv$3 assist$3) same (penetration) same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:39
L14	0	8 and ((penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:39
L15	1	8 not 9	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:40
L16	742	6 and ((method process technique) with (treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT;	OR	OFF	2018/08/05 19:45

			IBM_TDB			
L17	181	16 and ('ALA' "5-aminolevulinic acid")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 19:46
L18	0	17 and (polyethylene near3 barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 19:47
L19	0	17 and (polyethylene with barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 19:48
L20	4	17 and (polyethylene same barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 19:48
L21	4	20 and ((method process technique) with (treat$5 enhanc$3 improv$3 assist$3) with (body tissue skin) with (photodynamic phototherap$5 (photo adj dynamic) (photo adj therap$7)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:48
L22	0	21 and ((enhanc$3 improv$3 assist$3) same (body tissue skin) same (penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:48
L23	0	21 and ((penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 19:48
L24	187	6 and ((enhanc$3 improv$3 assist$3) same (body tissue skin) same (penetration) same topical same (composition agent))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2018/08/05 21:07
L25	66	24 and ('ALA' "5-aminolevulinic acid")	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	ON	2018/08/05 21:08

			JPO; DERWENT; IBM_TDB			
L26	4	25 and (polyethylene same barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:08
L27	23	("0000002" | "20030105163" | "20040157905" | "20090324727" | "20160317831" | "5079262" | "5211938" | "5441531" | "5474528" | "5489279" | "5505726" | "5782895" | "5856566" | "6231593" | "6335465" | "6559183" | "8609073" | "9241957" | "9339540" | "9387341" | "9561276" | "9723991" | "D613872").PN.	US-PGPUB; USPAT	OR	OFF	2018/08/05 21:14
L28	21	27 and ('ALA' "5-aminolevulinic acid")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:17
L29	0	28 and (polyethylene same barrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:17
L30	0	28 and (polyethylene same penetration)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:17
L31	2	28 and (polyethylene same penetrat$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/08/05 21:17

8/ 5/ 2018 9:20:51 PM
C:\ Users\ afarah.USPTO\ Documents\ EAST\ Workspaces\ 15869164.wsp

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	Unassigned
Date Submitted: January 12, 2017				Filing Date	1/12/2018
				First Named Inventor	Scott LUNDAHL
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	1	of	1	Attorney Docket Number	067286-0399

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2017/0106205-A1	04-20-2017	BOYAJIAN ET AL.	
	A2	2017/0157379-A1	06-08-2017	BOYAJIAN ET AL.	
	A3	2017/0216616-A1	08-03-2017	BOYAJIAN ET AL.	
	A4	5,954,703	09-21-1999	GOLUB	
	A5	6,223,071-B1	04-24-2001	LUNDAHL ET AL.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[3] (if known)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A6	WO-2017/066270-A1	04-20-2017	DUSA PHARMACEUTICALS, INC.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A7	GEORGE J. SCHMIEDER DO ET AL., A Multicenter, Randomized, Vehicle-Controlled Phase 2 Study of Blue Light Photodynamic Therapy With Aminolevulinic Acid HCl 20% Topical Solution for the Treatment of Actinic Keratoses on the Upper Extremities: The Effect of Occlusion During the Drug Incubation Period, Journal of Drugs in Dermatology, Volume 11, Issue 12, December 2012, 10 pages	
	A8	Z. APALLA ET AL., Skin Cancer: Preventive Photodynamic Therapy in Patients With Face and Scalp Cancerization. A Randomized Placebo-Controlled Study, British Journal of Dermatology, 2010, 162, pp. 171-175	

Examiner Signature	/AHMED M FARAH/	Date Considered	08/05/2018

4838-7078-9210.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M.F/

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	15/869,164
Date Submitted: April 12, 2018				**Filing Date**	1/12/2018
				First Named Inventor	Scott LUNDAHL
(use as many sheets as necessary)				Art Unit	3769
				Examiner Name	Ahmed M. Farah
Sheet	1	of	2	Attorney Docket Number	067286-0399

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B1	2003/0105163-A1	06-05-2003	KENNEDY ET AL.	
	B2	2004/0157905-A1	08-12-2004	KENNEDY ET AL.	
	B3	2009/0324727-A1	12-31-2009	FOGUET ROCA	
	B4	2016/0317831-A1	11-03-2016	LUNDAHL	
	B5	5,079,262	01-07-1992	KENNEDY ET AL.	
	B6	5,211,938	05-18-1993	KENNEDY ET AL.	
	B7	5,441,531	08-15-1995	ZARATE ET AL.	
	B8	5,474,528	12-12-1995	MESEROL	
	B9	5,489,279	02-06-1996	MESEROL	
	B10	5,505,726	04-09-1996	MESEROL	
	B11	5,782,895	07-21-1998	ZARATE ET AL.	
	B12	5,856,566	01-05-1999	GOLUB	
	B13	6,231,593-B1	05-15-2001	MESEROL	
	B14	6,335,465-B1	01-01-2002	GOLUB	
	B15	6,559,183-B1	05-06-2003	SCHMID ET AL.	
	B16	8,609,073-B2	12-17-2013	LUNDAHL ET AL.	
	B17	9,241,957-B2	01-26-2016	LUNDAHL ET AL.	
	B18	9,339,540-B2	05-17-2016	LUNDAHL	
	B19	9,387,341-B2	07-12-2016	LUNDAHL	
	B20	9,561,276-B2	02-07-2017	LUNDAHL	
	B21	9,723,991-B2	08-08-2017	LUNDAHL ET AL.	
	B22	D 613,872-S	04-13-2010	CAROTA ET AL.	
	B23	D 768,291-S	10-04-2016	CAROTA ET AL.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

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	B24	DAVID M. PARISER, ET AL., Randomized Vehicle-Controlled Study of Short Drug Incubation Aminolevulinic Acid Photodynamic Therapy for Actinic Keratoses of the Face or Scalp, American Society for Dermatologic Surgery, Inc., March 2016, vol. 42(3), pp. 296-304	

Examiner Signature		Date Considered	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M.F/

PTO/SB/08 (modified)

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** Date Submitted: April 12, 2018 *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	15/869,164
				Filing Date	1/12/2018
				First Named Inventor	Scott LUNDAHL
				Art Unit	3769
				Examiner Name	Ahmed M. Farah
Sheet	2	of	2	Attorney Docket Number	067286-0399

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B25	DUSA PHARMACEUTICALS, INC., Levulan PDT Versus Vehicle for Extremity Actinic Keratoses (AK), U.S. National Library of Medicine, ClinicalTrials.gov, First Posted October 25, 2011, Last Update Posted March 14, 2013, 80 pgs.	
	B26	DUSA PHARMACEUTICALS, INC., Maximal Use Systemic Exposure (MUSE) Study of Levulan Kerastick, U.S. National Library of Medicine, ClinicalTrials.gov, First Posted November 3, 2014, Last Update Posted January 13, 2017, 68 pgs.	
	B27	DUSA PHARMACEUTICALS, INC., Maximal Use Systemic Exposure Study of Levulan Kerastick (MUSE 2), U.S. National Library of Medicine, ClinicalTrials.gov, First Posted December 11, 2015, Last Update Posted September 18, 2017, 69 pgs.	
	B28	DUSA PHARMACEUTICALS, INC., Safety and Efficacy Study of Photodynamic Therapy With Levulan Kerastick Blue Light for Actinic Keratoses on the Upper Extremities, U.S. National Library of Medicine, ClinicalTrials.gov, First Posted May 14, 2014, Last Update Posted September 16, 2015, 112 pgs.	
	B29	DUSA PHARMACEUTICALS, INC., Short-Incubation Levulan Photodynamic Therapy Versus Vehicle for Face/Scalp Actinic Keratosis (AK), U.S. National Library of Medicine, ClinicalTrials.gov, First Posted November 22, 2011, Last Update Posted October 28, 2016, 184 pgs.	
	B30	GEORGE J. SCHMIEDER ET AL., A Multicenter, Randomized, Vehicle-Controlled Phase 2 Study of Blue Light Photodynamic Therapy With Aminolevulinic Acid HC1 20% Topical Solution for the Treatment of Actinic Keratoses on the Upper Extremities: The Effect of Occlusion During the Drug Incubation Period, Journal of Drugs in Dermatology, Volume 11, Issue 12, December 2012, pp. 1483-1489	

Examiner Signature	/AHMED M FARAH/	Date Considered	08/05/2018

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M.F/

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	15/869,164
				Filing Date	1/12/2018
Date Submitted: May 10, 2018				**First Named Inventor**	Scott LUNDAHL
				Art Unit	3769
(use as many sheets as necessary)				Examiner Name	Ahmed M. Farah
Sheet	1	of	2	Attorney Docket Number	067286-0399

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document / Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

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	C1	ANTONELLA TOSTI ET AL., Clobetasol Propionate 0.05% Under Occlusion In The Treatment Of Alopecia Totalis/Universalis, J. Am Acad Dermatol, July 2003, Volume 49, Number 1, pp. 96-98.	
	C2	BARRY I. GALITZER, Effect Of Retinoid Pretreatment On Outcomes Of Patients Treated By Photodynamic Therapy For Actinic Keratosis Of The Hand And Forearm, Journal of Drugs in Dermatology, October 2011, Volume 10, Issue 10, pp.1124-1132.	
	C3	EUGENE M. FARBER ET AL., Therapy Of Mycosis Fungoides With Topically Applied Fluocinolone Acetonide Under Occlusive Dressing, Cancer, 1966, Volume 19(2), pp. 237-245.	
	C4	H. MATSUMURA ET AL, Effect Of Occlusion On Human Skin, Contact Dermatitis, 1995, 33, pp. 231-235.	
	C5	HERSCHEL S. ZACKHEIM ET AL., Topical Corticosteroids for Mycosis Fungoides, Experience in 79 Patients, Arch Dermatol, August 1998, Vol. 134, pp. 949-954.	
	C6	LAWRENCE FRANK ET AL., Flurandrenolone And Occlusion In Psoriasis: Prolonged Topical Treatment, Arch Dermatol, March 1964, Vol. 89(3), pp.404-410.	
	C7	LIONEL FRY ET AL., Effect Of Plastic Occlusive Dressings On Psoriatic Epidermis, Br. J. Dermatol, 1970, 82, pp.458-462.	
	C8	MICHAEL DAVID ET AL., Psoriasis Therapy: Comparative Studies With A Hydrocolloid Dressing, Plastic Film Occlusion, And Triamcinolone Acetonide Cream, Journal of the American Academy of Dermatology, 1989, 21, pp. 511-514.	

Examiner Signature		Date Considered	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M.F/

PTO/SB/08 (modified)

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** Date Submitted: May 10, 2018 *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	15/869,164
				Filing Date	1/12/2018
				First Named Inventor	Scott LUNDAHL
				Art Unit	3769
				Examiner Name	Ahmed M. Farah
Sheet	2	of	2	Attorney Docket Number	067286-0399

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	C9	SULZBERGER ET AL., Thin Pliable Plastic Films in Topical Dermatologic Therapy, Arch Dermatol, 1961, 84(6), pp.1027-1028.	
	C10	TAUB ET AL., A Randomized, Blinded, Bilateral Intraindividual, Vehicle-Controlled Trial Of The Use Of Photodynamic Therapy With 5-Aminolevulinic Acid And Blue Light For The Treatment Of Actinic Keratoses Of The Upper Extremities, Journal of Drugs in Dermatology, September 2011, Volume 10, Issue 9, pp.1049-1056.	

Examiner Signature	/AHMED M FARAH/	Date Considered	08/05/2018

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M.F/

UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Aug 7 2018

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Kiri Lee Sharon

S-signature:
/Kiri Lee Sharon/

Registration Number:
71828

U.S. Application Number:
15869164

Confirmation Number:
3488

E-mail Address:
ksharon@foley.com

Phone Number:
2022954092

Proposed Time of Interview:
8-14-2018 11:00 AM ET

Prefered Interview Type:
Telephonic

I am the applicant or applicant's representative for this application.

Topic for Discussion:

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	15/869,164
Date Submitted: May 10, 2018				**Filing Date**	1/12/2018
				First Named Inventor	Scott LUNDAHL
				Art Unit	3769
(use as many sheets as necessary)				Examiner Name	Ahmed M. Farah
Sheet	1	of	2	Attorney Docket Number	067286-0399

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document / Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

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	C1	ANTONELLA TOSTI ET AL., Clobetasol Propionate 0.05% Under Occlusion In The Treatment Of Alopecia Totalis/Universalis, J. Am Acad Dermatol, July 2003, Volume 49, Number 1, pp. 96-98.	
	C2	BARRY I. GALITZER, Effect Of Retinoid Pretreatment On Outcomes Of Patients Treated By Photodynamic Therapy For Actinic Keratosis Of The Hand And Forearm, Journal of Drugs in Dermatology, October 2011, Volume 10, Issue 10, pp.1124-1132.	
	C3	EUGENE M. FARBER ET AL., Therapy Of Mycosis Fungoides With Topically Applied Fluocinolone Acetonide Under Occlusive Dressing, Cancer, 1966, Volume 19(2), pp. 237-245.	
	C4	H. MATSUMURA ET AL, Effect Of Occlusion On Human Skin, Contact Dermatitis, 1995, 33, pp. 231-235.	
	C5	HERSCHEL S. ZACKHEIM ET AL., Topical Corticosteroids for Mycosis Fungoides, Experience in 79 Patients, Arch Dermatol, August 1998, Vol. 134, pp. 949-954.	
	C6	LAWRENCE FRANK ET AL., Flurandrenolone And Occlusion In Psoriasis: Prolonged Topical Treatment, Arch Dermatol, March 1964, Vol. 89(3), pp.404-410.	
	C7	LIONEL FRY ET AL., Effect Of Plastic Occlusive Dressings On Psoriatic Epidermis, Br. J. Dermatol, 1970, 82, pp.458-462.	
	C8	MICHAEL DAVID ET AL., Psoriasis Therapy: Comparative Studies With A Hydrocolloid Dressing, Plastic Film Occlusion, And Triamcinolone Acetonide Cream, Journal of the American Academy of Dermatology, 1989, 21, pp. 511-514.	

Examiner Signature		Date Considered	

Substitute for form 1449/PTO				***Complete if Known***	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	15/869,164
				Filing Date	1/12/2018
Date Submitted: May 10, 2018				**First Named Inventor**	Scott LUNDAHL
				Art Unit	3769
(use as many sheets as necessary)				Examiner Name	Ahmed M. Farah
Sheet	2	of	2	Attorney Docket Number	067286-0399

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	C9	SULZBERGER ET AL., Thin Pliable Plastic Films in Topical Dermatologic Therapy, Arch Dermatol, 1961, 84(6), pp.1027-1028.	
	C10	TAUB ET AL., A Randomized, Blinded, Bilateral Intraindividual, Vehicle-Controlled Trial Of The Use Of Photodynamic Therapy With 5-Aminolevulinic Acid And Blue Light For The Treatment Of Actinic Keratoses Of The Upper Extremities, Journal of Drugs in Dermatology, September 2011, Volume 10, Issue 9, pp.1049-1056.	

Examiner Signature		Date Considered	

Electronic Acknowledgement Receipt

EFS ID:	32591357
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Customer Number:	22428
Filer:	Kiri Lee Sharon/Effie Hale
Filer Authorized By:	Kiri Lee Sharon
Attorney Docket Number:	067286-0399
Receipt Date:	10-MAY-2018
Filing Date:	12-JAN-2018
Time Stamp:	15:37:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDSTrans.pdf	101100 2cb85c2df18e6ecedf9c63f19e02d8dd8a38b6cc	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	IDS_SB08.pdf	95327 1d2f76146ff9a64f1fd3d1d13a8013260ee17233	no	2
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Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	TOSTI.pdf	116735 5c5bad08e3ef88413bb7edccb0b38bbe5f0147b9	no	3
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Information:					
4	Non Patent Literature	GALITZER.pdf	790255 f2a8fb41dbac1462b61e765490329d58795fd156	no	9
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Information:					
5	Non Patent Literature	MATSUMURA.pdf	749332 e9bd4c5ba160e33d0b65defc1fc19fc61c87aaeb	no	5
Warnings:					
Information:					
6	Non Patent Literature	FRANK.pdf	1983195 4cff3cb5eb60351654319549b87aef08262e1bd2	no	7
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Information:					
7	Non Patent Literature	FRY.pdf	341728 c875806da89c4f6f1e7992f7f8d649865c9effb3	no	6
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Information:					
8	Non Patent Literature	DAVID.pdf	1192288 131efee8f99541f5315811de43d61bc0550b3411	no	4
Warnings:					
Information:					

9	Non Patent Literature	TAUB.pdf	666425 bf6694e35e5965bd0d1f8e827ee5c772246c714e	no	8
Warnings:					
Information:					
10	Non Patent Literature	SULZBERGER.pdf	720350 c838e22dc1a659e8bb92f10c422e0a3cf18bb5f0	no	2
Warnings:					
Information:					
11	Non Patent Literature	ZACKHEIM.pdf	5078974 8cdea9afce02f55bb4ec659d1baa146dd1f26afd	no	6
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Information:					
12	Non Patent Literature	FARBER.pdf	4080366 8b87d128001bef8c970ff9780fabfae41b2af868	no	9
Warnings:					
Information:					
			Total Files Size (in bytes):	15916075	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Application No.:	15/869,164
Filing Date:	1/12/2018
Examiner:	Ahmed M. Farah
Art Unit:	3769
Confirmation No.:	3488

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.56

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicant does not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

CONCISE EXPLANATION OF RELEVANCE

The cited documents are in English.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date May 10, 2018

By /Kiri Lee Sharon/

FOLEY & LARDNER LLP
Customer Number: 22428
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Appl. No.:	15/869,164
Filing Date:	1/12/2018
Examiner:	Ahmed M. Farah
Art Unit:	3769
Confirmation No.:	3488

RESPONSE TO RESTRICTION REQUIREMENT

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This communication responds to the requirements for restriction and species election set forth in the Office Action mailed April 3, 2018.

Requirement for Restriction

The Office Action requires election of one of the following groups, as set forth on page 2 of the Office Action:

(1) Group I – claims 1-8 and 16-23, drawn to alternative methods of enhancing penetration of a topical composition into a tissue for photodynamic therapy, classified in A61K41/0061.

(2) Group II – claims 9-15, drawn to a method of photodynamic therapy of a body/skin tissue, classified in A61N 5/062.

Without acquiescing to the propriety of the restriction requirement, Applicant hereby elects Group I, claims 1-8 and 16-23, without traverse.

Requirement for Election of Species

The Office Action requires election of one of the following species, as set forth on page 4 of the Office Action:

(A) Species A – claims directed to a method of enhancing penetration of a topical composition into a tissue, characterized by applying 5-aminolevulinic acid (molecular formula $C_5H_9NO_3$) to a body tissue to be treated, see paras. [0007] and [0010] of the specification.

(B) Species B – claims directed to a method of enhancing penetration of a topical composition into a skin tissue, characterized by applying 5-aminolevulinic acid hydrochloride (molecular formula $C_5H_{10}ClNO_3$) to a body tissue to be treated, see para. [0011] of the specification.

Without acquiescing to the propriety of the requirement for election of species, Applicant hereby elects Species A, claims directed to a method of enhancing penetration of a topical composition into a tissue, characterized by applying 5-aminolevulinic acid (molecular formula $C_5H_9NO_3$), with traverse. At least claims 1-13 and 15-20 encompass the elected species, with at least claims 1, 9 and 16 being generic.

Applicant respectfully traverses the requirement for species election for the following reasons. Applicant submits that the assertion in the Office Action that "[t]here is a search and/or examination burden . . . because at least the following reason(s) apply: the species or groupings of patentably indistinct species require a different field of search (e.g., searching different classes /subclasses or electronic resources, or employing different search strategies or search queries" does not support that there is in fact a serious burden. The Office Action provides no explanation or reasoning about why the species would require a different field of search. Applicant respectfully submits that there would be no serious burden to search both species, at

least because a search for 5-aminolevulinic acid would yield results including 5-aminolevulinic acid hydrochloride. *See* para. [0050] of the specification, showing the structural formula of ALA HCl and describing the hydrochloride salt of aminolevulinic acid as an example of anhydrous ALA. For at least these reasons, Applicant respectfully submits that the requirement for election of species should be withdrawn.

Conclusion

Applicant reserves the right to pursue non-elected subject matter in one or more divisional applications.

Receipt of an Office Action on the merits is awaited.

The Examiner is invited to contact the undersigned if it is believed that a telephone discussion would be helpful to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: April 13, 2018

By /Kiri Lee Sharon/

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Kiri Lee Sharon
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Registration No. 71,828

Electronic Acknowledgement Receipt

EFS ID:	32331814
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Customer Number:	22428
Filer:	Glenn Law/Don Kim
Filer Authorized By:	Glenn Law
Attorney Docket Number:	067286-0399
Receipt Date:	13-APR-2018
Filing Date:	12-JAN-2018
Time Stamp:	11:20:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	Restriction_Response.pdf	117684 84d56a85c8e5de2349de7955d139b7a24fc708bf	no	4

Warnings:

Information:	
Total Files Size (in bytes):	117684

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	15/869,164
Date Submitted: April 12, 2018				**Filing Date**	1/12/2018
				First Named Inventor	Scott LUNDAHL
				Art Unit	3769
(use as many sheets as necessary)				Examiner Name	Ahmed M. Farah
Sheet	1	of	2	Attorney Docket Number	067286-0399

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B1	2003/0105163-A1	06-05-2003	KENNEDY ET AL.	
	B2	2004/0157905-A1	08-12-2004	KENNEDY ET AL.	
	B3	2009/0324727-A1	12-31-2009	FOGUET ROCA	
	B4	2016/0317831-A1	11-03-2016	LUNDAHL	
	B5	5,079,262	01-07-1992	KENNEDY ET AL.	
	B6	5,211,938	05-18-1993	KENNEDY ET AL.	
	B7	5,441,531	08-15-1995	ZARATE ET AL.	
	B8	5,474,528	12-12-1995	MESEROL	
	B9	5,489,279	02-06-1996	MESEROL	
	B10	5,505,726	04-09-1996	MESEROL	
	B11	5,782,895	07-21-1998	ZARATE ET AL.	
	B12	5,856,566	01-05-1999	GOLUB	
	B13	6,231,593-B1	05-15-2001	MESEROL	
	B14	6,335,465-B1	01-01-2002	GOLUB	
	B15	6,559,183-B1	05-06-2003	SCHMID ET AL.	
	B16	8,609,073-B2	12-17-2013	LUNDAHL ET AL.	
	B17	9,241,957-B2	01-26-2016	LUNDAHL ET AL.	
	B18	9,339,540-B2	05-17-2016	LUNDAHL	
	B19	9,387,341-B2	07-12-2016	LUNDAHL	
	B20	9,561,276-B2	02-07-2017	LUNDAHL	
	B21	9,723,991-B2	08-08-2017	LUNDAHL ET AL.	
	B22	D 613,872-S	04-13-2010	CAROTA ET AL.	
	B23	D 768,291-S	10-04-2016	CAROTA ET AL.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B24	DAVID M. PARISER, ET AL., Randomized Vehicle-Controlled Study of Short Drug Incubation Aminolevulinic Acid Photodynamic Therapy for Actinic Keratoses of the Face or Scalp, American Society for Dermatologic Surgery, Inc., March 2016, vol. 42(3), pp. 296-304	

Examiner Signature		Date Considered	

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	15/869,164
Date Submitted: April 12, 2018				**Filing Date**	1/12/2018
				First Named Inventor	Scott LUNDAHL
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Sheet	2	of	2	Attorney Docket Number	067286-0399

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B25	DUSA PHARMACEUTICALS, INC., Levulan PDT Versus Vehicle for Extremity Actinic Keratoses (AK), U.S. National Library of Medicine, ClinicalTrials.gov, First Posted October 25, 2011, Last Update Posted March 14, 2013, 80 pgs.	
	B26	DUSA PHARMACEUTICALS, INC., Maximal Use Systemic Exposure (MUSE) Study of Levulan Kerastick, U.S. National Library of Medicine, ClinicalTrials.gov, First Posted November 3, 2014, Last Update Posted January 13, 2017, 68 pgs.	
	B27	DUSA PHARMACEUTICALS, INC., Maximal Use Systemic Exposure Study of Levulan Kerastick (MUSE 2), U.S. National Library of Medicine, ClinicalTrials.gov, First Posted December 11, 2015, Last Update Posted September 18, 2017, 69 pgs.	
	B28	DUSA PHARMACEUTICALS, INC., Safety and Efficacy Study of Photodynamic Therapy With Levulan Kerastick Blue Light for Actinic Keratoses on the Upper Extremities, U.S. National Library of Medicine, ClinicalTrials.gov, First Posted May 14, 2014, Last Update Posted September 16, 2015, 112 pgs.	
	B29	DUSA PHARMACEUTICALS, INC., Short-Incubation Levulan Photodynamic Therapy Versus Vehicle for Face/Scalp Actinic Keratosis (AK), U.S. National Library of Medicine, ClinicalTrials.gov, First Posted November 22, 2011, Last Update Posted October 28, 2016, 184 pgs.	
	B30	GEORGE J. SCHMIEDER ET AL., A Multicenter, Randomized, Vehicle-Controlled Phase 2 Study of Blue Light Photodynamic Therapy With Aminolevulinic Acid HC1 20% Topical Solution for the Treatment of Actinic Keratoses on the Upper Extremities: The Effect of Occlusion During the Drug Incubation Period, Journal of Drugs in Dermatology, Volume 11, Issue 12, December 2012, pp. 1483-1489	

Examiner Signature		Date Considered	

Electronic Acknowledgement Receipt

EFS ID:	32325945
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Customer Number:	22428
Filer:	Kiri Lee Sharon/Effie Hale
Filer Authorized By:	Kiri Lee Sharon
Attorney Docket Number:	067286-0399
Receipt Date:	12-APR-2018
Filing Date:	12-JAN-2018
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Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	IDS_SB08.pdf	96608 641b10ad441b3b8872fdf0aae1911a7edae40df8	no	2
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This is not an USPTO supplied IDS fillable form					
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8	Non Patent Literature	NPLRef_SafetyEfficacyStudy_CP108.pdf	15151873 84c528409ece6506dd44632301f27c5c83a10de9	no	112
Warnings:					
Information:					

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11	Non Patent Literature	NPLRefShortIncubationCP105_Part3.pdf	7909188 40f9523658fc50a2cc7e70b5cb348aa854be8665	no	20
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Information:					
		Total Files Size (in bytes):	143709557		

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Title:	METHODS FOR PHOTODYNAMIC THERAPY
Application No.:	15/869,164
Filing Date:	1/12/2018
Examiner:	Ahmed M. Farah
Art Unit:	3769
Confirmation No.:	3488

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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CONCISE EXPLANATION OF RELEVANCE

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Respectfully submitted,

Date April 12, 2018

By /Kiri Lee Sharon/

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Kiri Lee Sharon
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Registration No. 71,828

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399	3488

22428 7590 04/03/2018

Foley & Lardner LLP
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SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
FARAH, AHMED M	

ART UNIT	PAPER NUMBER
3769	

NOTIFICATION DATE	DELIVERY MODE
04/03/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@foley.com

Office Action Summary	Application No. 15/869,164	Applicant(s) LUNDAHL ET AL.	
	Examiner AHMED FARAH	Art Unit 3769	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/12/2018*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-23* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-23* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-8 and 16-23, drawn to alternative methods of enhancing penetration of a topical composition into a tissue for photodynamic therapy, classified in A61K 41/0061.

II. Claims 9-15, drawn to a method of photodynamic treatment of a body/skin tissue, classified in A61N 5/062.

The inventions are distinct, each from the other because of the following reasons:

3. Inventions I and II are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct if they do not overlap in scope and are not obvious variants, and if it is shown that at least one subcombination is separately usable. In the instant case, subcombination II has separate utility such as photodynamic treatment of a patient's skin. Furthermore, photodynamic treatment of the skin tissue can be performed without first enhancing penetration of the topical agent into the skin, e.g., by injecting the composition into the skin tissue . See MPEP § 806.05(d).

The examiner has required restriction between subcombinations usable together. Where applicant elects a subcombination and claims thereto are subsequently found allowable, any claim(s) depending from or otherwise requiring all the limitations of the allowable subcombination will be examined for patentability in accordance with 37 CFR

1.104. See MPEP § 821.04(a). Applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

4. Restriction for examination purposes as indicated is proper because all the inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply: the inventions require a different field of search (e.g., searching different classes /subclasses or electronic resources, or employing different search strategies or search queries).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after

the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

5. This application contains claims directed a patentably distinct specie. The invention of Group I contains claims directed to the following patentably distinct species:

- Species A (claims directed to a method of enhancing penetration of a topical composition into tissue characterized by applying 5-aminolevulinic acid (molecular formula $C_5H_9NO_3$) to a body tissue to be treated, see Par. 0007 and 0010 of the specification), and
- Specie B (claims directed to method of enhancing penetration of a topical composition to a skin tissue characterized by applying 5-aminolevulinic acid hydrochloride (molecular formula: $C_5H_{10}ClNO_3$) to a body tissue to be treated, see Par. 0011).

6. The species are independent or distinct because *the claims to the different species recite the mutually exclusive characteristics of such species*. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, no claim is generic.

***Note**: if the applicant elects the invention of Group I, he/she is required to elect one of the species A or B for the prosecution on the merits.*

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply: the species or groupings of patentably indistinct species require a different field of search (e.g., searching different classes /subclasses or electronic resources, or employing different search strategies or search queries).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement

will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AHMED FARAH whose telephone number is (571)272-

4765. The examiner can normally be reached on Mon, Tues, Thurs, and Fr. between 9:30 AM 7:30 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomson William can be reached on (571) 272-3718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AHMED FARAH/
Primary Examiner, Art Unit 3769

March 28, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399	3488

22428 7590 03/20/2018

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	

ART UNIT	PAPER NUMBER
3763	

NOTIFICATION DATE	DELIVERY MODE
03/20/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@foley.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Doc Code:
TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 15/869,164

1. THE REQUEST FILED January 12, 2018 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination**;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

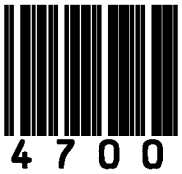
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Cheryl Gibson-Baylor at (571)272-3213, Office of Petitions. In his/her absence, calls may be directed to Brian W. Brown, (571)272-5338.

Cheryl Gibson-Baylor
/Cheryl Gibson-Baylor/
[*Signature*]

Petitions Paralegal Specialist
(Title)

Office of Petitions: Routing Sheet



Application No. 15869164

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [X] **GRANTED**
- [ ] **DISMISSED**
- [ ] **DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month: 3

Application No.: 15869164

15869164

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456
For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: GIBSON-BAYLOR, CHERYL

Count (1) - Palm Credit 15869164

Decision: GRANT

FINANCE WORK NEEDED
☐ Select Check Box for YES

GRANT

Decision Type: 643 - Track One request

643

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on: 3/15/2018

Office of Petitions Internal Document - Ver. 5.0

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/869,164

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	23 minus 20 =	* 3			OR	x 100 =	300
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 460 =	460
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2480

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/869,164	01/12/2018	1629	2420	067286-0399	23	4

CONFIRMATION NO. 3488

UPDATED FILING RECEIPT

22428
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

Date Mailed: 03/06/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Scott LUNDAHL, Lexington, MA;
Michael Guttadauro, Carlisle, MA;

Applicant(s)

DUSA Pharmaceuticals, Inc., Wilmington, MA;

Assignment For Published Patent Application

DUSA Pharmaceuticals, Inc., Wilmington, MA

Power of Attorney: The patent practitioners associated with Customer Number 22428

Domestic Applications for which benefit is claimed - None.
A proper domestic benefit claim must be provided in an Application Data Sheet in order to constitute a claim for domestic benefit. See 37 CFR 1.76 and 1.78.

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 02/05/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/869,164**

Projected Publication Date: 07/18/2019

Non-Publication Request: No

Early Publication Request: No

Title

METHODS FOR PHOTODYNAMIC THERAPY

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Application No.:	15/869,164
Filing Date:	1/12/2018
Examiner:	Unassigned
Art Unit:	1629
Confirmation No.:	3488

TRANSMITTAL OF FEES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant filed a response to Notice To File Corrected Application Papers on February 28, 2018, along with a Declaration. The surcharge for filing of the Declaration was inadvertently omitted. Applicant hereby submits a payment in the amount of $160.00 to cover the fee associated with filing the Declaration by credit card via EFS-Web.

Respectfully submitted,

Date March 1, 2018

By /Kiri Lee Sharon/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5426
Facsimile: (202) 672-5399

Glenn Law
Attorney for Applicant
Registration No. 34,371

Telephone: (202) 295-4092
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Kiri Lee Sharon
Attorney for Applicant
Registration No. 71,828

Electronic Patent Application Fee Transmittal

Application Number:	15869164
Filing Date:	12-Jan-2018
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Filer:	Kiri Lee Sharon/Effie Hale
Attorney Docket Number:	067286-0399

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	160	160
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Electronic Acknowledgement Receipt

EFS ID:	31932009
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Customer Number:	22428
Filer:	Kiri Lee Sharon/Effie Hale
Filer Authorized By:	Kiri Lee Sharon
Attorney Docket Number:	067286-0399
Receipt Date:	01-MAR-2018
Filing Date:	12-JAN-2018
Time Stamp:	13:58:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$160
RAM confirmation Number	030218INTEFSW14001101
Deposit Account	190741
Authorized User	Effie Hale

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	TransmittalDeclFee.pdf	139260 4c67441bad4e145c78f4e889203c76309e1c8dca	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30327 372728eeb42648de4d279ddcdd8ddf70715467a7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	169587		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Application No.:	15/869,164
Filing Date:	1/12/2018
Examiner:	Unassigned
Art Unit:	1629
Confirmation No.:	3488

REPLY TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This communication responds to the Notice to File Corrected Application Papers mailed February 7, 2018, in the above-identified patent application.

Amendments to the Drawings begin on page 2 of this document, and include the attached replacement drawing sheets and annotated sheets showing changes.

Remarks begin on page 3.

Please amend the application as follows:

AMENDMENTS TO THE DRAWINGS

The drawing sheets attached in connection with the above-identified application containing FIGS. 4-8 are being presented as new formal drawing sheets to be substituted for the previously submitted drawing sheets. Appended to this amendment are annotated copies of the previous drawing sheets which have been marked to show changes presented in the replacement sheets of the drawing. The specific changes made to the drawings are as follows. FIGS. 5-8 are amended. FIGS. 5-8, as previously presented, were not in the form of line drawings. These figures have been converted to line drawings, as reflected in the accompanying replacement drawing sheets. No new matter is added.

REMARKS

Favorable consideration of the foregoing amendments to the drawings is respectfully requested.

The Notice to File Corrected Application Papers dated February 7, 2018 states that: "The drawings submitted to the Office are not electronically reproducible because portions of figures 5-8 are missing and/or blurry." In order to resolve the concerns stated in the Notice, the foregoing replacement drawings submitted herewith. The replacement drawing sheets contain FIGS. 5-8 in line drawing form, so as to be readily electronically reproducible. For at least these reasons, Applicant respectfully submits that the figures of the application as amended comply with applicable drawing requirements. No new matter has been added.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date February 26, 2018

By /Kiri Lee Sharon/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5426
Facsimile: (202) 672-5399

Glenn Law
Attorney for Applicant
Registration No. 34,371

Telephone: (202) 295-4092
Facsimile: (202) 672-5399

Kiri Lee Sharon
Attorney for Applicant
Registration No. 71,828

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399

CONFIRMATION NO. 3488

FORMALITIES LETTER

22428
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

OC000000097155773

Date Mailed: 02/07/2018

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings submitted to the Office are not electronically reproducible because portions of figures 5-8 are missing and/or blurry.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **160** surcharge.
- $(0) previous unapplied payment amount.
- $ **160** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Scott LUNDAHL
  Michael Guttadauro

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

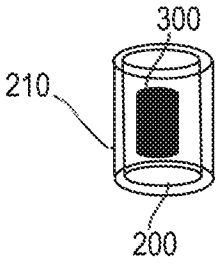
Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mhaile/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210
200

FIG. 4

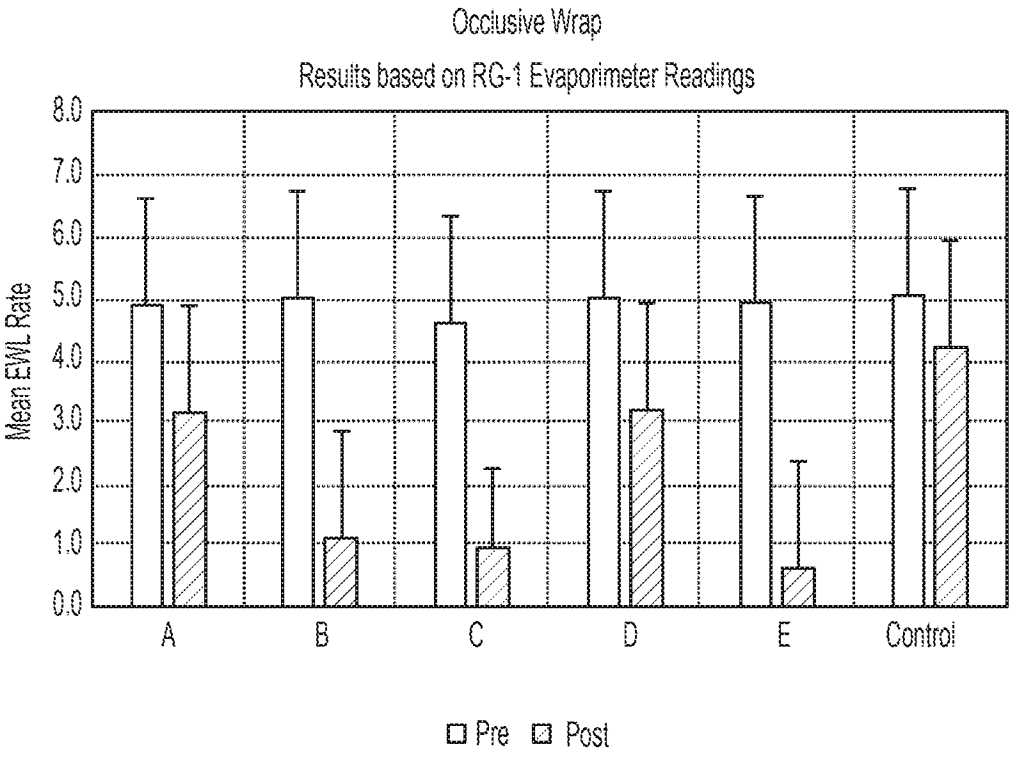
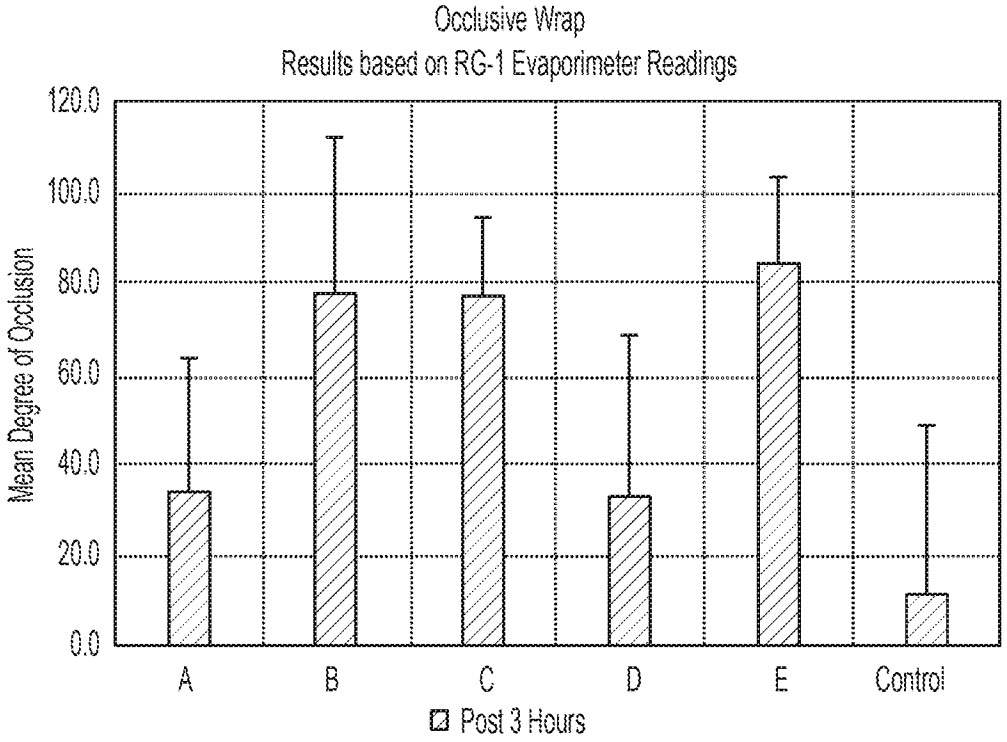

Occlusive Wrap
Results based on RG-1 Evaporimeter Readings
Mean EWL Rate
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
A
B
C
D
E
Control
Pre
Post

FIG. 5


Occlusive Wrap
Results based on RG-1 Evaporimeter Readings
Mean Degree of Occlusion
120.0
100.0
80.0
60.0
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20.0
0.0
A
B
C
D
E
Control
Post 3 Hours

FIG. 6

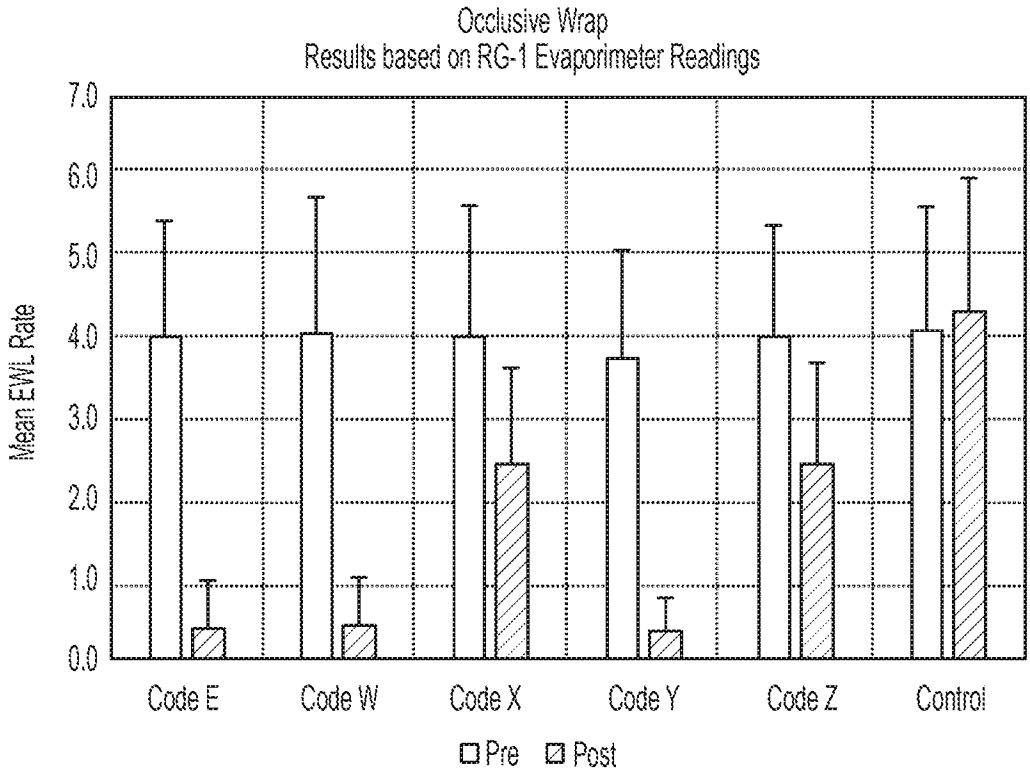

Occlusive Wrap
Results based on RG-1 Evaporimeter Readings
Mean EWL Rate
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Code E
Code W
Code X
Code Y
Code Z
Control
Pre
Post

FIG. 7

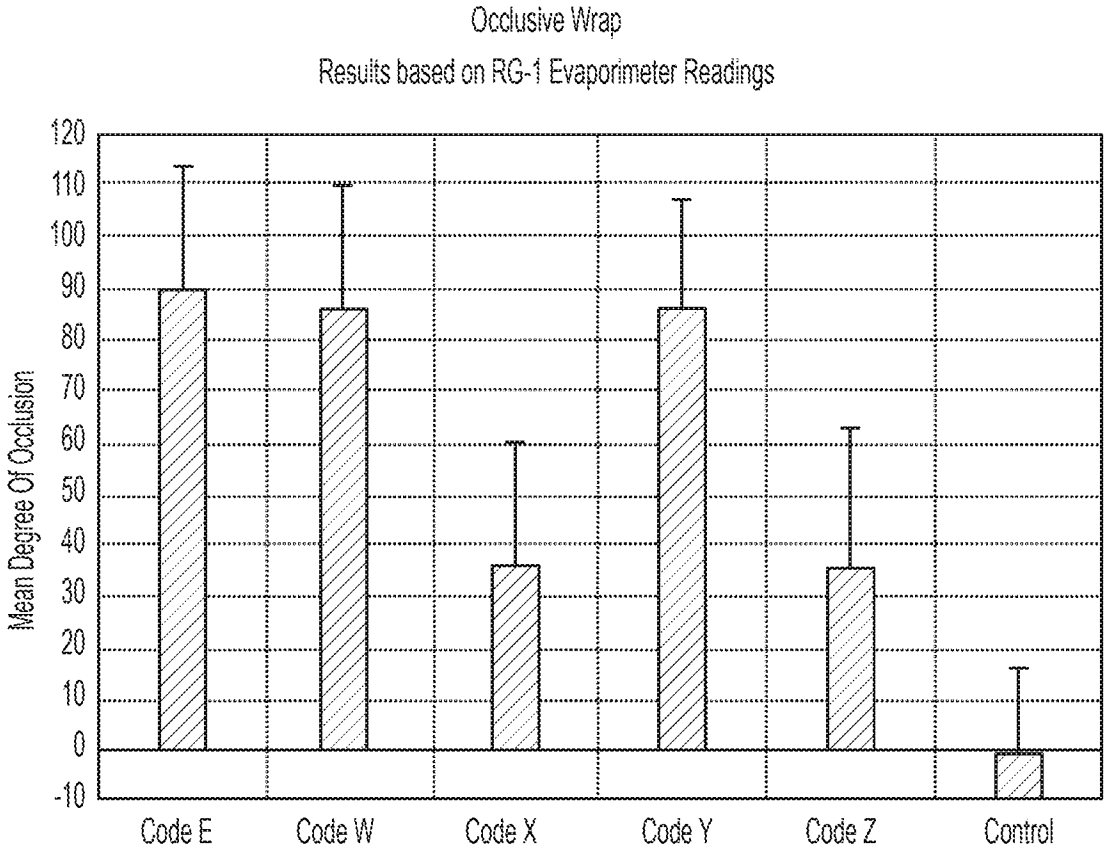

Occlusive Wrap
Results based on RG-1 Evaporimeter Readings
Mean Degree Of Occlusion
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Code E
Code W
Code X
Code Y
Code Z
Control

FIG. 8

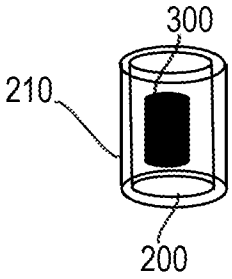
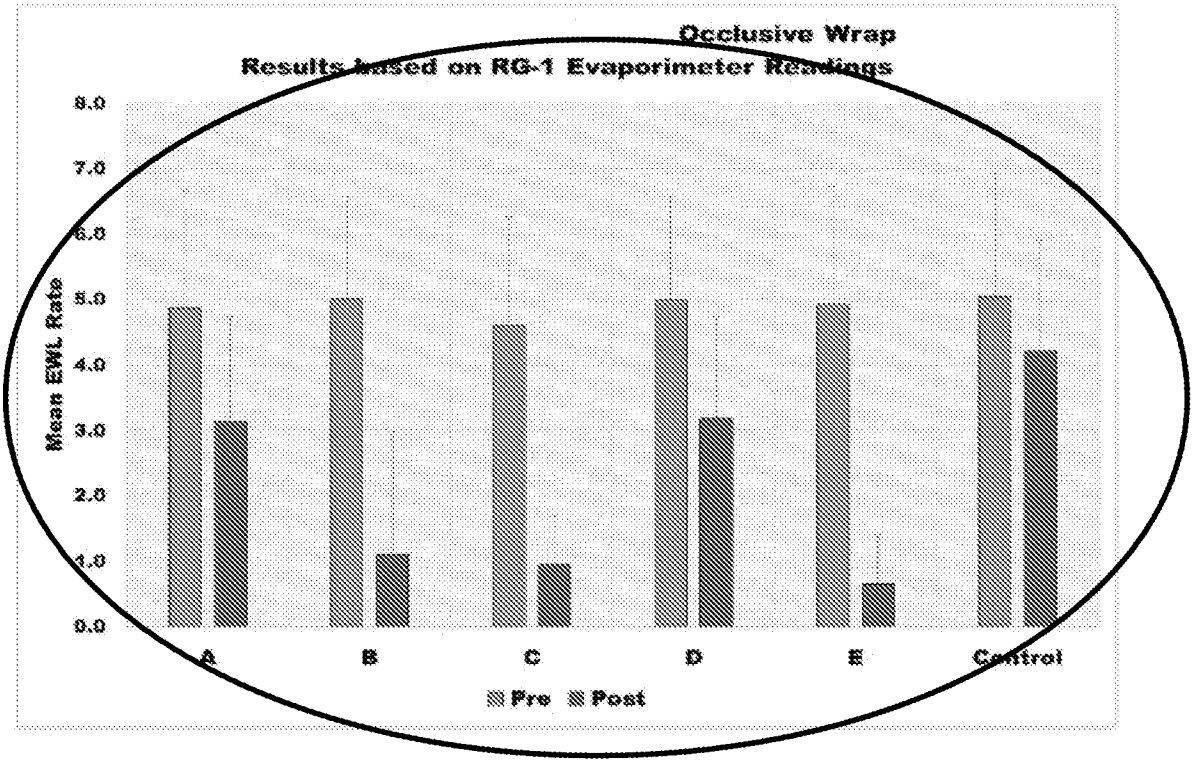


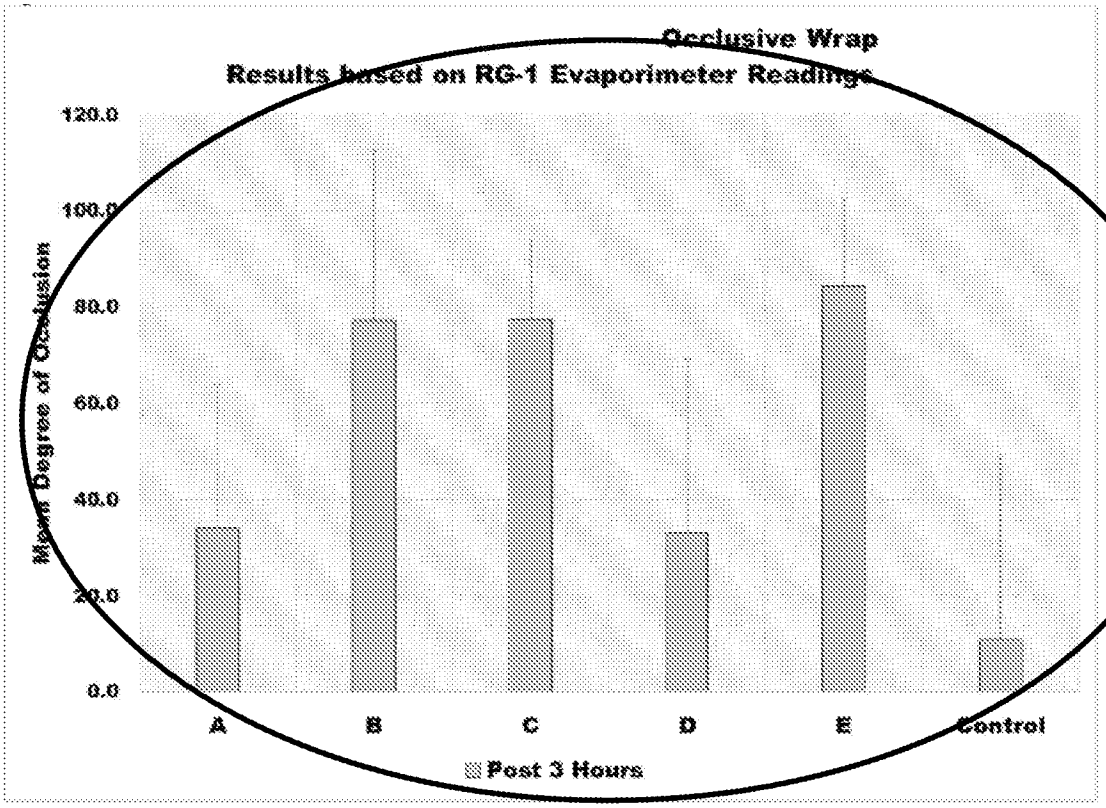
FIG. 4



replaced with line drawing

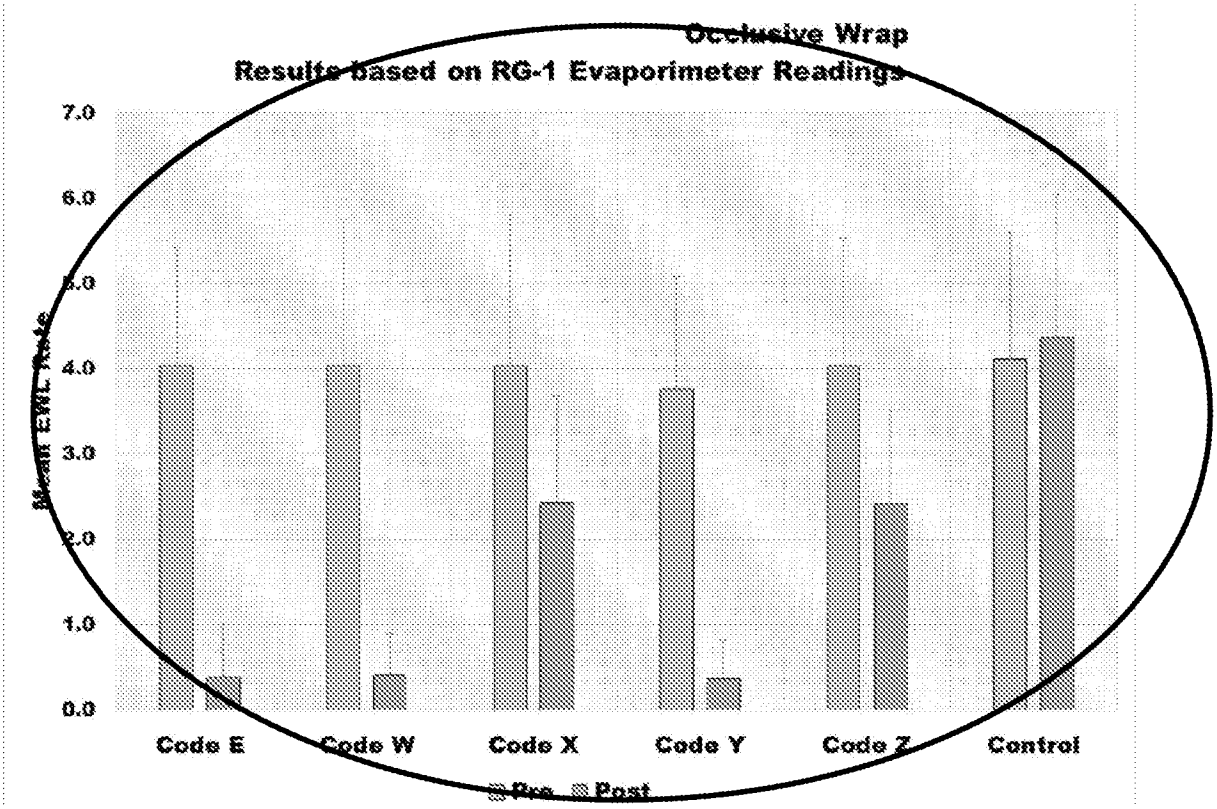
FIG. 5

ANNOTATED SHEET



replaced with line drawing

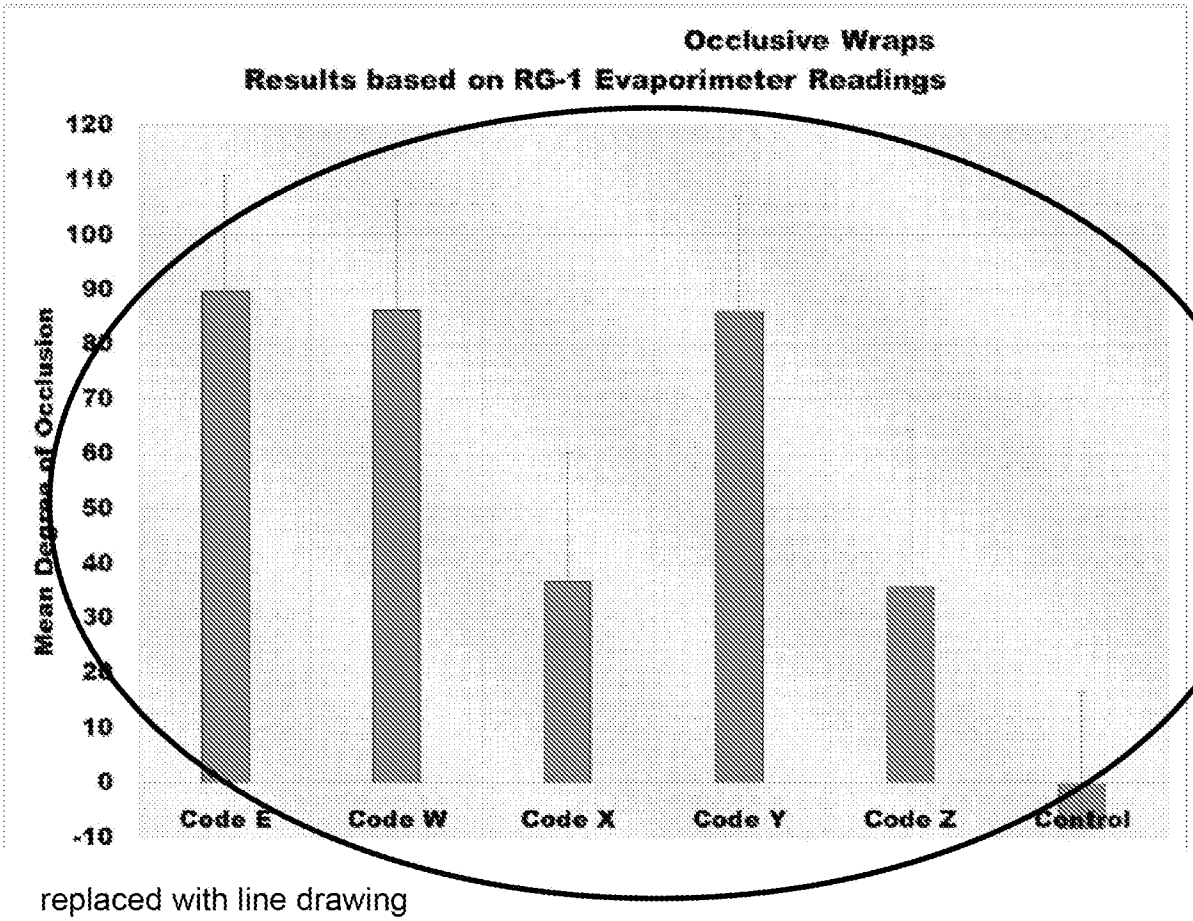
FIG. 6



replaced with line drawing

FIG. 7

ANNOTATED SHEET



replaced with line drawing

FIG. 8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Scott LUNDAHL
Title:	METHODS FOR PHOTODYNAMIC THERAPY
Appl. No.:	15/869,164
Filing Date:	1/12/2018
Examiner:	Unassigned
Art Unit:	1629
Confirmation No.:	3488

TRANSMITTAL OF DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Notice to File Corrected Application Papers mailed February 7, 2018 in the above-identified patent application, transmitted herewith is an executed Declaration (3 pages) regarding the subject patent application.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date February 28, 2018

By /Kiri Lee Sharon/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5426
Facsimile: (202) 672-5399

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Glenn Law
Attorney for Applicant
Registration No. 34,371

Kiri Lee Sharon
Attorney for Applicant
Registration No. 71,828

PTO/AIA/08 (modified)

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) __ Declaration Submitted With Initial Filing OR _X_ Declaration Submitted After Initial Filing (surcharge (37 CFR 1.16(f)) required)		
	Attorney Docket Number	067286-0399
	First Named Inventor	Scott LUNDAHL
	COMPLETE IF KNOWN	
	Application Number	15/869,164
	Filing Date	1/12/2018
	Art Unit	Unassigned
	Examiner Name	Unassigned

METHODS FOR PHOTODYNAMIC THERAPY

(Title of the Invention)

As a below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application,

OR

☒ United States Application Number or PCT International application number 15/869,164 filed on 1/12/2018.

The above-identified application was made or authorized to be made by me.

I believe I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Authorization To Permit Access To Application by Participating Office

☐ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

PTO/AIA/08 (modified)

DECLARATION — Utility or Design Patent Application

Docket Number: 067286-0399 Application No: 15/869,164

Direct all correspondence to:	☒	The address associated with Customer Number:	22428	OR ☐ Correspondence address below
Name				
Address				
City		State		Zip
Country		Telephone		Email

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files* . Documents not retained in an application file (such as the PTO-2038) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: *Deposit Accounts and Electronic Funds Transfer Profiles* .

LEGAL NAME OF SOLE OR FIRST INVENTOR:

(*E.g.*,Given Name (first and middle (if any)) and Family Name or Surname)

Scott LUNDAHL

Inventor's Signature	Scott Lundahl	Date (optional)	1/29/18
Residence: City Lexington	State MA		Country U.S.A.
Mailing Address	c/o DUSA Pharmaceuticals, Inc. 25 Upton Drive		
City Wilmington	State Massachusetts	Zip 01887	Country United States of America

☒ Additional inventors are being named on the 1 supplemental sheet(s) PTO/AIA/10 attached hereto

PTO/AIA/10 (modified)

SUPPLEMENTAL SHEET FOR DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet (for PTO/AIA/08,09) Page 1 of 1

Legal Name of Additional Joint Inventor, if any:			
(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)			
Michael GUTTADAURO			
Inventor's Signature		Date (optional) 1/23/18	
Residence: City Carlisle	State MA	Country U.S.A.	
Mailing Address c/o DUSA Pharmaceuticals, Inc. 25 Upton Drive			
City Wilmington	State Massachusetts	Zip 01887	Country United States of America

Electronic Acknowledgement Receipt

EFS ID:	31914448
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Customer Number:	22428
Filer:	Kiri Lee Sharon/Effie Hale
Filer Authorized By:	Kiri Lee Sharon
Attorney Docket Number:	067286-0399
Receipt Date:	28-FEB-2018
Filing Date:	12-JAN-2018
Time Stamp:	14:30:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	Resp_NFCAP.pdf	890099 bd3404f0390ceb63aaf0ca59c49acc8762c2ed4c	no	5

Warnings:

Information:					
2	Drawings-only black and white line drawings	ReplacementDrwgs.pdf	373067 7c87a2f3f9469c614db05c26d06eff4441a6c465	no	3
Warnings:					
Information:					
3	Drawings-only black and white line drawings	AnnotatedDrwgs.pdf	3264472 162862f255ab0614dbd54ad783042669137f575e	no	3
Warnings:					
Information:					
4	Transmittal Letter	TransmittalDeclaration.pdf	197176 38e1edea6969c83f28abaa64e89eb1da9ba5dd1e	no	2
Warnings:					
Information:					
5	Oath or Declaration filed	Declaration.pdf	4079444 4f7166615ce8d65678b557312a6beae438bac753	no	3
Warnings:					
Information:					
		Total Files Size (in bytes):	8804258		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/869,164	01/12/2018	1629	2260	067286-0399	23	4

CONFIRMATION NO. 3488

FILING RECEIPT

22428
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

OC000000097185772

Date Mailed: 02/07/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Scott LUNDAHL, Lexington, MA;
Michael Guttadauro, Carlisle, MA;

Applicant(s)

DUSA Pharmaceuticals, Inc., Wilmington, MA;

Assignment For Published Patent Application

DUSA Pharmaceuticals, Inc., Wilmington, MA

Power of Attorney: The patent practitioners associated with Customer Number 22428

Domestic Applications for which benefit is claimed - None.
A proper domestic benefit claim must be provided in an Application Data Sheet in order to constitute a claim for domestic benefit. See 37 CFR 1.76 and 1.78.

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 02/05/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/869,164**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

METHODS FOR PHOTODYNAMIC THERAPY

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/869,164

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	23 minus 20 =	* 3			OR	x 100 =	300
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 460 =	460
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2480

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/869,164	01/12/2018	Scott LUNDAHL	067286-0399

CONFIRMATION NO. 3488

22428
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

FORMALITIES LETTER

OC000000097185773

Date Mailed: 02/07/2018

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings submitted to the Office are not electronically reproducible because portions of figures 5-8 are missing and/or blurry.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **160** surcharge.
- $(**0**) previous unapplied payment amount.
- $ **160** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Scott LUNDAHL
  Michael Guttadauro

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mhaile/

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	Unassigned
Filing Date	1/12/2018
First Named Inventor	Scott LUNDAHL
Title	METHODS FOR PHOTODYNAMIC THERAPY
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	067286-0399

SIGNATURE of Applicant or Patent Practitioner

Signature		Date (Optional)	1/12/2018
Name	Glenn Law	Registration Number	34,371
Title (if Applicant is a juristic entity)	Attorney for Applicant		
Applicant Name (if Applicant is a juristic entity)	DUSA PHARMACEUTICALS, INC.		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 22428

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☐ The address associated with the above-mentioned Customer Number

OR

☑ The address associated with Customer Number: 22428

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

DUSA PHARMACEUTICALS, INC.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	
Name	Sean Linehan		
Title	VP, Regulatory Affairs + Intellectual Property		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name: Scott LUNDAHL

Title: METHODS FOR PHOTODYNAMIC THERAPY

Application No.: Unassigned

Filing Date: 1/12/2018

Examiner: Unassigned

Art Unit: Unassigned

Confirmation No.: Unassigned

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith. However, in accordance with MPEP § 609.04(a)(I), Applicant hereby states that for items for which the date of publication supplied

does not include the month of publication, the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), within three (3) months of the filing date of the application.

CONCISE EXPLANATION OF RELEVANCE

The cited documents are in English.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account Number 19-0741.

Respectfully submitted,

Date January 12, 2017

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5426
Facsimile: (202) 672-5399

Glenn Law
Attorney for Applicant
Registration No. 34,371

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
Date Submitted: January 12, 2017				**Filing Date**	1/12/2018
				First Named Inventor	Scott LUNDAHL
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	1	of	1	Attorney Docket Number	067286-0399

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2017/0106205-A1	04-20-2017	BOYAJIAN ET AL.	
	A2	2017/0157379-A1	06-08-2017	BOYAJIAN ET AL.	
	A3	2017/0216616-A1	08-03-2017	BOYAJIAN ET AL.	
	A4	5,954,703	09-21-1999	GOLUB	
	A5	6,223,071-B1	04-24-2001	LUNDAHL ET AL.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[3] (if known)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A6	WO-2017/066270-A1	04-20-2017	DUSA PHARMACEUTICALS, INC.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A7	GEORGE J. SCHMIEDER DO ET AL., A Multicenter, Randomized, Vehicle-Controlled Phase 2 Study of Blue Light Photodynamic Therapy With Aminolevulinic Acid HCl 20% Topical Solution for the Treatment of Actinic Keratoses on the Upper Extremities: The Effect of Occlusion During the Drug Incubation Period, Journal of Drugs in Dermatology, Volume 11, Issue 12, December 2012, 10 pages	
	A8	Z. APALLA ET AL., Skin Cancer: Preventive Photodynamic Therapy in Patients With Face and Scalp Cancerization. A Randomized Placebo-Controlled Study, British Journal of Dermatology, 2010, 162, pp. 171-175	

Examiner Signature		Date Considered	

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 April 2017 (20.04.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/066270 A1

(51) International Patent Classification:
A61N 5/06 (2006.01)

(21) International Application Number:
PCT/US2016/056572

(22) International Filing Date:
12 October 2016 (12.10.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/241,902 15 October 2015 (15.10.2015) US

(71) Applicant: **DUSA PHARMACEUTICALS, INC.** [US/US]; 25 Upton Drive, Wilmington, Massachusetts 01887 (US).

(72) Inventors: **BOYAJIAN, Thomas**; c/o Dusa Pharmaceuticals, Inc., 25 Upton Drive, Wilmington, Massachusetts 01887 (US). **CAROTA, Mark**; c/o Dusa Pharmaceuticals, Inc., 25 Upton Drive, Wilmington, Massachusetts 01887 (US). **MAZEJKA, Brian**; c/o Dusa Pharmaceuticals, Inc., 25 Upton Drive, Wilmington, Massachusetts 01887 (US).

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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, DJ, 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, 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.

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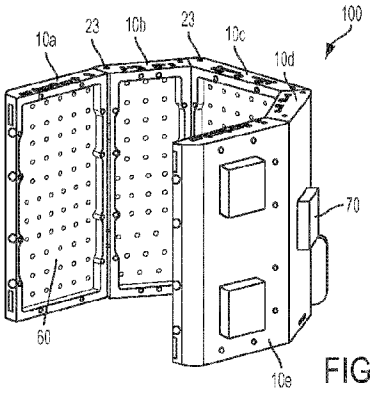


FIG. 2A

(57) Abstract: An adjustable illuminator for photodynamically diagnosing or treating a surface includes a plurality of first panels and at least one second panel. The plurality of first panels have wider widths and the at least one second panel has a narrower width. The narrower width is less than the wider widths. The illuminator further includes a plurality of light sources, each mounted to one of the plurality of first panels or the at least one second panel and configured to irradiate the surface with substantially uniform intensity visible light. The plurality of first panels and the at least one second panel are rotatably connected. The at least one second panel is connected on each side to one of the plurality of first panels. The second panel acts as a "lighted hinge" to reduce or eliminate optical dead spaces between adjacent panels when the illuminator is bent into a certain configuration.

WO 2017/066270 A1

ADJUSTABLE ILLUMINATOR FOR PHOTODYNAMIC THERAPY AND DIAGNOSIS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 62/241,902 filed on October 15, 2015, which is hereby incorporated by reference in its entirety.

FIELD

[0002] The invention relates generally to an adjustable illuminator that provides a uniform distribution of visible light in a number of configurations and is suitable for use in photodynamic therapy and diagnosis.

BACKGROUND

[0003] Photodynamic therapy (PDT), photodynamic diagnosis (PD), or photochemotherapy is generally used to treat and/or diagnose several types of ailments in or near the skin or other tissues, such as those in a body cavity. For example, PDT or PD may be used for treatment or diagnosis of actinic keratosis of the scalp or facial areas of a patient. In addition, PDT and PD may be used for treatment and diagnosis of other indications (e.g., acne, warts, psoriasis, photo-damaged skin, cancer) and other areas of the patient (e.g., arms, legs).

[0004] During one form of PDT or PD, a patient is first administered a photoactivatable agent or a precursor of a photoactivatable agent that accumulates in the tissue to be treated or diagnosed. The area in which the photoactivatable agent is administered is then exposed to visible light, which causes chemical and/or biological changes in the agent. These changes allow the agent to then selectively locate, destroy, or alter the target tissue while, at the same time, causing only mild and reversible damage to other tissues in the treatment area. One example of a precursor of a photoactivatable agent is 5-aminolevulinic acid ("ALA"), which is commonly used in PDT of actinic keratosis. As they are used here, the terms ALA or 5-aminolevulinic acid refer to ALA itself, precursors thereof and pharmaceutically acceptable salts of the same.

[0005] For effective treatment, it is desirable to have a power output that is uniform in intensity and color. Illuminators, such as those disclosed in U.S. Patent Nos. 8,758,418;

8,216,289; 8,030,836; 7,723,910; 7,190,109; 6,709,446; 6,223,071, which are incorporated by reference in their entireties for the techniques, methods, compositions, and devices related to PDT and PD, are typically used to provide the proper uniformity of light for treatment purposes. These devices generally include a light source (e.g., a fluorescent tube), coupling elements that direct, filter or otherwise conduct emitted light so that it arrives at its intended target in a usable form, and a control system that starts and stops the production of light when necessary.

SUMMARY

[0006] Because PDT can be used to treat a variety of treatment areas, some illuminators utilize two or more panels, each panel having a light source to emit light at the intended target area. These panels are coupled together so as to be rotatable relative to each other. By incorporating multiple, rotatable panels, the overall size and shape of the area that is illuminated can be changed according to the intended treatment area.

[0007] In conventional adjustable illuminators, the panels are equally sized by width and length and are typically driven at the same power level. The panels are further joined at their edges by hinges so as to be rotatable to achieve a desired configuration. However, due to the edges of the panels and the presence of the hinges, the light source(s) of one panel does not immediately adjoin the light source(s) of an adjacent panel. As a result, light is not emitted from a "gap" between the light sources. The lack of light emitting from such areas, together with the uniform supply of power to the panels, can cause optical "dead space" in certain portions of the target treatment area. These portions, in turn, receive less overall light, resulting in a lower dose of treatment in those portions. In some instances, the dose of treatment can be lowered by as much as a factor of five when compared with those areas receiving an optimal amount of light.

[0008] Generally, these conventional illuminators are used for phototherapy of acne, which typically does not require the administration of a photoactivatable agent for effective treatment. Thus, exposure to the light alone is generally sufficient treatment. Moreover, because multiple treatment sessions can be utilized to effectively treat the condition, uniformity of light across the target area during a given treatment is less of a concern in some situations. However, some forms of treatment involving PDT, such as the use of ALA to treat actinic keratosis, require specific and highly uniform intensity and color of light to

achieve effectiveness. In these instances, successful PDT relies on the targeted delivery of both the correct quantity of the photoactivatable agent and the correct quantity (i.e., power and wavelength) of light to produce the desired photochemical reactions in the target cells. Thus, to achieve this, the light source must provide illumination to the target area and this illumination must be uniform with respect to both wavelength and power. The optical dead space that can occur at or near the hinges of conventional adjustable illuminators reduces the uniformity of the light along the treatment area, thereby reducing the effectiveness of PDT for these specific treatments. Moreover, these illuminators are also configured to adjust within a limited range, such that only a limited amount of surfaces on a patient's body may be treated, such as a patient's face and scalp. In addition, due to the various contours of a patient's body, the uniformity of light delivered by these conventional illuminators may vary substantially depending on the treatment area of the patient.

[0009] Therefore, it is an object of some embodiments of the present invention to reduce or eliminate these dead spaces and provide for a more uniform light distribution in an adjustable illuminator designed for PDT or PD of a variety of targeted areas. In addition, it is an object of some embodiments of the present invention to provide an infinitely adjustable illuminator that can effectively deliver a uniformity of light across various areas of a patient's body, such as a patient's extremities (e.g., arms and legs) or torso, in addition to a patient's face and scalp. Thus, a uniform light may be delivered to a targeted treatment area regardless of the shape and location of the contoured surface of the patient's body.

[0010] One embodiment of the present invention uses a plurality of panels, wherein at least one panel is of a different width than the other panels. This panel is positioned between two other panels and, in a way, acts as a "lighted hinge" to provide enough "fill-in" light to reduce or eliminate the optical dead spaces when the panels are bent into a certain configuration. Preferably, five panels in total are used to provide for an optimal increase in the total size of possible treatment areas. Two of the panels are preferably of a smaller width than the other three larger panels. These panels are positioned in an alternating manner such that each of the smaller-width panels is situated in between two of the three larger panels to allow for both adjustability and increased uniformity. Furthermore, to further reduce or eliminate optical dead spaces, the panels are preferably coupled together using nested hinges, thereby reducing the area in which no light source is present on the illuminator. In order to even further reduce or eliminate optical dead spaces, it is preferable that the light sources on

each of the panels are individually configurable to provide specific power output to certain areas of the light sources on the panels to compensate for decreased uniformity. For example, the power outputted to each individual diode in an array of light emitting diodes (LED) may be individually adjusted.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Features, aspects, and advantages of the present invention will become apparent from the following description and the accompanying exemplary embodiments shown in the drawings, which are briefly described below.

[0012] FIGS. 1A-1B show top views of a main body of an illuminator according to an exemplary embodiment.

[0013] FIGS. 2A-2B show perspective views of the main body of the illuminator of FIGS. 1A-1B.

[0014] FIGS. 3A-3B show detailed views of the nested hinges of the main body of the illuminator of FIGS. 1A-1B.

[0015] FIG. 4 shows a perspective view of the illuminator having the main body of FIGS. 1A-1B mounted to a stand.

[0016] FIG. 5 shows a schematic view illustrating an addressable configuration of LEDs mounted on the main body of the illuminator of FIGS. 1A-1B.

[0017] FIG. 6 shows a schematic view illustrating widths and lengths of individual panels of the main body of the illuminator of FIGS. 1A-1B.

[0018] FIG. 7 shows a graph illustrating light dosage across a treatment area according to a conventional paneled illuminator.

[0019] FIG. 8 shows a graph illustrating light dosage across the same treatment area as FIG. 7 using an illuminator according to one embodiment of the present invention.

DETAILED DESCRIPTION

[0020] FIGS. 1A-1B and 2A-2B illustrate one embodiment of a configurable illuminator according to the present invention. The illuminator includes a main body 100, which

preferably has five individual panels 10a-10e, each of which are connected in a rotatable manner via nested hinges 50. Each panel contains an array of light emitting diodes (LED) 60, which may be configured in an evenly spaced pattern across the face of the panel. The number of individual LEDs arranged in a given array is not particularly limited. Alternatively, other types of light sources may be used, such as fluorescent or halogen lamps.

[0021] Preferably, each LED array 60 extends as far to the edges as possible. In addition, the LED arrays 60 are preferably dimensioned to provide an overall lighted area for a given treatment area based on a range from the 5th percentile of corresponding female sizes to the 95th percentile of corresponding male sizes for that particular treatment area. The LED arrays 60 emit light at an appropriate wavelength according to the intended treatment or to activate the particular photoactivatable agent used in treatment or diagnosis. For example, when ALA is used as a precursor of a photoactivatable agent for the treatment of actinic keratosis, the LED arrays 60 preferably emit blue light having wavelengths at or above 400 nanometers (nm), for example, about 430 nm, about 420 nm or, for example, 417 nm. However, the LED arrays 60 may also emit visible light in other ranges of the spectrum, such as in the green and/or red ranges between 400 and 700 nm, for example, about 625 nm to 640 nm or, for example, 635 nm. For example, the LED arrays 60 may also emit light having wavelengths of 510 nm, 540 nm, 575 nm, 630 nm, or 635 nm. In addition, the LED arrays 60 may be configured to emit light continuously or the LED arrays 60 may be configured to flash the diodes on and off based on a predetermined interval. Furthermore, the LED arrays 60 may be configured such that only one wavelength of light (e.g., blue) is emitted. Alternatively, the LED arrays 60 may be configured such that two or more wavelengths of light are emitted from the arrays. For example, the LED arrays 60 may be configured to alternately emit blue light and red light for treatment purposes.

[0022] As shown in FIGS. 1A-1B and 2A-2B, the five panels 10a-10e are of different widths relative to one another. In particular, in certain embodiments, three panels 10a, 10c, 10e are configured to have wider widths, while two panels 10b, 10d have smaller, narrower widths, each of the narrower widths of the two panels 10b, 10d being less than each of the wider widths of the three panels 10a, 10c, 10e. In some embodiments, the wider widths of the three larger panels 10a, 10c, 10e are approximately equal. In other embodiments, the wider widths of the three larger panels 10a, 10c, 10e are different relative to one another. In addition, the narrower widths of the two panels 10b, 10d may be approximately equal or may

be different relative to one another. The panels are further arranged in an alternating configuration, with the narrower panels (e.g., 10b) positioned in between two wider panels (e.g., 10a, 10c). As shown in FIG. 6, in some embodiments, the narrower panels 10b, 10d are configured to have a width that is about 30% to 60% less than the width of the wider panels 10a, 10c, 10e. In other embodiments, the narrower panels 10b, 10d are configured to have a width that is about 30% to 50% less than the width of the wider panels 10a, 10c, 10e.

[0023] As shown in FIGS. 1A-1B and 2A-2B, the panels 10a-10e are rotatably connected by hinges 50. The hinges 50 may take the form of nested hinges, which may include hinges that substantially reduce or eliminate optical dead spaces. As shown in FIGS. 2A-2B, on at least one side of a panel, a tab 23 may extend out from both the top and bottom of the panel. The tabs 23 are configured such that a side of an adjacent panel may be received between the tabs 23, as shown in FIG. 2A. Thus, as best seen in FIGS. 2A-2B and 6, the height of the adjacent panel (e.g., panel 10a) is slightly smaller than the height of the tabbed panel (e.g., panel 10b) into which the adjacent panel is received. As shown in FIG. 6, the middle panel (i.e., panel 10c) is preferably configured as having the largest height, such that it is tabbed on both sides and may receive the sides of adjacent panels on each side. As seen in FIGS. 1A-1B, each of the tabs 23 further includes an opening to receive a bolt to connect adjacent panels together.

[0024] As shown in further detail in FIGS. 3A-3B, between the tabs 23 are the nested hinges 50, which are mounted to the inner side surfaces of adjacent panels (e.g., 10a, 10b) to allow for rotation of the panels. A flange 51 of the hinge 50 is mounted to the inner side surface of a panel via bolts 53. The inner side surface of a panel may include a recess in which the flange 51 may be placed. The inner side surface of the panel may also include an additional recess to accommodate the joint of the hinge 50 such that the joint of the hinge 50 becomes substantially flush with an outer front surface of the panel. Such configurations may allow for the outside vertical edges of adjoining panels to be positioned closer to one another. By spacing the vertical edges of adjoining panels closer, optical dead spaces may be further reduced or eliminated. In addition, the hinges 50 together with the tabs 23 may reduce the number of pinch points present in the system.

[0025] As shown in FIGS. 1A-1B, the main body 100 of the illuminator may include a mounting head 40. The mounting head 40 may allow for the main body 100 to be mounted to a movable stand 80, which is shown in FIG. 4, to allow a user to easily move the main body

100 to the appropriate treatment position. The stand 80 includes a base 81 and a vertical pillar 82. The base 81 may further include wheels 87 at its bottom in order to allow the user to horizontally move the illuminator to an appropriate position. The wheels 87 may include locks, such that the stand 80 is prevented from further horizontal movement once positioned. In addition, the vertical pillar 82 may be attached to the base 81 at a pivot point 83. The pivot point 83 allows the vertical pillar 82 to be rotated to increase the range of positioning for the illuminator. At a top end, the vertical pillar 82 includes a connecting arm 85, which may serve as a mounting structure for the main body 100. The connecting arm 85 includes a hinge point 86 such that the main body 100 can be moved vertically relative to the stand 80. The vertical pillar 82 may also be configured as a telescopic structure, such that the user can change the height of the vertical pillar 82. This allows for an increased range of vertical movement for the main body 100, which can allow the user to position the main body 100 at lower portions of a treatment area, such as a patient's legs or feet. The stand 80 may also include a stabilization arm 84. Once the stand 80 and main body 100 is positioned, the stabilization arm 84 may be attached to the main body 100 to prevent unwanted movement of the main body 100 during treatment. As further shown in FIG. 4, a controller and power supply 90 is mounted to the stand 80 in order to supply electrical power to the main body 100 and allow the user to control the main body 100 for treatment purposes. Alternatively, the controller and power supply 90 may be directly mounted to the main body 100. In order to provide a cooling system for the LED arrays 60, one or more fans 70 may be mounted onto each of the panels, as shown in FIG. 4.

[0026] At least one control unit is also connected to the panels to regulate power to the lights to achieve the required uniformity and intensity for the target treatment. The control unit may be implemented as hardware, software, or a combination of both, such as a memory device storing a computer program and a processor to execute the program. Alternatively, each panel may have a dedicated control unit to regulate power to the individual LED array on a given panel to allow for more particular fine-tuning of the illuminator, which may further enhance uniformity and increase efficiency. For example, under Lambert's cosine law, light intensity at a given point on a "Lambertian" surface (such as skin) is directly proportional to the cosine of the angle between the incoming ray of light and the normal to the surface. Thus, a ray of light that is directed to the front of a curved surface (e.g., a head of a patient) will arrive in a substantially perpendicular manner to that area and will result in 100% absorbance. However, a ray of light that arrives at a side edge of the curved surface

will arrive in a substantially parallel manner. According to Lambert's cosine law, the intensity, and thus absorption, of the light at the side edge will approach zero, making treatment at that area ineffective. Thus, a "fall off" of light exposure tends to occur at the edges of a curved surface. In addition, "fall off" increases as the distance between the light source and the point on the surface increases.

[0027] Configuring an illuminator to conform to the curved surface (e.g., a U-shaped configuration designed to "wrap around" the curvature of the surface) aids in reducing this effect and increases overall uniformity. However, to sufficiently increase uniformity, the light source should be larger relative to the target treatment area in order to fully encompass the body part to be treated and also provide light from all angles to any target point on the treatment area. In order to increase the uniformity of light exposure to the treatment area while maintaining a practical size of the illuminator, the LED arrays 60 may be individually configured to increase the intensity of light emitting from certain diodes to compensate for this fall-off effect.

[0028] An example in which the LED arrays 60 may be individually configured is shown in FIG. 5. Here, the LED arrays 60 are divided into three general areas, which may be described as "addressable strings." Areas 1, 3, and 5 correspond to an addressable string configuration that may be included in the wider panels 10a, 10c, and 10e, while areas 2, 4, and 6 correspond to an addressable string configuration that may be included in the narrower panels 10b and 10d. The current to each area is adjusted in order to adjust the intensity of light emitting from each of the areas. For example, a higher current may be supplied to areas 1 and 2 than the current supplied to areas 3 and 4 such that areas 1 and 2 emit a higher intensity of light than areas 3 and 4. Similarly, a higher current may be supplied to areas 3 and 4 than the current supplied to areas 5 and 6. Thus, a higher intensity of light is emitted overall from the edges, which may allow for a reduction in any fall-off effect. Alternatively, the illuminator may be configured to adjust each individual diode present in a given LED array 60, allowing for an even greater fine-tuning effect. Furthermore, by using either pre-programmed settings or sensors to detect the curvature of the surface to be treated, the LED arrays 60 can be individually configured to emit more intense light to only those areas that require it. This allows for an increase in uniformity of light exposure in an efficient manner as power output and/or light intensity is increased to only certain diodes, in accordance with need.

[0029] The addressable strings of the LED arrays 60 may also include varying amounts of individual diodes mounted within the particular area. For example, for the wider panels 10a, 10c, and 10e, 12 diodes may be mounted in each of areas 1, while 9 diodes may be mounted in each of areas 3 and 41 diodes may be mounted in area 5, resulting in a total of 83 individual diodes included within each of the wider panels 10a, 10c, and 10e. For the narrower panels 10b and 10d, 8 diodes may be mounted in each of areas 2, while 9 diodes may be mounted in each of areas 4, and 23 diodes may be mounted in area 6, resulting in a total of 57 individual diodes included within each of the narrower panels 10b and 10d. However, the number and arrangement of diodes included within each of the LED arrays 60 is not particularly limited. For example, the wider panels 10a, 10c, and 10e may each contain a total amount of diodes that ranges from about 80 diodes to about 350 diodes. Similarly, the narrower panels 10b and 10d may each contain a total amount of diodes that ranges from about 50 diodes to about 250 diodes. By varying the arrangement of the diodes within each of the addressable strings of the LED arrays 60, power output and/or the intensity of light emitted from a given array may be better controlled and fine-tuned.

[0030] In addition, individually regulating power to the LED arrays 60 can also contribute to the reduction or elimination of the optical dead spaces that may otherwise occur at the hinge points. Specifically, power output and/or the emitted light intensity may be increased close to the edges of the array that are closest to the nested hinges to compensate for the lack of light emitting from the meeting point of panels. The narrower panels 10b, 10d are also preferably operated at a higher power level and/or at a higher emitted light intensity compared to the wider panels 10a, 10c, 10e in order to provide additional fill-in light. Furthermore, individual power regulation may aid in compensating for manufacturing variance that can occur in individual diodes. Finally, by fine-tuning each array 60, the panels can be easily deployed for other applications as each array is specifically configurable to address the lighting needs of the specific application.

[0031] The illuminator may further include a timer, which can indicate to the user the appropriate length of exposure time for the particular treatment. The illuminator may also be programmed with pre-stored light dosing parameters to allow the user to select a desired treatment type. The pre-stored parameters may include, for example, pre-stored settings for exposure time, light intensity, and outputted wavelength. Based on the selected treatment, the illuminator is automatically configured to provide the correct lighting dosage by being

supplied with the appropriate power output to achieve the required uniformity for the treatment. Alternatively, the illuminator can be provided with sensors that detect the size of the treatment area positioned in front of the illuminator. The sensors then determine the correct light dosing parameters based on the sensed treatment area. The illuminator may also further include actuators and may be programmed to be moved automatically depending on the selected treatment. Once a treatment is selected, the illuminator may be automatically positioned into the proper configuration by the actuators without requiring the user to move the system by hand. Alternatively, the sensors may detect the adjusted position of the illuminator manually set by the user. The detected position of the illuminator may then be used to indicate the intended treatment area. Correct light dosing parameters for the specific treatment area may then be provided based on the detected position set by the user.

[0032] The adjustable illuminator of the present invention allows for an infinite amount of configurations that can be adapted for the targeted treatment area. The configurations may range from a flat-plane emitter (as shown in FIGS. 1B and 2B) to a substantially U-shaped configuration (as shown in FIGS. 1A and 2A). The adjustable illuminator may also be configured such that the two end panels 10a, 10e can be pulled back relative to the three middle panels 10b, 10c, 10d, such that a smaller U-shaped configuration may be created by the middle panels. Thus, the adjustable illuminator allows for the treatment of additional areas of a patient's body. In other words, not only can the adjustable illuminator effectively deliver a uniform light intensity to traditional surfaces such as the face or scalp, but the adjustable illuminator can also provide a device that can easily be configured to treat other portions of a patient's body, in particular, those having smaller curved surfaces, such as the arms and legs. Moreover, the adjustable illuminator may also be easily positioned to deliver a uniform light intensity to larger treatment areas, such as the back or chest.

[0033] As described above, the narrower panels 10b, 10d are dimensioned such that the panels act as "lighted hinges." Thus, when the wider panels 10a, 10c, 10e are adjusted into the desired form, the illuminator "bends" at the narrower panels 10b, 10d, where traditionally the "bend" would occur substantially at the hinge itself. Thus, instead of an unlighted "bent" portion as would occur in the conventional illuminator, the present illuminator provides a "bent" portion that is also configured to emit light, thereby helping to reduce optical dead space without requiring large amounts of power differentiation among the light sources of each panel to provide the required fill-in light. The effects of this configuration can be best

seen in a comparison of FIGS. 7 and 8. FIG. 7 illustrates the light uniformity produced by a conventional illuminator, measured with a cosine response detector, which mimics the response of a patient's skin to the incident of light as described above, at a distance of two inches. Total light dose, in terms of J/cm^2, was measured based on emitted irradiance (W/cm^2) over time (in seconds). The targeted treatment area shown is a patient's head, where height is shown as the y-axis and rotation angle from the center of the emitting surface is shown as the x-axis. As can be seen in FIG. 7, higher light doses of about 10 J/cm^2 occur at the center of the face (for example, at region A), near the patient's nose, where the patient is facing closest to, and substantially perpendicular to, the middle-most panel. Total light dose then begins to drop as movement away from the center of the face occurs where the effects of cosine "fall-off" and optical dead spaces are more prevalent. For example, light dose is reduced by about 20% at the patient's cheek areas (for example, at region B), and by about 80% toward the outer boundaries of the patient's face (for example, at region E), such as the ears and forehead. Thus, as shown in FIG. 7, conventional adjustable illuminators utilizing equally-sized panels operating at the same power output level produce a varying field of light uniformity, making it undesirable and ineffective for those treatments requiring highly specific light uniformity.

[0034] FIG. 8, on the other hand, illustrates the light uniformity produced by an embodiment of the present invention. The targeted treatment area is the same as that measured in FIG. 7. However, compared to FIG. 7, the light output uniformity produced by the illuminator is greatly enhanced across the patient's face and exhibits little to no deviation from the light output measured in the center of the patient's face to the light output measured at the edges of the patient's face. For example, as shown in FIG. 8, total light doses of about 10 J/cm^2 (for example, at region A') occur across all regions of the face, including the center of the face (for example, the patient's nose), the patient's check areas, and the outer boundaries of the patient's cheek areas, such as the ears and forehead. Moreover, total light dose drops off minimally (for example, at region B') at the extreme outer boundaries of the patient's face. In one embodiment, the measured output over the active emitting area (over the entire active emitting area) is within 60% of the measured maximum (over the entire active emitting area) measured with a cosine response detector over all operation distances. More preferably, the measured output over the emitting area is within 70% of the measured maximum over a distance of two and four inches. Even more preferably, the measured

output over the emitting area is within 80% of the measured maximum over a distance of two and four inches.

[0035] One example of a treatment method for precancerous lesions, such as actinic keratosis, by PDT utilizing an adjustable illuminator described above in conjunction with ALA will now be described.

[0036] Essentially anhydrous ALA is admixed with a liquid diluent just prior to its use. The ALA admixture is topically applied to the lesions using a point applicator to control dispersion of the ALA admixture. After the initial application of the ALA admixture has dried, one or more subsequent applications may be similarly applied. Approximately 2 mg/cm^2 of ALA is administered. Formation of photosensitive porphyrin and photosensitization of the treated lesions occurs over the next 14-18 hours, during which time exposure to direct sunlight or other bright light sources should be minimized. Between 14 and 18 hours after administration of the ALA, the lesions are irradiated by the adjustable illuminator according to the present invention. The illuminator irradiates the lesions with a uniform blue light for a prescribed period. According to a preferred treatment, the visible light has a nominal wavelength of 417 nm. The illuminator may irradiate the lesions with a uniform red light for a prescribed period. In certain embodiments, the illuminator irradiates the lesions with a uniform blue light for a first prescribed period and then irradiates the lesions with a uniform red light for a second prescribed period. For example, in some embodiments, the illuminator is configured to irradiate the lesions with a uniform blue light (e.g., 417 nm) at a low intensity (e.g., about 0.1 J/cm^2 to about 2 J/cm^2) to photobleach, for example, protoporphyrin IX (PpIX) present at the surface of the patient's skin, and irradiate the lesions with a uniform red light (e.g., 635 nm) at a high intensity (e.g., about 30 J/cm^2 to about 150 J/cm^2) to activate PpIX present at deeper layers of the patient's skin, thus avoiding potential damage to the upper layers of the patient's skin. The illuminator may be configured to simultaneously irradiate the patient's skin with the low intensity blue light and the high intensity red light or sequentially irradiate the patient's skin with the low intensity blue light and the high intensity red light. In certain embodiments, the illuminator is configured to irradiate the patient's skin with the low intensity blue light for about one hour to about three hours and irradiate the patient's skin with the high intensity red light for about 20 minutes to about 30 or 40 minutes, either at the same time the patient's skin is irradiated with the low

intensity blue light or after the patient's skin has been irradiated with the low intensity blue light.

[0037] The invention thus provides a method for photodynamically diagnosing or treating a contoured surface of a patient, which includes providing the adjustable illuminator described above, placing the patient in the illuminator, and illuminating the patient to diagnose or treat the patient. The patient may be illuminated to treat actinic keratosis, acne, photo-damaged skin, cancer, warts, psoriasis, or other dermatological conditions. The method may also be used to remove hair and diagnose cancer.

[0038] Since the total light dose (J/cm^2) is equal to irradiance (W/cm^2) multiplied by time (sec), the only additional parameter that needs to be controlled for delivery of the correct treatment light dose is exposure time. This may be accomplished by the timer described above, which can control the electrical power supplied to the LED arrays 60 appropriately, and which can be set by the physician. Data has shown that 10 J/cm^2 delivered from a source with an irradiance density of 10 mW/cm^2, or an irradiance density of about 9.3 to about 10.7 mW/cm^2, produces clinically acceptable results for desired treatment areas (e.g., face, scalp, extremities). From the equation above, this light dose will require an exposure time of 1000 seconds (16 min. 40 sec). In addition, due to the addressable nature of the adjustable illuminator, the illuminator may be used to treat a patient at higher power such that less time is required for effective treatment. For example, the adjustable illuminator may deliver an irradiance density of 20 mW/cm^2 for an exposure time of 500 seconds (8 min. 20 sec) to deliver a clinically acceptable light dose of 10 J/cm^2. Alternatively, the adjustable illuminator may include higher power ranges, such as 30 mW/cm^2, over an exposure time resulting in a light dose of 10 J/cm^2. A selected light dose may also be administered by additionally or alternatively varying the irradiance density over treatment time.

[0039] Additional advantages and modifications will readily occur to those skilled in the art. Therefore, the invention in its broader aspects is not limited to the specific details and representative devices and methods, shown and described herein. Accordingly, various modifications may be made without departing from the spirit and scope of the general inventive concept as defined by the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. An adjustable illuminator for photodynamically diagnosing or treating a surface, comprising:

a plurality of first panels, the plurality of first panels having wider widths;

at least one second panel, the at least one second panel having narrower width, wherein the narrower width is less than each of the wider widths of the plurality of first panels; and

a plurality of light sources, each mounted to one of the plurality of first panels or the at least one second panel, the plurality of light sources configured to irradiate the surface with substantially uniform intensity visible light;

wherein the plurality of first panels and the at least one second panel are rotatably connected, and

wherein the at least one second panel is connected on each side to one of the plurality of first panels.

2. The adjustable illuminator of claim 1, wherein the narrower width of the at least one second panel is about 30% to 60% less than the wider widths of the plurality of first panels.

3. The adjustable illuminator of claim 1, wherein the wider widths of the plurality of first panels are approximately equal.

4. The adjustable illuminator of claim 1, wherein the plurality of light sources are light-emitting diodes.

5. The adjustable illuminator of claim 1, wherein the plurality of light sources are configured to emit light having a wavelength from 400 nanometers to 430 nanometers.

6. The adjustable illuminator of claim 5, wherein the plurality of light sources are configured to emit light having a wavelength of 417 nanometers.

7. The adjustable illuminator of claim 1, wherein the plurality of light sources are configured to emit light having a wavelength of 625 nanometers to 640 nanometers.

8. The adjustable illuminator of claim 7, wherein the plurality of light sources are configured to emit light having a wavelength of 635 nanometers.

9. The adjustable illuminator of claim 5, wherein the plurality of light sources are further configured to emit light having a wavelength of 625 nanometers to 640 nanometers.

10. The adjustable illuminator of claim 4, wherein each of the plurality of first panels includes a light source having about 80 to about 350 individual light-emitting diodes, and wherein the at least one second panel includes a light source having about 50 to about 250 individual light-emitting diodes.

11. The adjustable illuminator of claim 1, wherein the plurality of first panels and the at least one second panel are connected by nested hinges configured to reduce optical dead space.

12. The adjustable illuminator of claim 11, wherein the nested hinges are mounted to inner side surfaces of adjacent panels.

13. The adjustable illuminator of claim 12, wherein at least one of the plurality of first panels and the at least one second panel includes tabs outwardly extending from a top side and a bottom side, the tabs being configured to receive an adjacent panel therein.

14. The adjustable illuminator of claim 1, wherein a power output to a light source of the at least one second panel is greater than a power output to light sources of the plurality of first panels.

15. The adjustable illuminator of claim 1, wherein a measured output of the adjustable illuminator over an active emitting area is at least 60% of the measured maximum over all operation distances.

16. The adjustable illuminator of claim 1, wherein power output to light sources at perimeters of the plurality of light sources is greater than power output to light sources at central regions of the plurality of light sources.

17. The adjustable illuminator of claim 1, further comprising a plurality of control units, each of the control units configured to regulate power output to a respective one of the plurality of first panels or the at least one second panel.

18. The adjustable illuminator of claim 1, wherein the plurality of first panels includes three first panels.

19. The adjustable illuminator of claim 18, wherein the at least one second panel includes two second panels having narrower widths.

20. The adjustable illuminator of claim 19, wherein the narrower widths of the two second panels are approximately equal.

21. The adjustable illuminator of claim 1, further comprising a controller, wherein the controller is configured to adjust an overall light dose based on a selected treatment area.

22. The adjustable illuminator of claim 1, further comprising a controller, wherein the controller is configured to cause the adjustable illuminator to emit a light dose based on a selected treatment time period.

23. The adjustable illuminator of claim 1, further comprising at least one sensor, wherein the at least one sensor is configured to detect a size and/or shape of the surface.

24. The adjustable illuminator of claim 23, further comprising a controller, wherein the controller is configured to adjust an overall light dose based on the detected size and/or shape of the surface.

25. The adjustable illuminator of claim 23, further comprising a plurality of actuators, wherein the actuators are configured to adjust a positioning of the plurality of first panels and the at least one second panel based on the detected size and/or shape of the surface.

26. The adjustable illuminator of claim 1, wherein the illuminator is configured such that a measured output over an active emitting area is at least 60% of a measured maximum over all operation distances.

27. An adjustable illuminator for photodynamically diagnosing or treating a patient, comprising:

at least three first panels having wider widths;

at least two second panels having narrower widths, wherein each of the narrower widths of the at least two second panels is less than each of the wider widths of the at least three first panels;

wherein the at least three first panels and the at least two second panels are connected in an alternative manner such that the at least two second panels are connected at each side to one of the at least three first panels.

28. The adjustable illuminator of claim 27, wherein the wider widths of the at least three first panels are approximately equal.

29. The adjustable illuminator of claim 27, wherein the narrower widths of the at least two second panels are approximately equal.

30. A method of photodynamically diagnosing or treating a patient, comprising:

illuminating the patient with an adjustable illuminator having a plurality of first panels having wider widths and at least one second panel having a narrower width, wherein the narrower width is less than each of the wider widths;

varying outputs of the plurality of first panels and the at least one second panel such that a measured output over an active emitting area is at least 60% of the measured maximum over all operation distances.

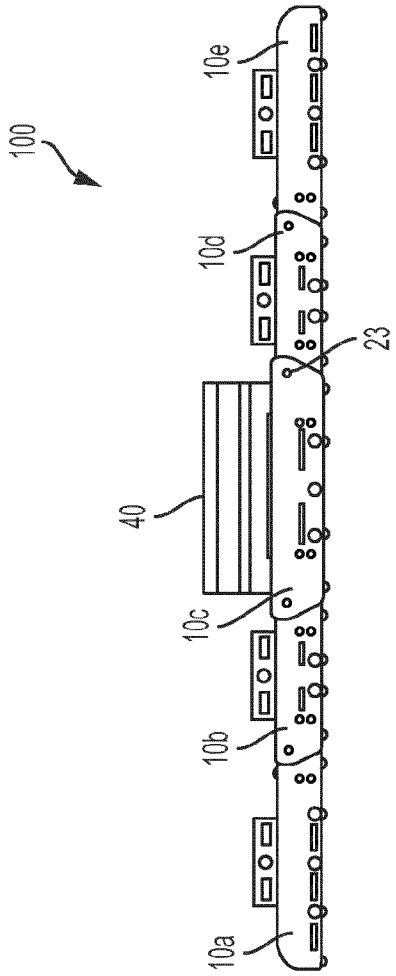


FIG. 1B

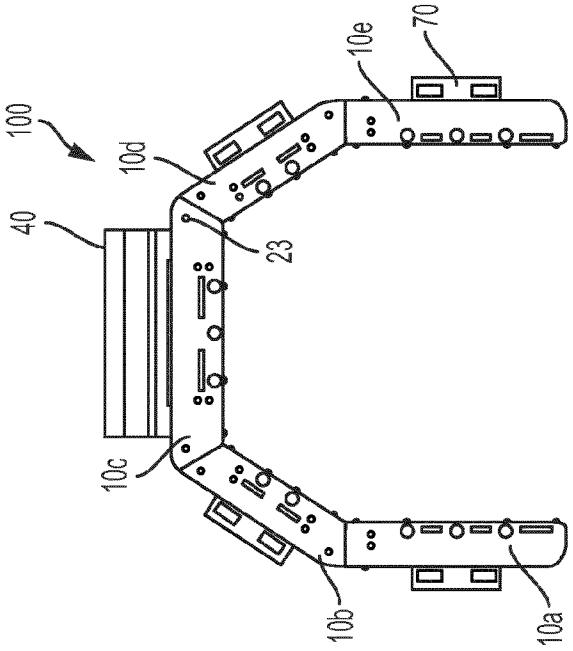


FIG. 1A

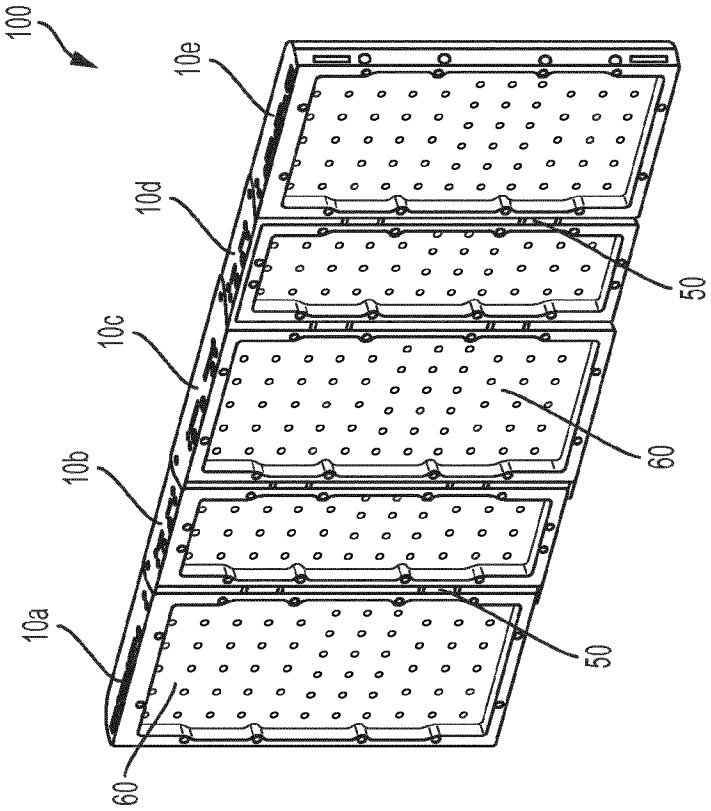
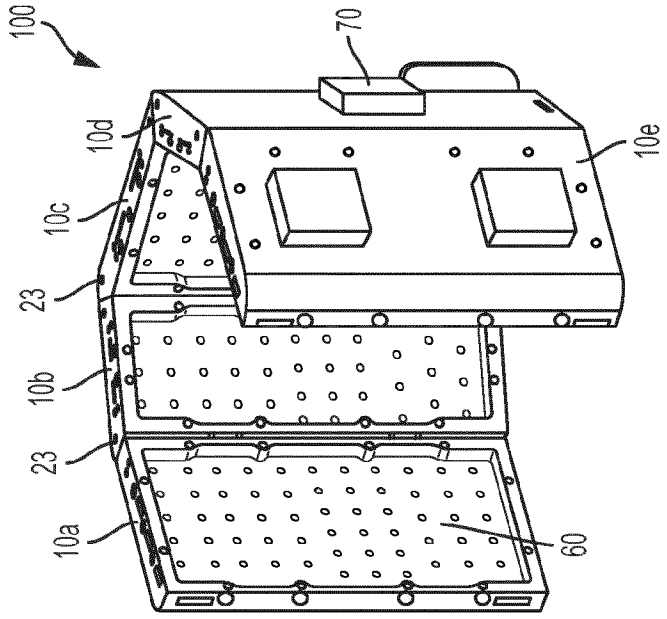

100
10e
10d
10c
10b
10a
50
60
50
60

FIG. 2B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10d
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10c
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FIG. 2A

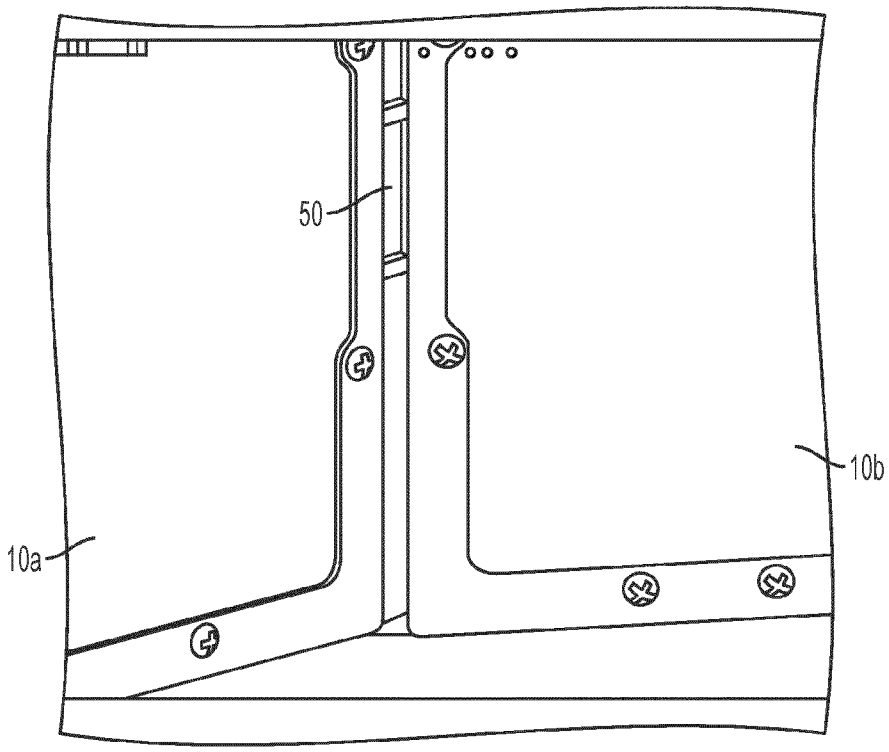


FIG. 3A

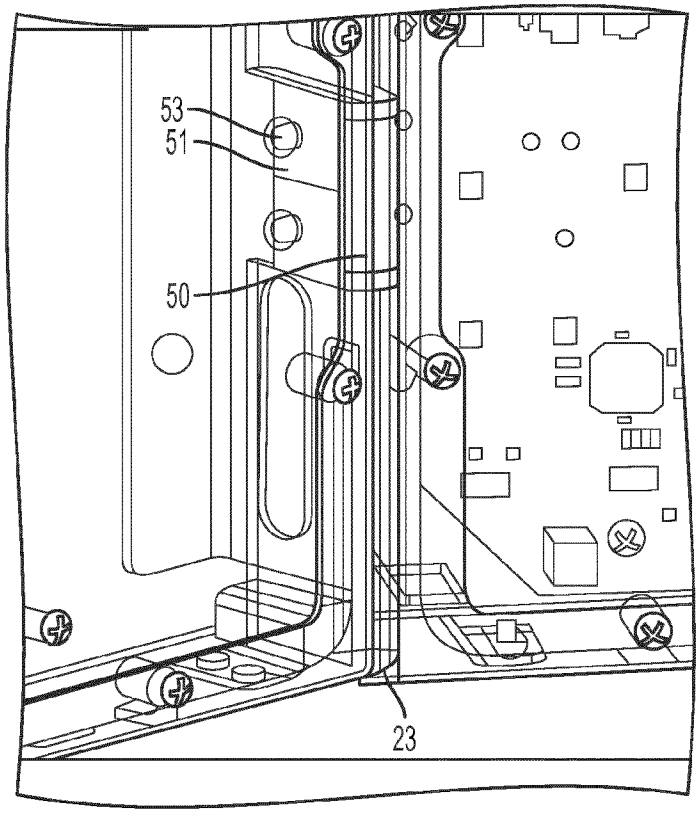


FIG. 3B

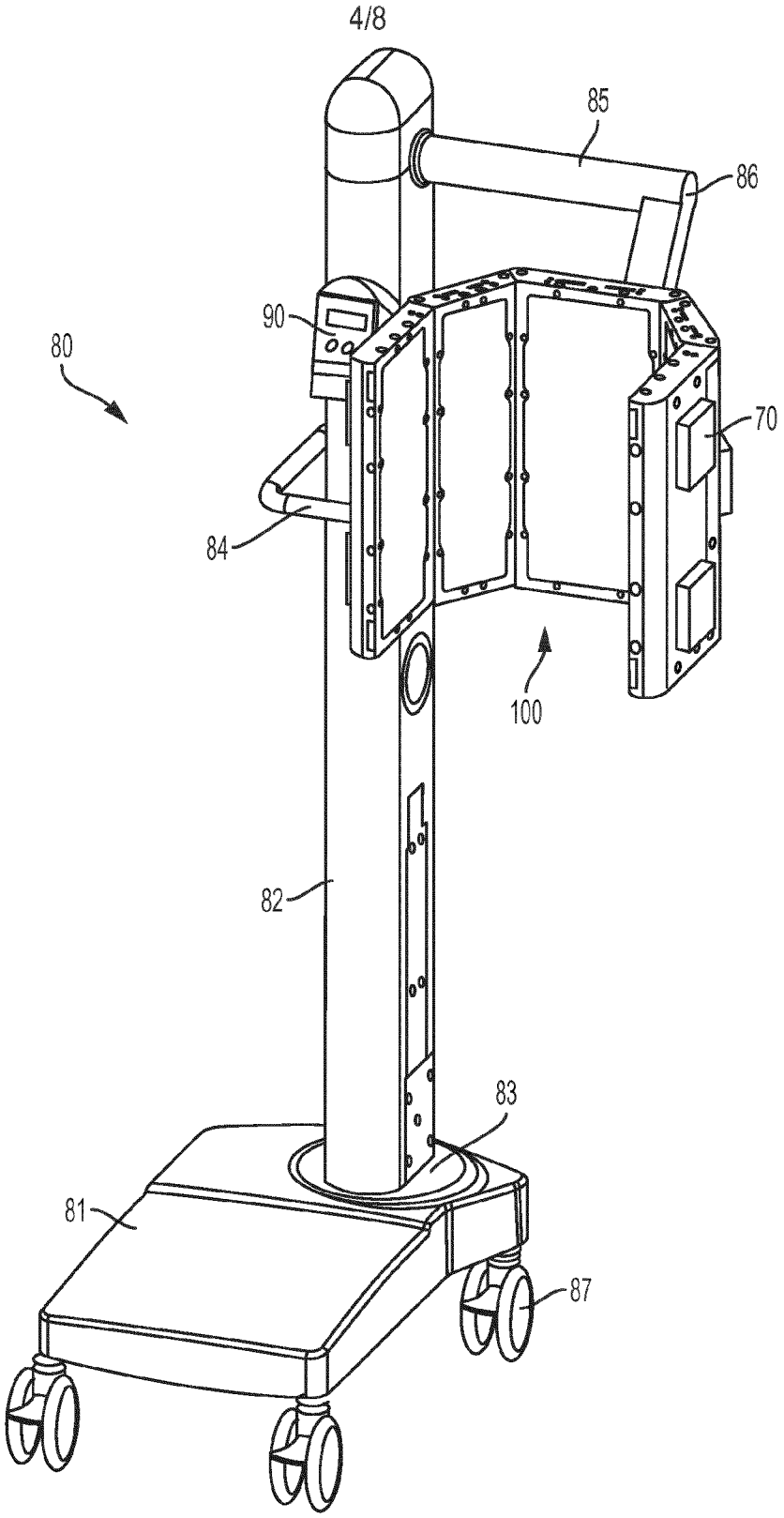


FIG. 4

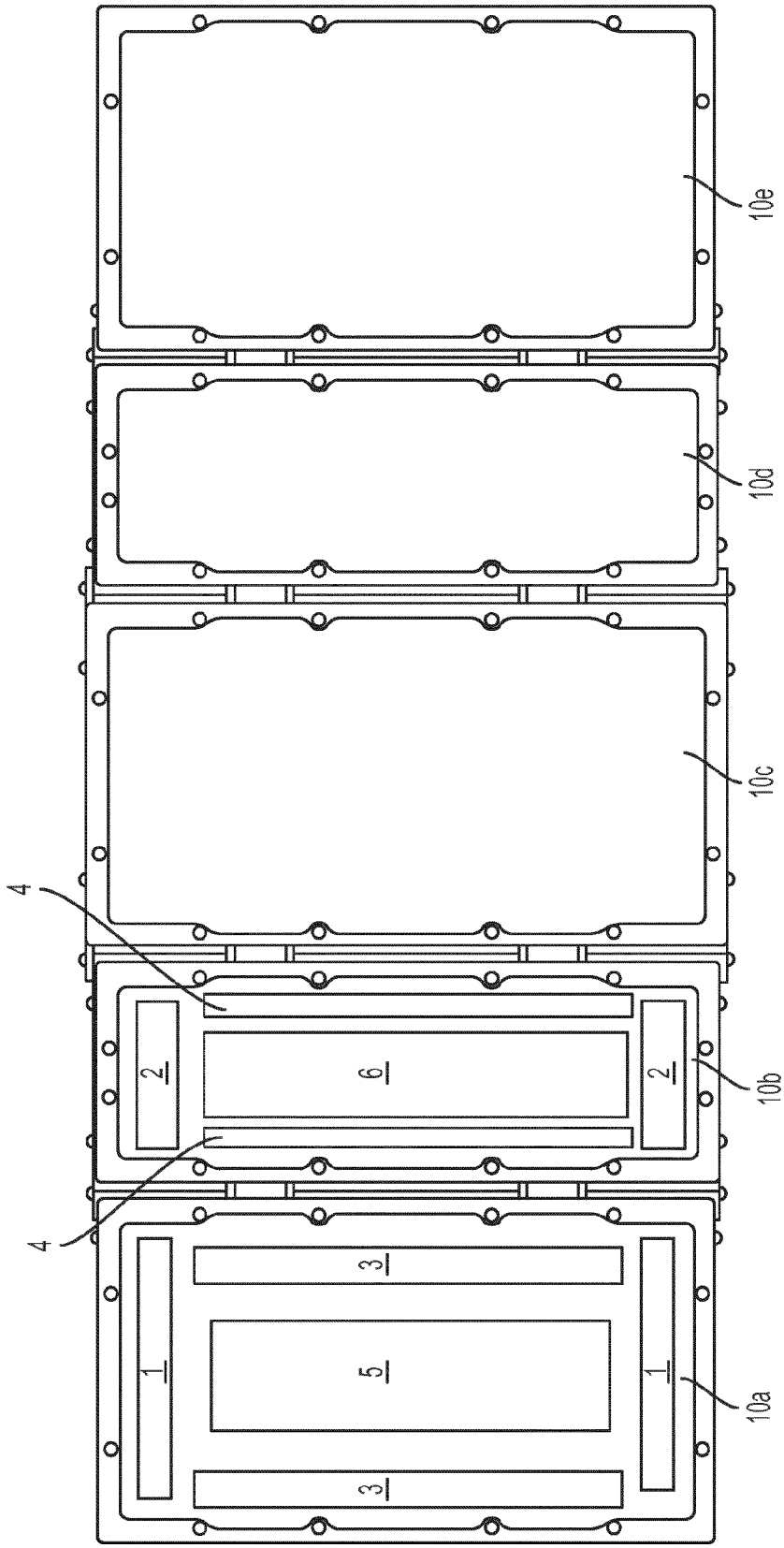


FIG. 5

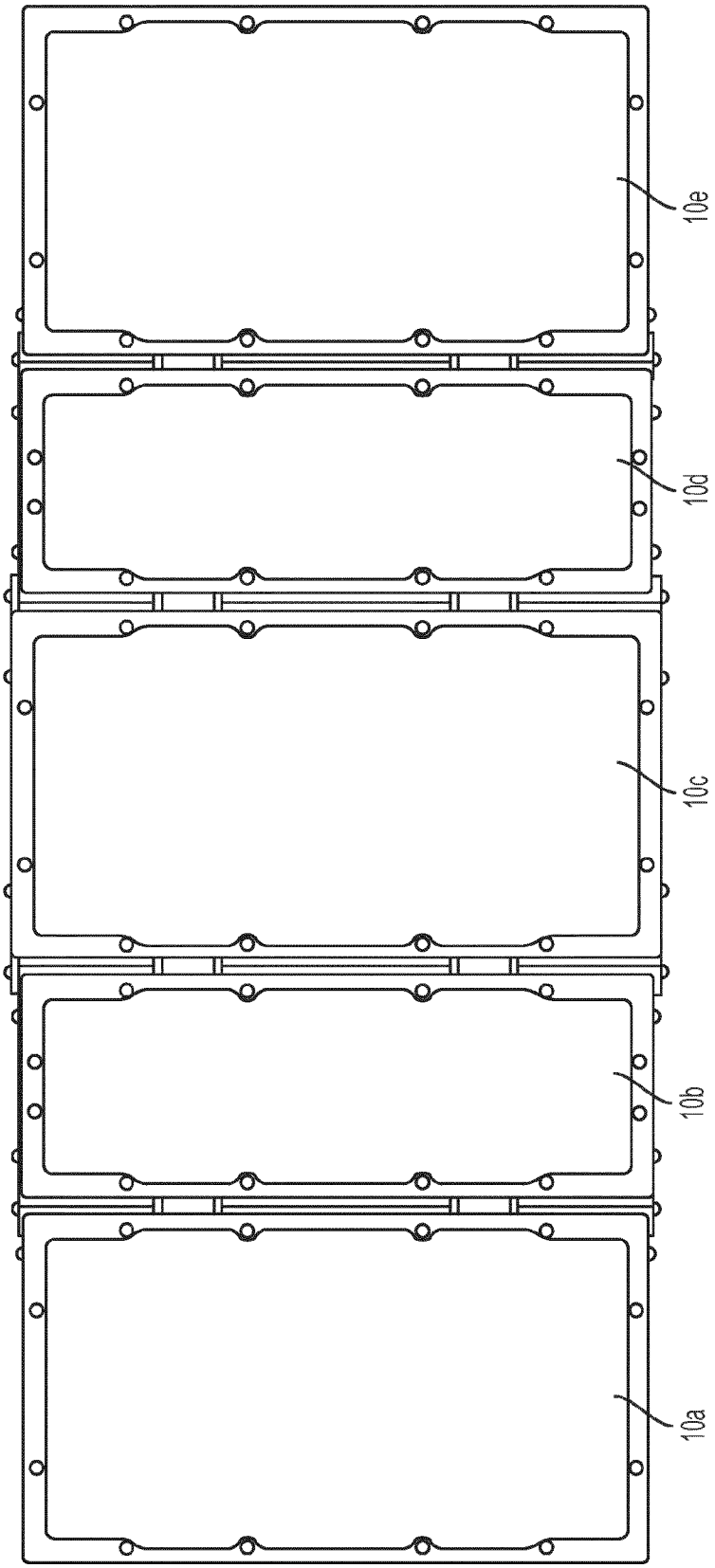


FIG. 6

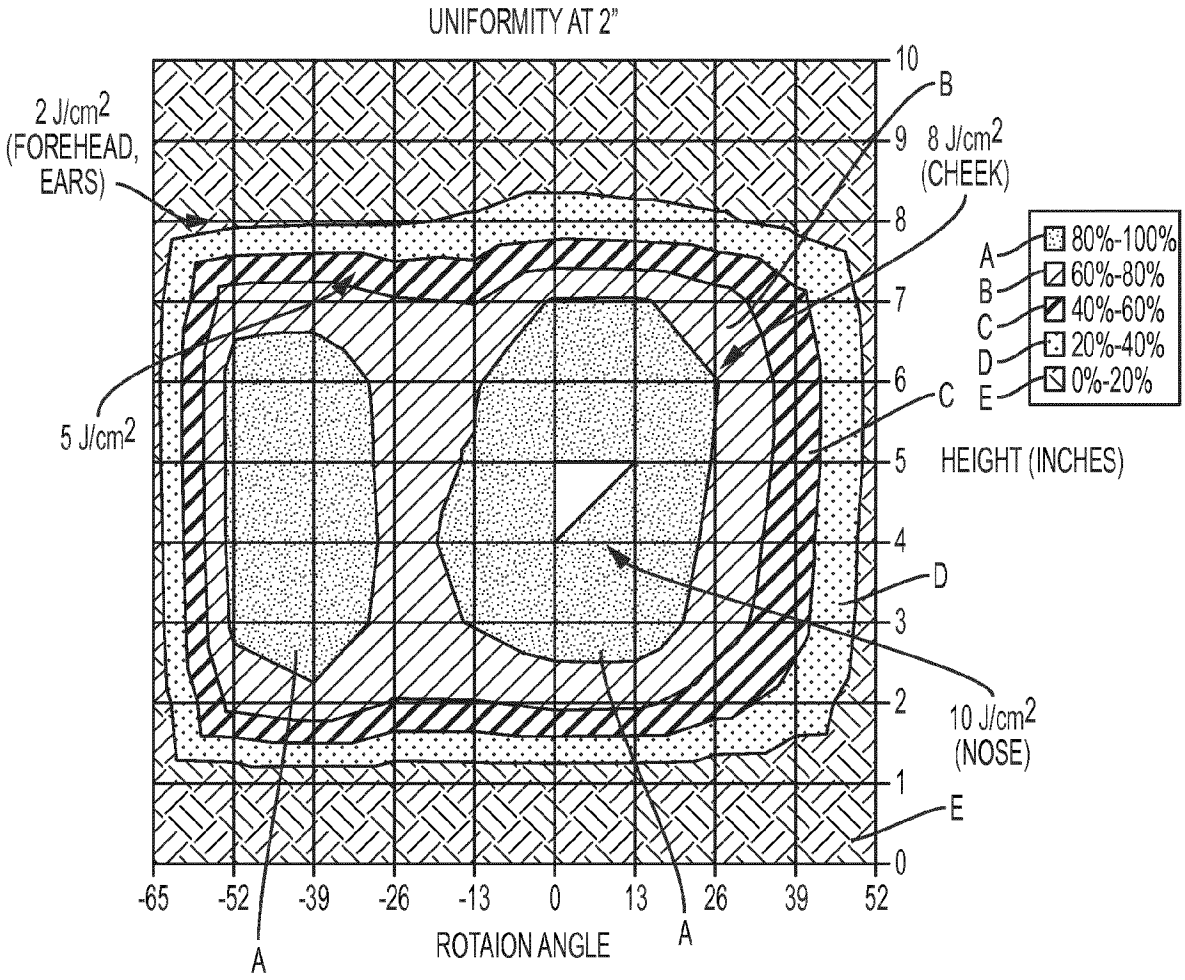

UNIFORMITY AT 2"
2 J/cm2 (FOREHEAD, EARS)
8 J/cm2 (CHEEK)
5 J/cm2
10 J/cm2 (NOSE)
A 80%-100%
B 60%-80%
C 40%-60%
D 20%-40%
E 0%-20%
HEIGHT (INCHES)
ROTAION ANGLE
-65 -52 -39 -26 -13 0 13 26 39 52
0 1 2 3 4 5 6 7 8 9 10

FIG. 7

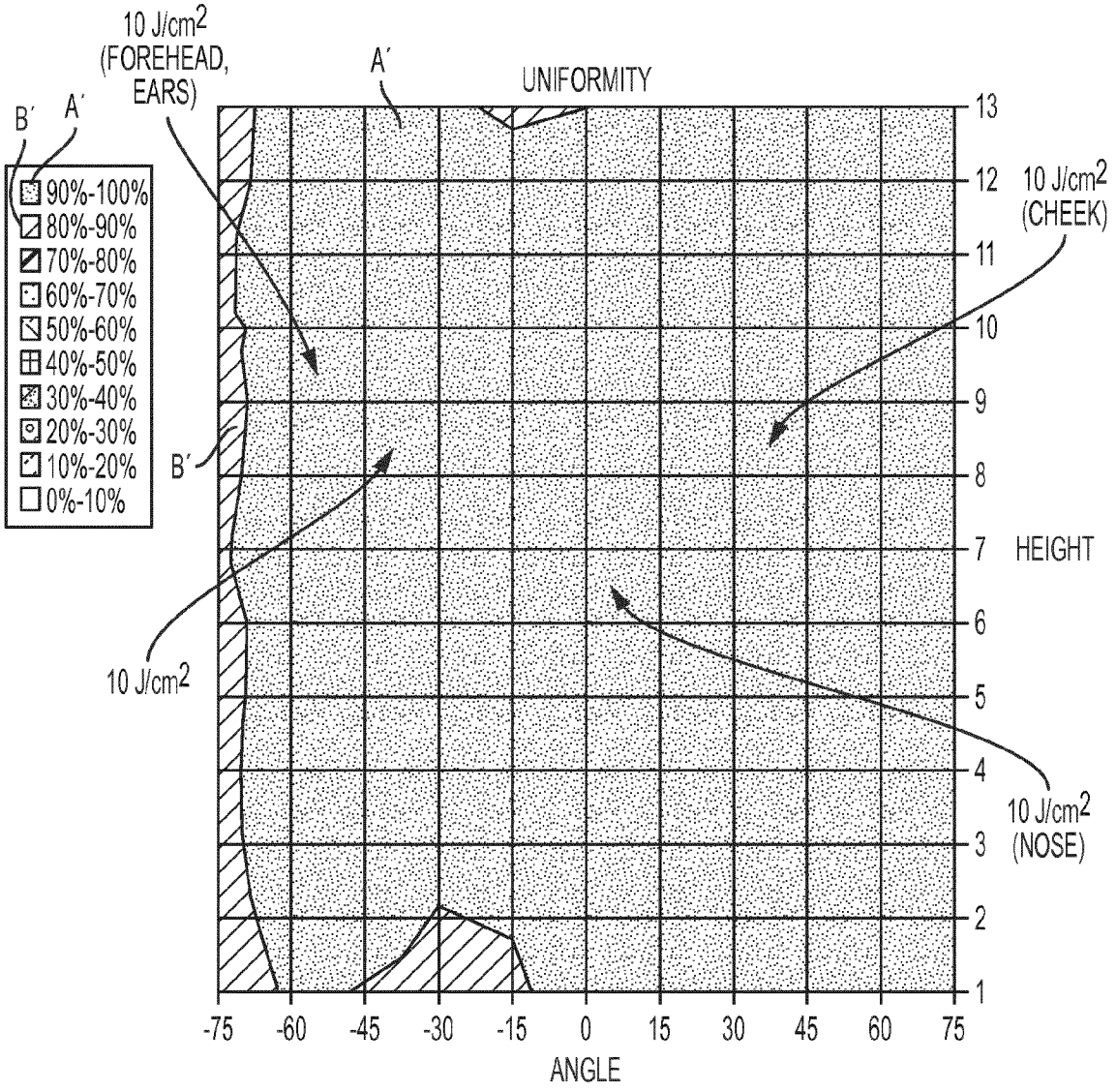

10 J/cm2
(FOREHEAD,
EARS)
A´
UNIFORMITY
B´
A´
90%-100%
80%-90%
70%-80%
60%-70%
50%-60%
40%-50%
30%-40%
20%-30%
10%-20%
0%-10%
B´
10 J/cm2
(CHEEK)
10 J/cm2
10 J/cm2
(NOSE)
HEIGHT
13
12
11
10
9
8
7
6
5
4
3
2
1
-75
-60
-45
-30
-15
0
15
30
45
60
75
ANGLE

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/056572

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N5/06
ADD.

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)
A61N

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)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2007/112427 A2 (TOBIN STEPHEN M [US]) 4 October 2007 (2007-10-04) abstract paragraphs [0002], [0025], [0026], [0033] - [0040] figures 2,9,11	1-17, 21-26 18-20, 27-29
Y A	WO 2011/124912 A1 (DOUGAL GORDON REX PATERSON [GB]) 13 October 2011 (2011-10-13) abstract page 10, lines 16-25 figures 1A,1C	18-20, 27-29 1-17

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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
19 December 2016	13/01/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grochol, Jana

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/056572

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 2006/241726 A1 (WHITEHURST COLIN [GB]) 26 October 2006 (2006-10-26) abstract paragraph [0069] figures 1,2a,2b -----	1-29
A	US 2005/075703 A1 (LARSEN ERIC [CH]) 7 April 2005 (2005-04-07) abstract paragraphs [0069] - [0072] figure 1 -----	1-29

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/056572

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. [X] Claims Nos.: 30
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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:

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 an 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/056572

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007112427 A2	04-10-2007	CA 2664898 A1	04-10-2007
		US 2007283655 A1	13-12-2007
		WO 2007112427 A2	04-10-2007
WO 2011124912 A1	13-10-2011	EP 2555827 A1	13-02-2013
		US 2013066405 A1	14-03-2013
		WO 2011124912 A1	13-10-2011
US 2006241726 A1	26-10-2006	AU 2003207356 A1	17-09-2004
		JP 2006519047 A	24-08-2006
		JP 2011098207 A	19-05-2011
		US 2006241726 A1	26-10-2006
		US 2007038269 A1	15-02-2007
		WO 2004075984 A1	10-09-2004
		WO 2004075985 A2	10-09-2004
US 2005075703 A1	07-04-2005	AT 309030 T	15-11-2005
		CA 2444891 A1	15-08-2002
		DE 60207202 D1	15-12-2005
		DE 60207202 T2	03-08-2006
		DK 1359977 T3	20-03-2006
		EP 1359977 A1	12-11-2003
		ES 2252423 T3	16-05-2006
		NO 20033237 A	22-09-2003
		US 2005075703 A1	07-04-2005
		WO 02062420 A1	15-08-2002

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Filer:	Glenn Law/Effie Hale
Attorney Docket Number:	067286-0399

Filed as Large Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4000	4000
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	3	80	240
INDEPENDENT CLAIMS IN EXCESS OF 3	1201	1	420	420

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous-Filing:				
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**6400**

Electronic Acknowledgement Receipt

EFS ID:	31482379
Application Number:	15869164
International Application Number:	
Confirmation Number:	3488
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY
First Named Inventor/Applicant Name:	Scott LUNDAHL
Customer Number:	22428
Filer:	Glenn Law/Effie Hale
Filer Authorized By:	Glenn Law
Attorney Docket Number:	067286-0399
Receipt Date:	12-JAN-2018
Filing Date:	
Time Stamp:	09:52:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$6400
RAM confirmation Number	011218INTEFSW09543400
Deposit Account	190741
Authorized User	Effie Hale

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	Track1Request.pdf	119693 99f1f8b0fa5e26cd7232b3feef88b8735d06c1d7	no	1
Warnings:					
Information:					
2	Transmittal of New Application	UtilityTrans.pdf	168167 94c1bf24c9a80b56c9dad839ce1d7c4f79c80451	no	3
Warnings:					
Information:					
3	Application Data Sheet	ADS.pdf	784170 542e5b18dbc781037545b66fff7051b22dedc7a3	no	7
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
4		Spec.pdf	2106939 17365eea447527364040e4c1f5e49e258be71ec9	yes	27

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	22
Claims	23	26
Abstract	27	27

Warnings:	
Information:	

5	Drawings-only black and white line drawings	Drwgs.pdf	940550 97dc57fa91eaeffb981fa822974f9e3dca033e8c	no	12
Warnings:					
Information:					
6	Power of Attorney	Poa.pdf	245900 7e661b857c4da7b3f9a7b2cd0028740c88dc604b	no	2
Warnings:					
Information:					
7		IDSTrans_SB08.pdf	262617 37c03ad60b17c6ec60a121b342a47d226c181a8b	yes	3

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	1	2
Information Disclosure Statement (IDS) Form (SB08)	3	3

Warnings:					
Information:					
8	Foreign Reference	WO2017_066270.pdf	1804583 15fc515f2966371139a302f92118ba14bdfec021	no	30
Warnings:					
Information:					
9	Non Patent Literature	NPLRef_Schmieder.pdf	921654 402058e99c2411b17d12a53ff541b72a8da4dfb2	no	10
Warnings:					
Information:					
10	Non Patent Literature	NPLRef_Apalla.pdf	527426 fb16ebcec57ecf5a102f2948cb60eadb71d6efc5	no	5
Warnings:					
Information:					

11	Fee Worksheet (SB06)	fee-info.pdf	43050 8e5794c1e7809095a8e1ffe5cf61787b83aca7be	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	7924749

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Scott LUNDAHL	Nonprovisional Application Number (if known):	Unassigned
Title of Invention:	METHODS FOR PHOTODYNAMIC THERAPY		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature	Date 01-12-2018
Name (Print/Typed) Glenn Law	Practitioner Registration Number 34,371

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of _____ forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name: Scott LUNDAHL

Title: METHODS FOR PHOTODYNAMIC THERAPY

Application No.: Unassigned

Filing Date: 1/12/2018

Examiner: Unassigned

Art Unit: Unassigned

UTILITY PATENT APPLICATION TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is the nonprovisional utility patent application of:

Scott LUNDAHL
Michael GUTTADAURO

Enclosed are:

[X] Application Data Sheet (37 CFR 1.76).

[X] PTO/SB/424 - Request for Prioritized Examination.

[X] Description, Claim(s), and Abstract (27 pages).

[X] Drawings (12 sheets, Figures 1A-14).

[X] Power of Attorney (2 pages).

[X] Information Disclosure Statement.

[X] Form PTO/SB/08 with copies of 3 listed reference.

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets		EFS-Web Adjustment	Number of Sheets for EFS-Web
39	x	75%	30

The filing fee is calculated below at the large entity rate:

	Number Filed		Included in Basic Fee		Extra		Rate		Fee Totals
Basic Filing Fee							$280.00	=	$280.00
Search Fee							$600.00		$600.00
Examination Fee							$720.00		$720.00
Size Fee	30	-	100	= 0		x	$400.00		$0.00
Total Claims:	23	-	20	= 3		x	$80.00	=	$240.00
Independents:	4	-	3	= 1		x	$420.00	=	$420.00
If any Multiple Dependent Claim(s) present:						+	$780.00	=	$0.00
Surcharge under 37 CFR 1.16(f) for late filing of Executed Declaration						+	$140.00	=	$140.00
Non-electronic filing fee						+		=	$0.00
Prioritized Examination fee (Track I) under 37 C.F.R. § 1.17 (c)									$4,000.00
Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)									$140.00
TOTAL FILING FEE:								=	$6,540.00
Assignment Recordation Fee:						+		=	$0.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:						+	$140.00	=	
TOTAL FEE								=	$6,540.00

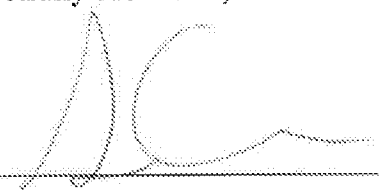
The above-identified fees of $6,540.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application, or credit any overpayment, to Deposit Account Number 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date JAN 12 2018

By 

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5426
Facsimile: (202) 672-5399

Glenn Law
Attorney for Applicant
Registration No. 34,371

PTO/AIA/14 (11-13)
Approved for use through 04/30/2017. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	067286-0399
	Application Number	
Title of Invention	METHODS FOR PHOTODYNAMIC THERAPY	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Scott		LUNDAHL	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Lexington	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o DUSA Pharmaceuticals, Inc.
Address 2	25 Upton Drive

City	Wilmington	State/Province	MA
Postal Code	01887	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Michael		GUTTADAURO	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Carlisle	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o DUSA Pharmaceuticals, Inc.
Address 2	25 Upton Drive

City	Wilmington	State/Province	MA
Postal Code	01887	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	067286-0399
	Application Number	
Title of Invention	METHODS FOR PHOTODYNAMIC THERAPY	

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	22428		
Email Address	IPDocketing@foley.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS FOR PHOTODYNAMIC THERAPY		
Attorney Docket Number	067286-0399	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	12	**Suggested Figure for Publication (if any)**	3

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	22428		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	067286-0399
	Application Number	
Title of Invention	METHODS FOR PHOTODYNAMIC THERAPY	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove			
Application Number	Country[j]	Filing Date (YYYY-MM-DD)	Access Code[j] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	067286-0399
	Application Number	
Title of Invention	METHODS FOR PHOTODYNAMIC THERAPY	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	067286-0399
	Application Number	
Title of Invention	METHODS FOR PHOTODYNAMIC THERAPY	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:	
If the Applicant is an Organization check here.	☒
Organization Name	DUSA Pharmaceuticals, Inc.

Mailing Address Information For Applicant:

Address 1	25 Upton Drive		
Address 2			
City	Wilmington	**State/Province**	MA
Country		Postal Code	01887
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	067286-0399
	Application Number	
Title of Invention	METHODS FOR PHOTODYNAMIC THERAPY	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	DUSA Pharmaceuticals, Inc.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	25 Upton Drive		
Address 2			
City	Wilmington	**State/Province**	MA
Country i		Postal Code	01887
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature				Date (YYYY-MM-DD)	2018-01-12
First Name	Glenn	Last Name	Law	Registration Number	34371

Additional Signature may be generated within this form by selecting the Add button.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	067286-0399
	Application Number	
Title of Invention	METHODS FOR PHOTODYNAMIC THERAPY	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

METHODS FOR PHOTODYNAMIC THERAPY

FIELD

[0001] The present disclosure relates generally to methods for photodynamic therapy.

BACKGROUND

[0002] Photodynamic therapy (PDT), photodynamic diagnosis (PD), or photochemotherapy is generally used to treat and/or diagnose several types of ailments in or near the skin or other tissues, such as those in a body cavity. For example, photodynamic therapy or photodynamic diagnosis may be used for treatment or diagnosis of actinic keratosis of the upper extremities (e.g., the dorsal surface of the hand or forearms), scalp or facial areas of a patient. In addition, such techniques may be used for treatment and diagnosis of other indications (e.g., acne, warts, psoriasis, photo-damaged skin, cancer) and other areas of the patient (e.g., the legs or portions of the arms other than the forearms).

[0003] During one form of photodynamic therapy, a patient is first administered a photoactivatable agent or a precursor of a photoactivatable agent that accumulates in the tissue to be treated. The area in which the photoactivatable agent is administered is then exposed to visible light, which causes chemical and/or biological changes in the agent. These changes allow the agent to then selectively locate, destroy, or alter the target tissue while, at the same time, causing at most only mild and reversible damage to other tissues in the treatment area. One example of a precursor of a photoactivatable agent is 5-aminolevulinic acid ("ALA"), which is commonly used in photodynamic therapy of actinic keratosis. As they are used here, the terms ALA or 5-aminolevulinic acid refer to ALA itself, precursors thereof, esters thereof and pharmaceutically acceptable salts of the same. Photosensitization following application of a topical composition (e.g., a topical solution or emulsion) containing ALA occurs through the metabolic conversion of aminolevulinic acid to protoporphyrin IX (PpIX), as discussed in more detail below. PpIX is a photosensitizer which accumulates in the skin.

[0004] For photodynamic therapy to be effective, it is desirable to have a power output that can be controlled for intensity and duration, among other factors. Illuminators are typically used to provide the proper uniformity of light for treatment purposes. These devices

generally include a light source (e.g., a fluorescent tube or LED), coupling elements that direct, filter or otherwise conduct emitted light so that it arrives at its intended target in a usable form, and a control system that starts and stops the production of light when necessary.

[0005] Photodynamic therapy may be carried out using certain compositions, such as ALA, in connection with illuminators as described above. Such compositions and/or devices are disclosed, for example, in (1) U.S. Patent No. 5,954,703 to Golub, entitled "Method and apparatus for applying 5-aminolevulinic acid," issued on September 21, 1999, (2) U.S. Patent No. 6,223,071 to Lundahl *et al.*, entitled "Illuminator for photodynamic therapy and diagnosis which produces substantially uniform intensity visible light," issued on April 24, 2001, (3) U.S. Patent Application No. 15/371,363 to Boyajian *et al.*, entitled "Method And Apparatus For Applying A Topical Solution," published on June 8, 2017 as U.S. Pub. No. 2017/0157379, (4) International Application No. PCT/US2016/056572 to Boyajian *et al.*, entitled "Adjustable Illuminator For Photodynamic Therapy And Diagnosis," published on April 20, 2017 as WO 2017/066270, (5) U.S. Patent Application No. 15/292,731 to Boyajian *et al.*, entitled "Adjustable Illuminator For Photodynamic Therapy And Diagnosis," published on April 20, 2017 as U.S. Pub. No. 2017/0106205, and (6) U.S. Patent Application No. 15/487,991 to Boyajian *et al.*, entitled "Adjustable Illuminators And Methods For Photodynamic Therapy And Diagnosis," published on August 3, 2017 as U.S. Pub. No. 2017/0216616. The entire contents of the foregoing patents and/or patent applications (1)-(6) are incorporated herein by reference for background information and the compositions, devices, processes and techniques relating to photodynamic therapy and diagnosis disclosed therein.

SUMMARY

[0006] Through research and experimentation in photodynamic therapeutic techniques, the inventors have found that covering a treatment area with polyethylene (such as low density polyethylene (LDPE)) for a period of time prior to light treatment is particularly effective to minimize transepidermal water loss from the treatment area. Surprisingly, it was found that a polymeric barrier having a degree of occlusion more than 65% (such as LDPE) was superior to other materials such as polyurethane and polyvinylidene chloride (PVdC). The low density polyethylene can be applied to a wide variety of treatment areas, such as the arms,

legs, chest, back, portions of the head, and the like, and can be used with drugs other than ALA.

[0007] According to one aspect of the disclosure, a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy is disclosed. The method includes topically applying ALA to a treatment area to be treated with photodynamic therapy. The method further includes, after the ALA is applied to the treatment area, covering the treatment area with a polymeric barrier have a degree of occlusion of 65% or more.

[0008] According to another aspect of the disclosure, a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy is disclosed. The method includes topically applying ALA to a treatment area to be treated with photodynamic therapy. The method further includes, after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier. The treatment area is covered with the low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area.

[0009] According to still another aspect of the disclosure, a method of photodynamic treatment of the stratum corneum is disclosed. The method includes applying 5-aminolevulinic acid (ALA) to a lesion on the stratum corneum and reducing evaporation from a portion of the stratum corneum including an area where the lesion is present. The method further includes heating the area where the lesion is present before or during illumination of the area where the lesion is present.

[0010] According to a further aspect of the disclosure, a method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier is disclosed. The method includes contacting a treatment site with a composition comprising the ALA so as to wet the treatment site, and, following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier.

[0011] According to an additional aspect of the disclosure, a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) HCl into tissue for photodynamic therapy is disclosed. The method includes topically applying the composition

to a treatment area to be treated with photodynamic therapy. The method further includes, after the composition is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area. The composition exhibits a mean plasma concentration (C_{max}) value of ALA less than about 110 ng/mL when the ALA HCl is applied in an amount of 354 mg.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The details of one or more embodiments are set forth in the accompanying drawings and the description below. Other features, aspects, and advantages will become apparent from the description, the drawings, and the claims. In the drawings, like reference numerals are used throughout the various views to designate like components. The drawings are briefly described below.

[0013] FIGS. 1A-1B show top views of a main body of an illuminator according to an exemplary embodiment.

[0014] FIGS. 2A-2B show perspective views of the main body of the illuminator of FIGS. 1A-1B.

[0015] FIG. 3 shows a perspective view of the illuminator having the main body of FIGS. 1A-1B mounted to a stand.

[0016] FIG. 4 shows a representative region to be treated in accordance with an exemplary embodiment.

[0017] FIG. 5 depicts evaporative water loss rates for a plurality of materials, in accordance with at least one embodiment.

[0018] FIG. 6 depicts the degree of occlusion for a plurality of materials, in accordance with at least one embodiment.

[0019] FIG. 7 depicts evaporative water loss rates for a plurality of materials, in accordance with at least one embodiment.

[0020] FIG. 8 depicts the degree of occlusion for a plurality of materials, in accordance with at least one embodiment.

[0021] FIG. 9 is a table containing baseline water loss data for the materials referred to in FIGS. 5-6.

[0022] FIG. 10 is a table containing water loss data following three hours of wear time for the materials referred to in FIGS. 5-6.

[0023] FIG. 11 is a table containing occlusion data for the materials referred to in FIGS. 5-6.

[0024] FIG. 12 is a table containing baseline water loss data for the materials referred to in FIGS. 7-8.

[0025] FIG. 13 is a table containing water loss data following three hours of wear time for the materials referred to in FIGS. 7-8.

[0026] FIG. 14 is a table containing occlusion data for the materials referred to in FIGS. 7-8.

[0027] It will be recognized that some or all of the figures are schematic representations for purposes of illustration. The figures are provided for the purpose of illustrating one or more embodiments with the explicit understanding that they will not be used to limit the scope or the meaning of the claims.

DETAILED DESCRIPTION

[0028] Various embodiments are described hereinafter. It should be noted that the specific embodiments are not intended as an exhaustive description or as a limitation to the broader aspects discussed herein. One aspect described in conjunction with a particular embodiment is not necessarily limited to that embodiment and can be practiced with any other embodiment(s).

[0029] The following terms are used throughout and are as defined below.

[0030] As used herein and in the appended claims, singular articles such as "a" and "an" and "the" and similar references in the context of describing the elements (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to

each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, "such as") provided herein, is intended merely to better illustrate the embodiments and does not pose a limitation on the scope of the claims unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential.

[0031] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising," "including," "containing," etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claimed technology. Additionally, the phrase "consisting essentially of" will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. The expression "comprising" means "including, but not limited to." Thus, other non-mentioned substances, additives, devices or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

[0032] Unless otherwise indicated, all numbers expressing quantities of properties, parameters, conditions, and so forth, used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations. Any numerical parameter should at least be construed in light of the number reported significant digits and by applying ordinary rounding techniques. The term "about" when used before a numerical designation, *e.g.*, temperature, time, amount, and concentration including range, indicates approximations which may vary by (+) or (-) 10%, 5% or 1%.

[0033] As will be understood by one of skill in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any

and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member.

EXEMPLARY ILLUMINATOR

[0034] FIGS. 1A-1B and 2A-2B illustrate one embodiment of a configurable illuminator as may be used in accordance with the present disclosure. The illuminator includes a main body 100, which preferably has a plurality of individual panels (e.g., panels 10a-10e, each of which are connected in a rotatable manner via nested hinges 50). As shown in FIGS. 2A-2B, on at least one side of a panel, a tab 23 may extend out from both the top and bottom of the panel. The tabs 23 are configured such that a side of an adjacent panel may be received between the tabs 23, as shown in FIG. 2A, and the hinges 50 are between the tabs 23. Each panel contains an array of light emitting diodes (LED) 60. The number of individual LEDs arranged in a given array is not particularly limited. Alternatively, other types of light sources may be used, such as fluorescent or halogen lamps. The LED arrays 60 emit light at an appropriate wavelength according to the intended treatment or to activate the particular photoactivatable agent used in treatment or diagnosis.

[0035] In at least one embodiment, when ALA is used as a precursor of a photoactivatable agent for the treatment of actinic keratosis, the LED arrays 60 preferably emit blue light having wavelengths at or above 400 nanometers (nm), for example, about 430 nm, about 420 nm or, for example, 417 nm. However, the LED arrays 60 may also emit visible light in other ranges of the spectrum, such as in the green and/or red ranges between 400 and 700 nm, for example, about 625 nm to 640 nm or, for example, 635 nm. For example, the LED arrays 60 may also emit light having wavelengths of 510 nm, 540 nm, 575 nm, 630 nm, or 635 nm. In addition, the LED arrays 60 may be configured to emit light continuously or the LED arrays 60 may be configured to flash the diodes on and off based on a predetermined interval. Furthermore, the LED arrays 60 may be configured such that only one wavelength of light (e.g., blue) is emitted. Alternatively, the LED arrays 60 may be configured such that two or

more wavelengths of light are emitted from the arrays. For example, the LED arrays 60 may be configured to alternately emit blue light and red light for treatment purposes. In one embodiment, the LED arrays may also emit red light having wavelengths of 570 to 670 nm.

[0036] In one embodiment of the present disclosure, blue light having a wavelength of approximately 417 nm is applied at an intensity of 10 mW/cm^2 for 1000 seconds to provide a dose of 10 J/cm^2. However, the intensity may be increased (for example, doubled) to reduce the treatment time. For example, the intensity may be increased so as to reduce the treatment time by about one-half. In other embodiments, red light (such as red light generated by light emitting diodes (LEDs) at, for example, 635 nm) may be used. The red light can provide a dose of, for example, 10 to 75 J/cm^2 (such as 37 J/cm^2), e.g., within 10 minutes.

[0037] The ALA can be applied using an applicator as described below, using, for example, a 20% solution of ALA, or can be applied by other means such as glove protected fingers or a spatula. The ALA can be applied in, for example, liquid or gel form and can be applied beyond the lesions to be treated. In certain applications, materials other than low density polyethylene may be used as long as they have a degree of occlusion of 65% or more. In certain applications, certain materials may be used as long as they have a degree of occlusion of 75% or more.

[0038] Referring again to the exemplary illuminator shown in FIGS. 1A-1B, the main body 100 of the illuminator may include a mounting head 40. The mounting head 40 may allow for the main body 100 to be mounted to a movable stand 80, which is shown in FIG. 3, to allow a user to easily move the main body 100 to the appropriate treatment position. The stand 80 includes a base 81 and a vertical pillar 82. The base 81 may further include wheels 87 at its bottom in order to allow the user to horizontally move the illuminator to an appropriate position. The wheels 87 may include locks, such that the stand 80 is prevented from further horizontal movement once positioned. In addition, the vertical pillar 82 may be attached to the base 81 at a pivot point 83.

[0039] At a top end, the vertical pillar 82 includes a connecting arm 85, which may serve as a mounting structure for the main body 100. The connecting arm 85 includes a hinge point 86 such that the main body 100 can be moved vertically relative to the stand 80. The stand 80 may also include a stabilization arm 84. Once the stand 80 and main body 100 is positioned, the stabilization arm 84 may be attached to the main body 100 to prevent

unwanted movement of the main body 100 during treatment. As further shown in FIG. 3, a controller and power supply 90 is mounted to the stand 80 in order to supply electrical power to the main body 100 and allow the user to control the main body 100 for treatment purposes. Alternatively, the controller and power supply 90 may be directly mounted to the main body 100. In order to provide a cooling system for the LED arrays 60, one or more fans 70 may be mounted onto each of the panels, as shown in FIG. 3.

[0040] The controller and power supply 90 may be also connected to the panels to regulate power to the light source to achieve a desired uniformity and intensity for the target treatment. The control unit may be implemented as hardware, software, or a combination of both, such as a memory device storing a computer program and a processor to execute the program. Alternatively, each panel may have a dedicated control unit to regulate power to the individual LED array on a given panel to allow for fine-tuning of the illuminator, which may further enhance uniformity and increase efficiency. The LED arrays 60 may be individually configured to increase the intensity of light emitted from certain diodes to achieve particular illumination effects.

[0041] The illuminator may further include a timer included in the controller and power supply 90, which can indicate to the user the appropriate length of exposure time for the particular treatment. The illuminator may also be programmed with pre-stored light dosing parameters to allow the user to select a desired treatment type. The pre-stored parameters may include, for example, pre-stored settings for exposure time, light intensity, and outputted wavelength. Based on the selected treatment, the illuminator is automatically configured to provide the correct lighting dosage by being supplied with the appropriate power output to achieve the required uniformity for the treatment.

[0042] Alternatively, the illuminator can be provided with sensors that detect the size of the treatment area positioned in front of the illuminator. The sensors then determine the correct light dosing parameters based on the sensed treatment area. The sensors may detect the adjusted position of the illuminator manually set by the user. The detected position of the illuminator may then be used to indicate the intended treatment area. Appropriate light dosing parameters for the specific treatment area may then be provided based on the detected position set by the user.

[0043] Adjustable illuminators as described above allow for an infinite amount of configurations that can be adapted for the targeted treatment area. The configurations may range from a flat-plane emitter (as shown in FIGS. 1B and 2B) to a substantially U-shaped configuration (as shown in FIGS. 1A and 2A). Not only can the adjustable illuminator effectively deliver a uniform light intensity to surfaces such as the face or scalp, but the adjustable illuminator can also provide a device that can easily be configured to treat other portions of a patient's body, in particular, those having smaller curved surfaces, such as the arms and legs, and in particular, the upper extremities Moreover, the adjustable illuminator may also be easily positioned to deliver a uniform light intensity to larger treatment areas, such as the back or chest.

[0044] The illuminator may irradiate the lesions with a uniform intensity red light for a prescribed period. In certain embodiments, the illuminator irradiates the lesions with a uniform intensity blue light for a first prescribed period and then irradiates the lesions with a uniform intensity red light for a second prescribed period. For example, in some embodiments, the illuminator is configured to irradiate the lesions with a uniform intensity blue light (e.g., 417 nm) at a low intensity (e.g., about 0.1 J/cm^2 to about 2 J/cm^2) to photobleach, for example, protoporphyrin IX (PpIX) present at the surface of the patient's skin, and irradiate the lesions with a uniform intensity red light (e.g., 635 nm) at a high intensity (e.g., about 30 J/cm^2 to about 150 J/cm^2) to activate PpIX present at deeper layers of the patient's skin, thus avoiding potential damage to the upper layers of the patient's skin.

[0045] Furthermore, since the total light dose (J/cm^2) is equal to irradiance (mW/cm^2) multiplied by time (sec), an additional parameter to be controlled for delivery of the correct treatment light dose is exposure time. This may be accomplished by the timer described above, which can control the electrical power supplied to the LED arrays 60 appropriately, and which can be set by the physician. Data has shown that 10 J/cm^2 delivered from a source with an irradiance density of 10 mW/cm^2, or an irradiance density of about 9.3 to about 10.7 mW/cm^2, produces clinically acceptable results for desired treatment areas (e.g., face, scalp, extremities). An adjustable illuminator may deliver an irradiance density of 20 mW/cm^2 for an exposure time of 500 seconds (8 min. 20 sec) to deliver a clinically acceptable light dose of 10 J/cm^2. In certain embodiments, a lower intensity may be used with a longer exposure time (e.g., 1,000 seconds of exposure time for a light dose of 10 J/cm^2). Alternatively, the adjustable illuminator may include higher power ranges, such as 30 mW/cm^2, over an

exposure time resulting in a light dose of 10 J/cm^2. A selected light dose may also be administered by additionally or alternatively varying the irradiance density over treatment time.

[0046] In at least one embodiment, a heating element (a heat source) may be provided. The heat source may be used to heat the region to be treated. According to one embodiment, a method of treatment includes warming up an illuminator so as to cause heat to be emitted from the illuminator, and exposing a treatment site to the illuminator. The heat accelerates the conversion of the ALA to porphyrin (e.g., photosensitive porphyrin or proto porphyrin). The relationship between temperature exposure and ALA conversion is non-linear, and the enzymatic pathways responsible for the conversion are highly sensitive to temperature. In at least one embodiment, increasing the temperature by approximately 2 °C may approximately double the rate of production of protoporphyrin IX (PpIX), for example.

[0047] The heat may be applied before or during illumination with the illuminator. For example, first, the ALA may be applied. Next, the heating element may be activated, to apply heat to the patient's skin for a first treatment period for a thermal soak, which may be 20-30 minutes, for example. During the heating, the treatment site may or may not be occluded. In other words, the treatment site may be heated while being occluded.

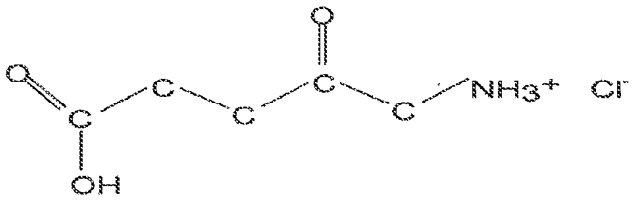
[0048] Following the first treatment period, light may be applied for a second treatment period, e.g., about 8-15 minutes. In at least one embodiment, the heat source may be an infrared quartz heater. In at least one embodiment, the heat source may comprise frame mounted resistance tape heaters or a plurality of heaters, including at least one selected from the group including IR LEDs, resistance cartridge heaters, positive temperature coefficient heaters, or IR quartz heaters, as mentioned above. The heat may be deliberately generated and directed towards the area to be treated, as opposed to ambient heat in the clinical setting or byproduct heat from one or more operating mechanisms of the illuminator.

ADMINISTRATION OF ALA

[0049] As indicated above, during photodynamic therapy, a total light dose is received by a patient over the course of treatment. The total light dose, in terms of J/cm^2, may be measured based on emitted irradiance (mW/cm^2) over time (in seconds). One example of a treatment

method for precancerous lesions, such as actinic keratosis, by photodynamic therapy utilizing an adjustable illuminator described above in conjunction with ALA will now be described.

[0050] Essentially anhydrous ALA is admixed with a liquid diluent just prior to its use. The anhydrous ALA may be, for example, the hydrochloride salt of aminolevulinic acid (ALA), an endogenous 5-carbon aminoketone. The chemical name for ALA HCl, as employed in the embodiments disclosed herein, is 5-amino-4-oxopentanoic acid hydrochloride (molecular weight = 167.59). ALA HCl is highly soluble in water. The structural formula of ALA HCl is represented below:



[0051] In at least one embodiment, the ALA is contained in powderized form inside a first ampule. In the first ampule, the amount of ALA as a dry solid may be between 300-400 mg. In at least one embodiment, the amount of ALA HCl is 354 mg. A second ampule contains a solution vehicle. The second ampule contains 1.5 mL of the solution vehicle. The solution vehicle comprises alcohol (i.e., alcohol as defined by the United States Pharmacopeia Convention) (ethanol content = 48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol.

[0052] The first and second ampules are contained inside a plastic applicator. The first and second ampules may be crushed, e.g., by applying finger pressure, or inside a device configured to exert pressure on the ampule. Once the ampules are crushed, the ALA formerly contained in the first ampule contacts the solution formerly contained in the second ampule, and dissolves in the solution vehicle. The applicator in which the ampules were provided may be shaken so as to disperse and dissolve the powdered ALA in the solution vehicle. Once combined, the resulting solution is applied to the patient within 2 hours of preparation.

[0053] In some embodiments, the ALA may be provided in a composition such as a ready-to-use solution or a reconstituted powder for solution, gel, cream or lotion formulation. In another embodiment, the composition comprises 5-aminolevulinic acid hydrochloride in an

amount of about 10% to about 70% w/w based on the total weight of the composition, preferably from about 20% to about 50% w/w based on the total weight of the composition, more preferably from about 30% to about 40% w/w based on the total weight of the composition.

[0054] In one embodiment, ALA may be applied in a topical composition with a concentration of 20%. The ALA admixture is topically applied to the lesions using a point applicator to control dispersion of the ALA admixture, in at least one embodiment, so as to achieve a substantially uniform wetting of the lesion surface with the ALA by contacting the ALA with the lesion surface. The term "substantial," or "substantially" as used herein, may refer to any value which lies within the range as defined by a variation of up to ±15 from the average value. However, in other embodiments, the ALA may be applied digitally (i.e., by first disposing the ALA on the gloved fingertips of a practitioner, who then dabs the ALA on the region to be treated), or with a tool such as a spatula.

OCCLUSION WITH BARRIER

[0055] Following application of the ALA to the region to be treated (i.e., the lesion), the region to be treated may be occluded with a polymer barrier. For example, as shown in FIG. 3, a polymer barrier 200 is wrapped around a region to be treated 300. While the exemplary embodiment shown in FIG. 3 depicts the barrier 200 as encircling the region 300, it should be understood that in certain embodiments, the barrier 200 may only occlude a portion of the region 300. Further, while barrier 200 is depicted as substantially cylindrical (e.g., so as to form a sleeve around region 300), the barrier 200 may have a variety of shapes.

[0056] The barrier 200 is shown with a clearance from the region 300 purely for ease of illustration in FIGS. 3 and 4. In at least one embodiment, however, the barrier 200 clings or adheres to the region 300 such that there is effectively no clearance between the barrier 200 and the region 300. The polyethylene barrier may have electrostatic properties that provide an adhesive clinging effect such that the barrier tends to stay close to the surface of the skin, even for prolonged periods. Such an effect may be particularly enhanced when the skin is wetted with the topical solution, i.e., when the treatment site is first wetted with the topical solution, and the barrier 200 is then applied directly on the wetted treatment site.

[0057] Experimental results confirmed that employing low density polyethylene (LDPE) for barrier 200 resulted in lower water loss rates and a superior degree of occlusion. In

particular, embodiments with low density polyethylene barriers 200 were particularly effective for photodynamic therapy.

[0058] FIG. 5 depicts evaporative water loss rates for a plurality of materials A-E as summarized below in Table 1. The LDPE barriers were found to be especially conducive to retaining water and allowing for greater penetration of the ALA into the region to be treated.

Material Code	Name	Distributor or Manufacturer	Material Description
A	Tegaderm™, Style 1629	3M	Polyurethane
B	Glad® Press'n Seal®	The Glad Products Company	LDPE
C	Glad® Cling Wrap	The Glad Products Company	LDPE
D	Stretch-Tite®	Polyvinyl Films, Inc.	Polyvinylidene chloride (PVdC)
E	Saran™ Premium Wrap	SC Johnson	LDPE

Table 1. Barrier Materials A-E

[0059] The measured water loss rates shown in FIG. 5 (and FIG. 7, discussed below) are transepidermal water loss rates measured on the dorsal forearms, measured both before and after the barrier 200 had been worn for 3 hours. The baseline water loss was measured for approximately 30 subjects, after a minimum 25-minute acclimation period in a controlled environment with less than 50% relative humidity and a temperature between 19-22 deg. Celsius. Such measurements correspond to the bar plots labeled "pre" in FIGS. 5 and 7. The subjects had mild to moderate photodamage on their dorsal forearms. The measurements were made using a calibrated RG1 Evaporimeter System (made by cyberDERM, Inc. of Broomall, PA) with DermaLab® transepidermal water loss probes (made by Cortex Technology of Hadsund, Denmark).

[0060] A vapor pressure gradient estimation method was used. The probes measure the temperature and relative humidity at fixed points along the skin, allowing derivation of a value corresponding to evaporative water loss in gm/m^2hr. Sampling was performed at 4

inputs/second. The baseline measurements indicate the barrier properties of the stratum corneum of each subject, prior to applying barrier 200 to the stratum corneum. The measurements taken 3 hours after application of the barrier 200 are indicative of the barrier properties of the materials shown in Tables 1-2. Such measurements correspond to the bar plots labeled "post" in FIGS. 5 and 7. Each barrier 200 was cut so as to cover a test site area of 5 cm by 5 cm prior to application. The barrier 200 was secured with hypoallergenic medical tape for the purpose of testing. An area of the subjects' skin without the barrier 200 was measured as a control.

[0061] FIG. 6 depicts degrees of occlusion for a plurality of materials in accordance with at least one embodiment. More specifically, FIG. 6 depicts the degree of occlusion for the materials shown in FIG. 5 and summarized above in Table 1. The degree of occlusion corresponds to the decrease in evaporative water loss rate when the subject wore the barrier 200 as compared to the baseline evaporative water loss rate. As indicated in FIG. 6, barrier material E, for example, blocked approximately 85% or more of the water vapor from evaporating from the skin surface. In one embodiment, a polymeric barrier having a degree of occlusion more than 65% is particularly effective for photodynamic therapy. In one embodiment, a polymeric barrier having a degree of occlusion more than 75% is particularly effective for photodynamic therapy. Greater occlusivity of LDPE materials such as material E enhances the penetration of ALA into the tissue by minimizing transepidermal water loss from the treatment area. The tissue may be skin, in particular, the stratum corneum, or other tissue of a human subject.

[0062] Similar to material E, materials B and C blocked approximately 75% of the water vapor from evaporating from the skin surface. Materials A and D, on the other hand, appeared to be semi-occlusive barriers.

[0063] FIG. 7 depicts evaporative water loss rates for a plurality of materials in accordance with at least one embodiment. More specifically, FIG. 7 depicts evaporative water loss rates for a plurality of materials W-Z and E as summarized below in Table 2. Barrier material E was the same material as shown in Table 1 and discussed above. Materials W-Z included LDPE and polyvinylidene chloride.

Material Code	Name	Distributor or Manufacturer	Material Description
W	Best-Yet Clear Plastic Wrap	C&S Wholesale Grocers, Inc.	LDPE
X	Boardwalk® PVC Food Wrap Film, BWK7204	Boardwalk	PVdC
Y	Shurfine® Strong and Stretchy ® Plastic Wrap	Western Family Foods, Inc.	LDPE
Z	Premium Plastic Wrap	Foodhold USA, LLC	PVdC
E	Saran™ Premium Wrap	SC Johnson	LDPE

Table 2. Barrier Materials W-Z and E

[0064] FIG. 8 depicts degrees of occlusion for a plurality of materials in accordance with at least one embodiment. More specifically, FIG. 8 depicts the degree of occlusion for the materials shown in FIG. 7 and summarized above in Table 2. As seen in FIG. 8, materials E, W, and Y were significantly more occlusive than materials X and Z. Materials X and Z block only approximately 35% of water vapor from evaporating and are thus semi-occlusive in nature. Material E, due to its flexible nature, easily wraps around the treatment site, which may promote water retention.

[0065] FIG. 9 is a table containing baseline water loss data for the materials referred to in FIGS. 5-6. In particular, FIG. 9 provides the baseline measurements for each subject for each material A-E shown in Table 1, including mean and standard deviation values. FIG. 10 is a table containing water loss data following three hours of wear time for the materials referred to in FIGS. 5-6. FIG. 11 is a table containing occlusion data for the materials referred to in FIGS. 5-6. FIG. 12 is a table containing baseline water loss data for the materials referred to in FIGS. 7-8. FIG. 13 is a table containing water loss data following three hours of wear time for the materials referred to in FIGS. 7-8. FIG. 14 is a table containing occlusion data for the materials referred to in FIGS. 7-8.

[0066] As discussed above, the barrier 200 is used to occlude at least a portion of the region to be treated, e.g., all or part of the dorsal surface of the hand. In some embodiments, and

particularly for larger treatment areas, such as the forearm, an additional structure may be provided to secure the barrier 200 in place. The low density polyethylene wrap may be secured in place with a dressing 210, shown in FIG. 4. In one embodiment, the dressing 210 is a surgical netting such as Surgilast® Tubular Elastic Dressing Retainer made by Derma Sciences Inc. of Plainsboro, New Jersey. The dressing 210 may be a tubular elastic stretch net designed to serve as a secondary dressing, which applies a relatively light pressure to keep barrier 200 securely in place without adhesive tape. That is, the secondary dressing 210 may exert slight compressive pressure on the barrier 200. The dressing 210 may be a sleeve which fits over and around barrier 200. In some embodiments, the secondary dressing and/or tape may be applied. Following application of the ALA and occlusion, treatment may be carried out in accordance with the exemplary implementations described below.

TREATMENT PROTOCOLS

[0067] Once the ALA is applied to the upper extremities, the upper extremities may be occluded for no more than three hours prior to light treatment. For example, the extremities may be occluded for 2-3 hours. As indicated above, the ALA is a porphyrin precursor which, when used as part of photodynamic therapy, may treat various conditions including minimally to moderately thick actinic keratoses of the face, scalp or the upper extremities. Accordingly, in at least one embodiment, one or more of a portion of the face, a portion or all of the scalp, or a portion or all of one or more of the upper extremities may be covered in an occlusive barrier.

[0068] Where the ALA is used to treat lesions of the face and scalp without the application of an occlusive barrier, following application of the ALA, formation of photosensitive porphyrin and photosensitization of the treated lesions occurs after 14-18 hours. Between 14 and 18 hours after administration of the ALA, the lesions are irradiated by an illuminator. The illuminator may, for example, irradiate the lesions with a uniform intensity blue light for a prescribed period. According to a preferred treatment, the visible light has a nominal wavelength of 417 ± 5 nm.

[0069] The time period for illumination where the ALA is used to treat a lesion on an upper extremity can be significantly shorter when performed with the application of an occlusive barrier than for the face or scalp sites. The time period is approximately 3 hours between (1) application of ALA to the upper extremities and occlusion, and (2) the illumination of the

upper extremities. If the occlusion time exceeds three hours for some treatment areas, then the skin where the ALA is applied may experience irritation. Excessive irritation may be marked by the presence of itching spots, wheals, flares, or other indicia, including symptoms persisting after the treatment session has ended. In particular, excessive irritation is marked by adverse cutaneous events such as scaling, crusting, ulceration, rashes, scabbing, tenderness and itching, for example. Three hours represents the nominal maximum time under which the upper extremity should be occluded following application of ALA, so as to avoid such excessive irritation while maintaining therapeutic efficacy. Therapeutic efficacy is the clearance of actinic keratosis lesion 12 weeks after PDT. The time period between the application of ALA to other body parts (other than the face, scalp and upper extremities) and illumination may be 3 hours, in some embodiments.

[0070] Once the occlusive barrier 200 is removed, light treatment as described above may be performed, e.g., application of red and/or blue light for a light dose of 10 J/cm^2. For example, once the barrier 200 is removed within 3 hours of being applied, blue light may be applied to the exposed treatment area to deliver a light dose of 10 J/cm^2, or red light may be applied for a 10 J/cm^2 to 75 J/cm^2 light dose. In some embodiments, the light may be delivered while the treatment site is still occluded. In some embodiments, light and heat may be delivered while the treatment site is still occluded.

[0071] To treat facial lesions, an illuminator as described above may be positioned such that the region to be treated is between 2 to 4 inches from a surface of the illuminator, with the patient's nose not less than 2 inches from the illuminator surface, and the forehead and cheeks no more than 4 inches from the surface. The sides of the patient's face and the patient's ears should be no closer than 2 inches from the illuminator surface.

[0072] To treat scalp lesions, an illuminator as described above may be positioned such that the region to be treated is between 2 to 4 inches from a surface of the illuminator, with the patient's scalp not less than 2 inches from the illuminator surface, and no more than 4 inches from the surface. The sides of the patient's face and the patient's ears should be no closer than 2 inches from the illuminator surface.

[0073] To treat lesions on the upper extremities, such as the dorsal surface of the hand or the forearms, an illuminator as described above may be positioned such that the region to be treated is between 2 to 4 inches from a surface of the illuminator. Equipment (e.g., a table)

may be used to support the upper extremity during light treatment so as to enhance the patient's comfort and stabilize the region to be treated.

[0074] Two open-label, pharmacokinetic studies were carried out to evaluate the potential for systemic exposure of ALA and ALA and protoporphyrin IX (PpIX) when applied topically under occlusion, in a maximal use setting in patients with multiple actinic keratoses (AK) lesions on the upper extremities. In accordance with at least one embodiment, a 20% w/w topical composition of 5-aminolevulinic acid (ALA) was directly applied topically via an applicator to the upper extremities of the patients followed by covering with an occlusive, polyethylene film for a 3 hour incubation period. Light treatment was administered after the incubation period. Each subject received 10 J/cm^2 of visible blue light delivered at 10 mW/cm^2.

[0075] In the first of the two studies, a total of 29 participants were enrolled. The participants were males and non-pregnant females, aged 18 years or older. Each eligible subject had at least six Grade 1 or Grade 2 AK lesions on one upper extremity treatment area and at least 12 Grade 1 or Grade 2 AK lesions on the other upper extremity treatment area. The subjects received one treatment and were followed until week four after treatment. The treatment area, designated at baseline for the duration of the study, was the extensor surface of both distal upper extremities, as defined in the protocol (i.e., the dorsal hands/forearms). In the second of the two studies, a total of 14 participants were enrolled. Males and non-pregnant females, aged 18 years or older, with at least six Grade 1 or Grade 2 AK lesions on one upper extremity treatment area and at least 12 Grade 1 or Grade 2 AK lesions on the other upper extremity treatment area, were eligible for the study.

[0076] The topical application of the ALA to the upper extremities resulted in lower systemic exposure to ALA and PpIX than intravenous and oral dosing. The method according to at least one embodiment includes application of up to two topical solution compositions each containing about 354 mg ALA. The dosing using the topical solution was compared to intravenous and oral dosing in an amount of about 100 mg ALA. As indicated above, strength of the ALA was about 20% by weight. The topical dosing was observed to result in a mean plasma concentration (C_{max}) value of ALA of less than about 110 ng/mL. The term "C_{max}," as used herein refers to maximum observed plasma concentrations based on actual values measured following study medication application.

[0077] In particular, following topical applications, the geometric mean maximum plasma concentration was about 98 ng/mL at a median of 2 hours following application, with the geometric mean area-under-the-curve (AUC_t) of 577 ng*h/mL, with variability from about 94% to about 170%. Following a baseline correction, the ALA geometric mean maximum plasma concentration was 80 ng/mL at a median of 2 hours, with a geometric mean AUC_t of 282 ng*h/mL. In an embodiment, the topical solution, when applied in a strength of about 20% by weight, exhibits a geometric mean area under curve (AUC_t) value of ALA less than about 350 ng•hr/mL. The term "AUC_t," as used herein, refers to the area under the plasma concentration-time curve up to the last quantifiable/non-negative plasma concentration.

[0078] In another experiment, following topical applications, the geometric mean maximum plasma concentration was about 61 ng/mL at a median of 2 hours following application, with the geometric mean AUC_t of 727 ng*h/mL, with variability from about 30% to about 152%. Following a baseline correction, the ALA geometric mean maximum plasma concentration was 39 ng/mL at a median of 2 hours, and a geometric mean AUC_t of 182 ng*h/mL. The estimated bioavailability following topical application of 354 mg ALA with occlusion was about 1.0%. In one embodiment, the systemic bioavailability following topical application of 354 mg ALA HCl is less than about 5%. The term "bioavailability" as used herein refers to the rate and extent of absorption and is determined by AUC_t and C_{max} values.

[0079] In accordance with at least one embodiment, a method of photodynamic therapy was carried out to treat lesions on the upper extremities in a multi-center randomized, parallel-group, evaluator-blinded and vehicle-controlled study of 269 patients with 4-15 mild to moderate actinic keratoses. The actinic keratoses were present on the upper extremities, more specifically, on the dorsal surface of the hands and/or the forearm area between the elbow and the base of the fingers. Subjects ranged from 45 to 90 years of age (mean 68 years) and 90% had Fitzpatrick Skin Type I, II or III. Subjects were randomized to treatment in a 1:1 ratio. ALA was applied to lesions on the dorsal surface of one hand or the forearm for each subject, and the dorsal surface of the hand or the forearm was then occluded with low density polyethylene barrier for three hours. Following removal of the low density polyethylene barrier, a 10 J/cm^2 dose of blue light was delivered at 10 mW/cm^2, with treatment repeated after 8 weeks if any lesion(s) remained in the treatment area.

[0080] Complete clearance (i.e., resolution of the actinic keratoses) was achieved by 31% of the subjects (that is, 42 out of 135 subjects) receiving ALA. Complete clearance was

achieved at twelve weeks after initial treatment, as compared to 13% of subjects (that is, 17 out of 134 subjects) receiving only the solution vehicle (without the ALA). Of the subjects who achieved complete clearance at twelve weeks, a twelve-month follow-up evaluation was performed, which indicated that those subjects had a recurrence rate of 58%. The recurrence rate corresponds to the percentage of subjects with at least one recurrent lesion during the 12 month follow up period following the evaluation at twelve weeks who had previously achieved complete clearance at twelve weeks following treatment.

[0081] The present disclosure thus provides a method for photodynamically treating a surface of a patient, and occluding the patient's skin as part of treatment. The patient may be illuminated to treat actinic keratosis, acne, photo-damaged skin, cancer, warts, psoriasis, or other dermatological conditions.

[0082] While this specification contains certain specific implementation details, these should not be construed as limitations on the scope of what may be claimed, but rather as descriptions of features specific to particular implementations. Certain features described in this specification in the context of separate implementations can also be implemented in combination in a single implementation. Conversely, various features described in the context of a single implementation can also be implemented in multiple implementations separately or in any suitable subcombination. Moreover, although features may be described above as acting in certain combinations and even initially claimed as such, one or more features from a claimed combination can in some cases be excised from the combination, and the claimed combination may be directed to a subcombination or variation of a subcombination.

[0083] It is important to note that the construction and arrangement of the illuminator system shown in the various example implementations are illustrative only and not restrictive in character. All changes and modifications that come within the spirit and/or scope of the described implementations are desired to be protected. It should be understood that some features may not be necessary and implementations lacking the various features may be contemplated as within the scope of the disclosure, the scope being defined by the claims that follow. When the language "a portion" is used the item can include a portion and/or the entire item unless specifically stated to the contrary.

[0084] Additional advantages and modifications will readily occur to those skilled in the art. Therefore, the invention in its broader aspects is not limited to the specific details and representative devices and methods, shown and described herein. Accordingly, various modifications may be made without departing from the spirit and scope of the general inventive concept as defined by the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

topically applying ALA to a treatment area to be treated with photodynamic therapy; and

after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area.

2. A method as set forth in claim 1, wherein the treatment area includes actinic keratosis.

3. A method as set forth in claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours to avoid excessive irritation while maintaining therapeutic efficacy.

4. A method as set forth in claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours and then light is applied to the treatment area.

5. A method as set forth in claim 1, wherein the treatment area is located on an upper extremity.

6. A method as set forth in claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours and then blue light is applied to the treatment area for a 10 J/cm^2 light dose.

7. A method as set forth in claim 5, wherein the low density polyethylene barrier is removed from the treatment area and then red light is applied to the treatment area for a 10 to 75 J/cm^2 light dose.

8. The method of claim 1, wherein the maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.

9. A method of photodynamic treatment of the stratum corneum, comprising:

applying 5-aminolevulinic acid (ALA) to a lesion on the stratum corneum;

reducing evaporation from a portion of the stratum corneum including an area where the lesion is present; and

heating the area where the lesion is present before or during illumination of the area where the lesion is present.

10. The method of claim 9, wherein reducing evaporation from the portion of the stratum corneum comprises occluding the portion with a low density polyethylene barrier.

11. The method of claim 10, further comprising:

removing the low density polyethylene barrier, and

positioning the area where the lesion is present between two inches and four inches from a surface of an illuminator.

12. The method of claim 10, further comprising:

securing the low density polyethylene barrier with a netting.

13. The method of claim 11, further comprising:

illuminating the area where the lesion is present following removal of the low density polyethylene barrier, and heating the area where the lesion is present prior to or during illumination,

wherein the illumination is performed within about 3 hours from a time when the area where the lesion is present is occluded with a low density polyethylene barrier.

14. The method of claim 9, wherein the ALA is applied in an ALA composition prepared with 300-400 mg ALA HCl.

15. The method of claim 10, further comprising:

reducing transepidermal water loss from the area where the lesion is present by causing the low density polyethylene barrier to adhere to the area where the lesion is present.

16. A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:

contacting a treatment site with a composition comprising the ALA so as to wet the treatment site; and

following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier.

17. The method of claim 16, further comprising:

removing the low density polyethylene barrier so as to expose the treatment site; and

illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm^2 dose of blue light.

18. The method of claim 16, further comprising:

removing the low density polyethylene barrier so as to expose the treatment site; and

illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm^2 to 75 J/cm^2 dose of red light.

19. The method of claim 16, wherein the low density polyethylene barrier is removed no later than three hours after the treatment site is covered.

20. The method of claim 16, further comprising:

removing the low density polyethylene barrier; and

positioning the treatment site between two inches and four inches from a surface of an illuminator.

21. A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) HCl into tissue for photodynamic therapy, the method comprising:

topically applying the composition to a treatment area to be treated with photodynamic therapy; and

after the composition is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area,

wherein the composition exhibits a mean plasma concentration (C_{max}) value of ALA less than about 110 ng/mL when the ALA HCl is applied in an amount of 354 mg.

22. The method of claim 21, wherein the topical composition, when applied in a strength of about 20% by weight, exhibits a mean area under curve (AUC_t) value of ALA less than about 350 ng•hr/mL.

23. The method of claim 21, further comprising removing the low density polyethylene barrier prior to light treatment.

ABSTRACT

A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy includes topically applying ALA to a treatment area to be treated with photodynamic therapy. The method further includes, after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier. The treatment area is covered with the low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area.

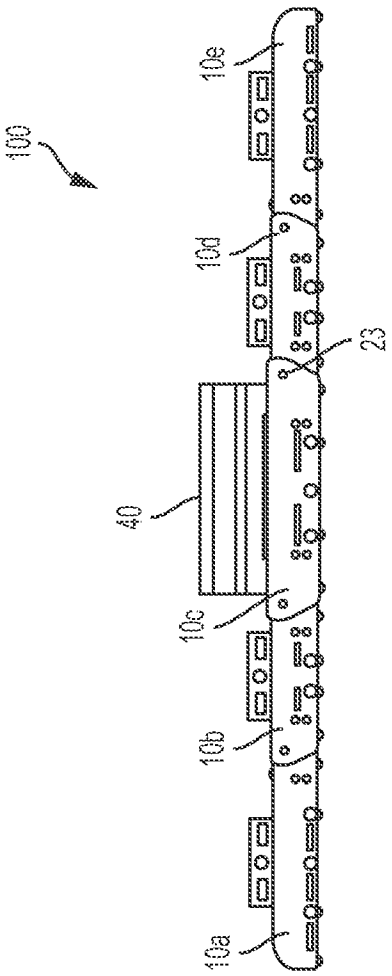


FIG. 1B

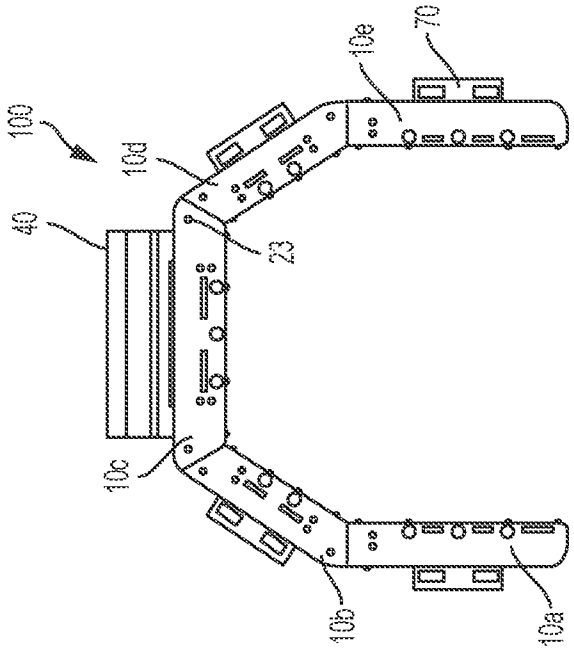


FIG. 1A

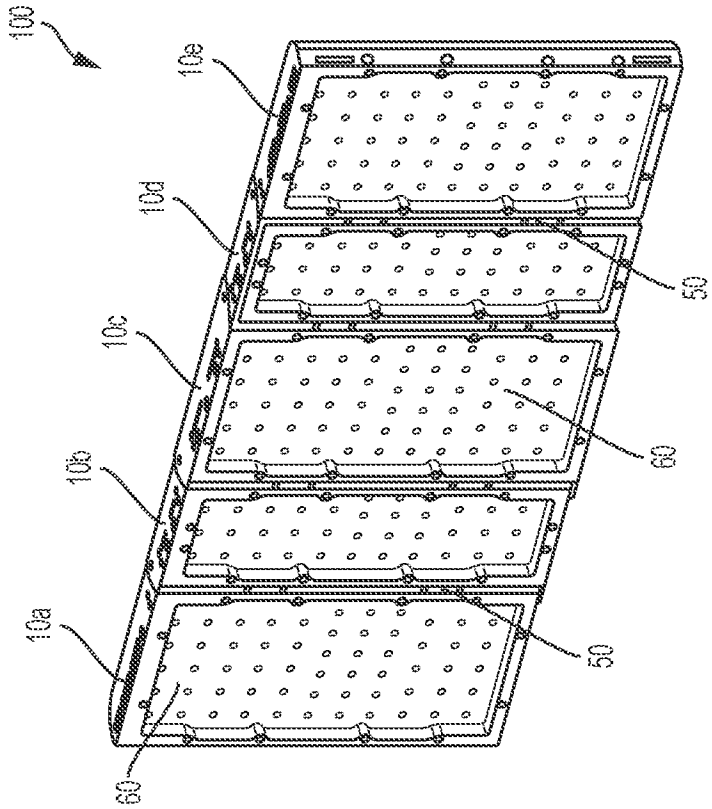

100
10e
10d
10c
10b
10a
50
60
50
60

FIG. 2B

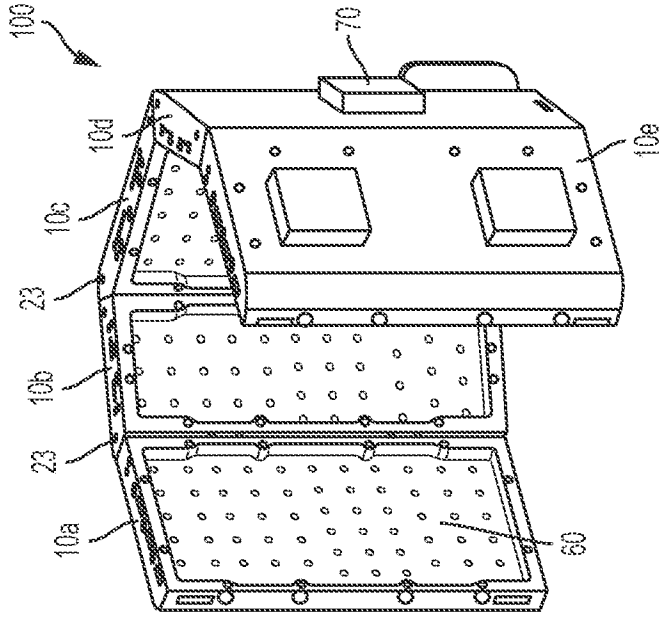

100
70
10d
10e
10c
23
10b
23
10a
60

FIG. 2A

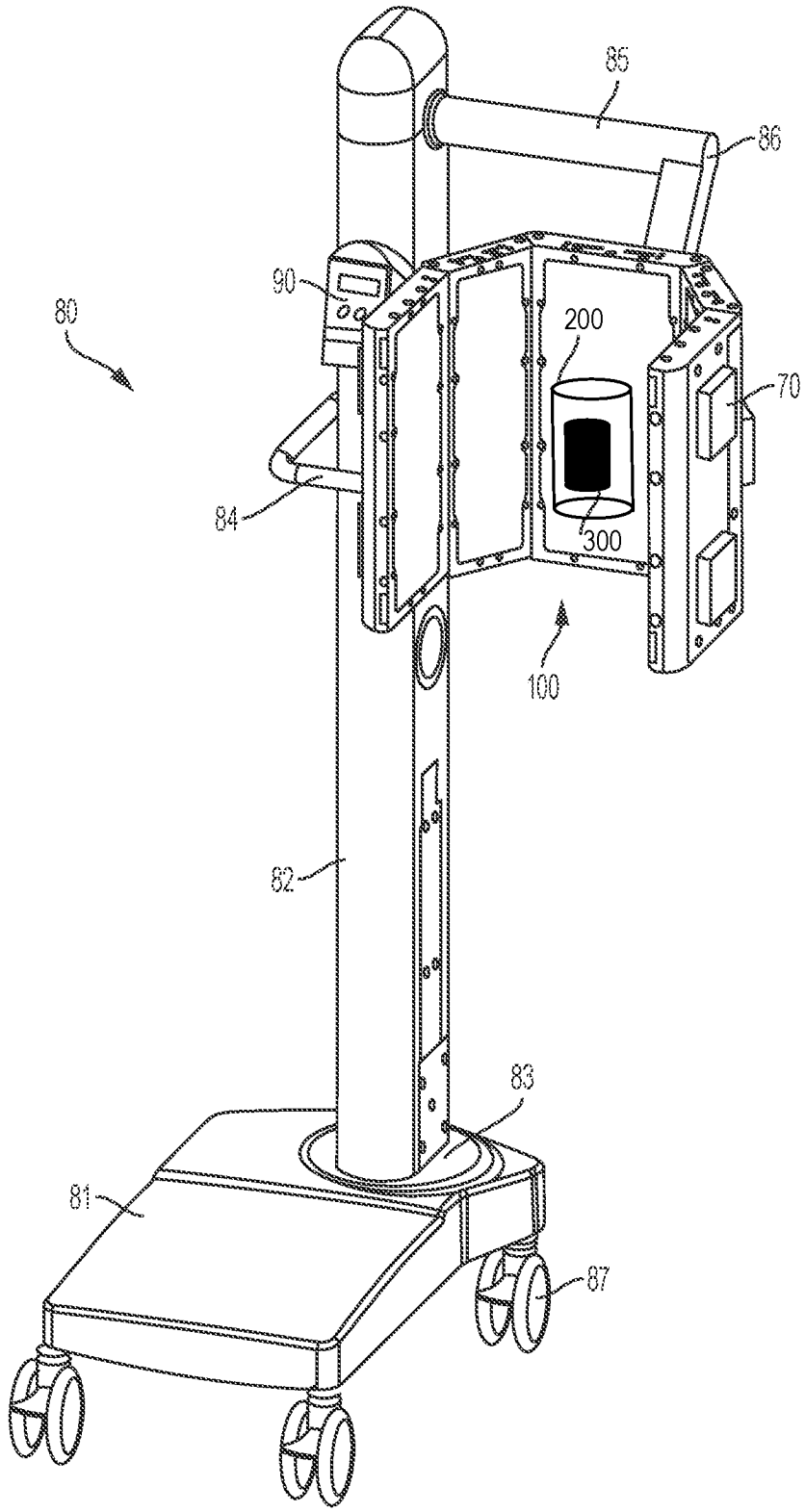


FIG. 3

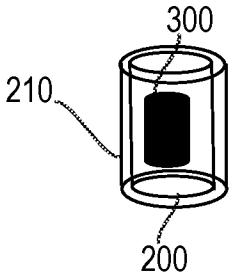

300
210
200

FIG. 4

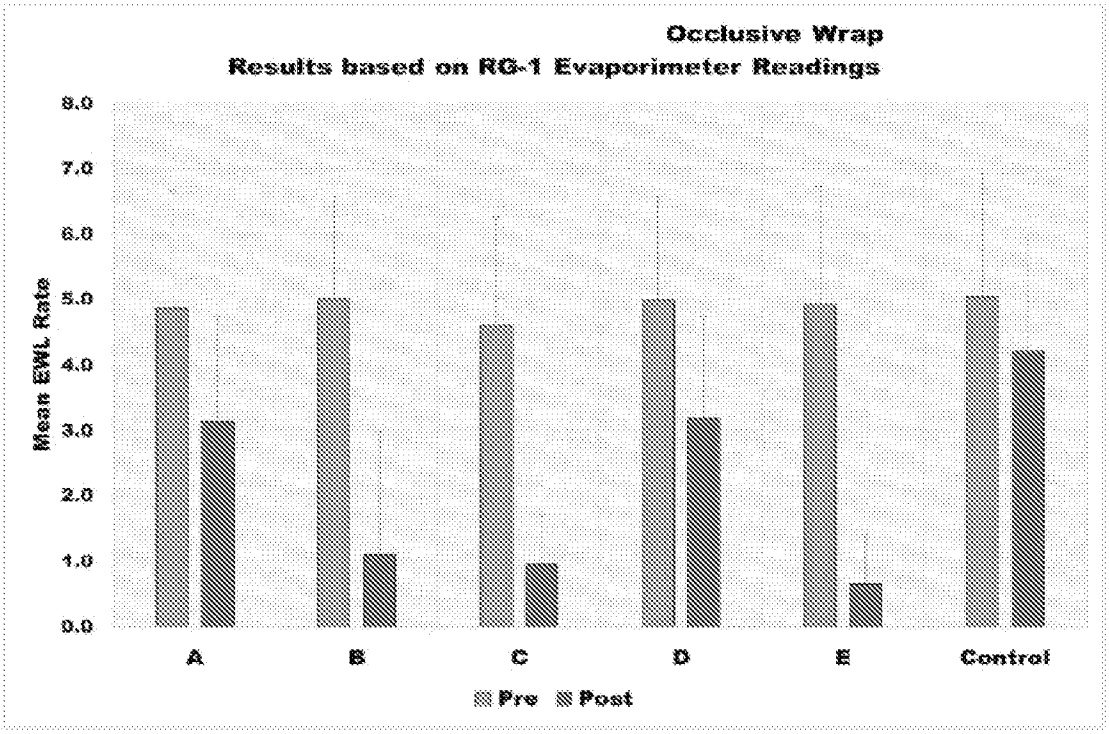

Occlusive Wrap
Results based on RG-1 Evaporimeter Readings
Mean EWL Rate
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
A
B
C
D
E
Control
Pre
Post

FIG. 5

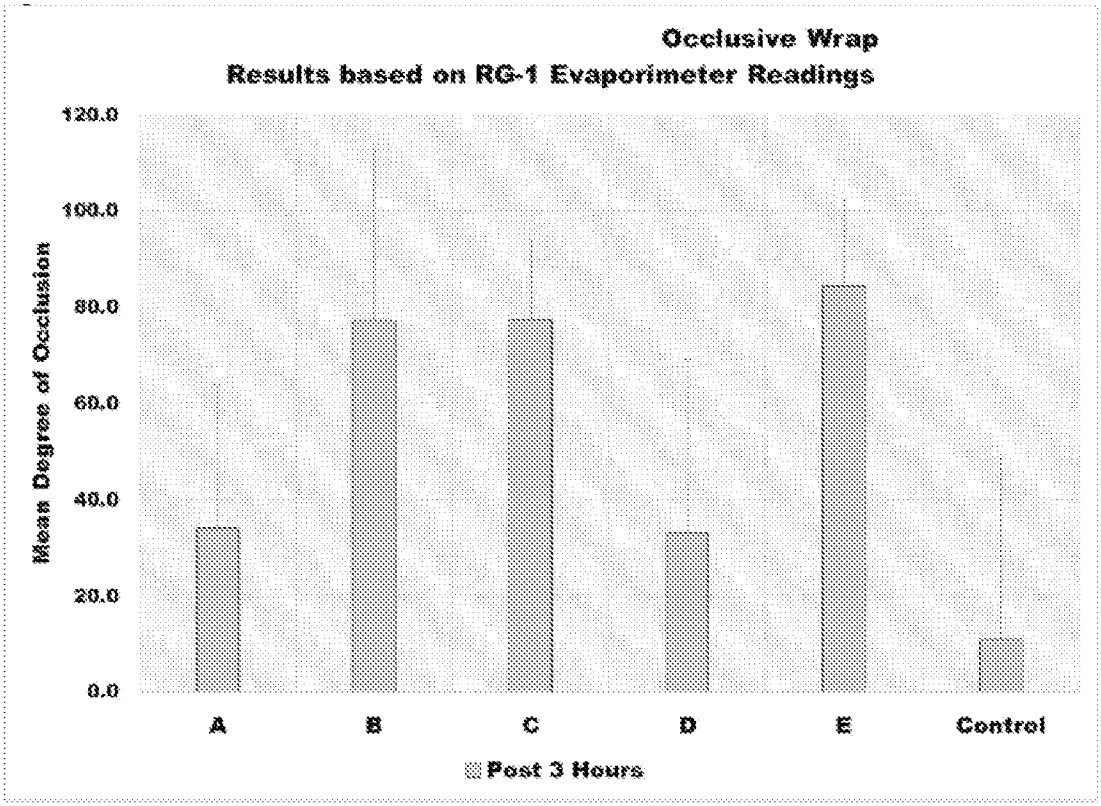

Occlusive Wrap
Results based on RG-1 Evaporimeter Readings
Mean Degree of Occlusion
120.0
100.0
80.0
60.0
40.0
20.0
0.0
A
B
C
D
E
Control
Post 3 Hours

FIG. 6

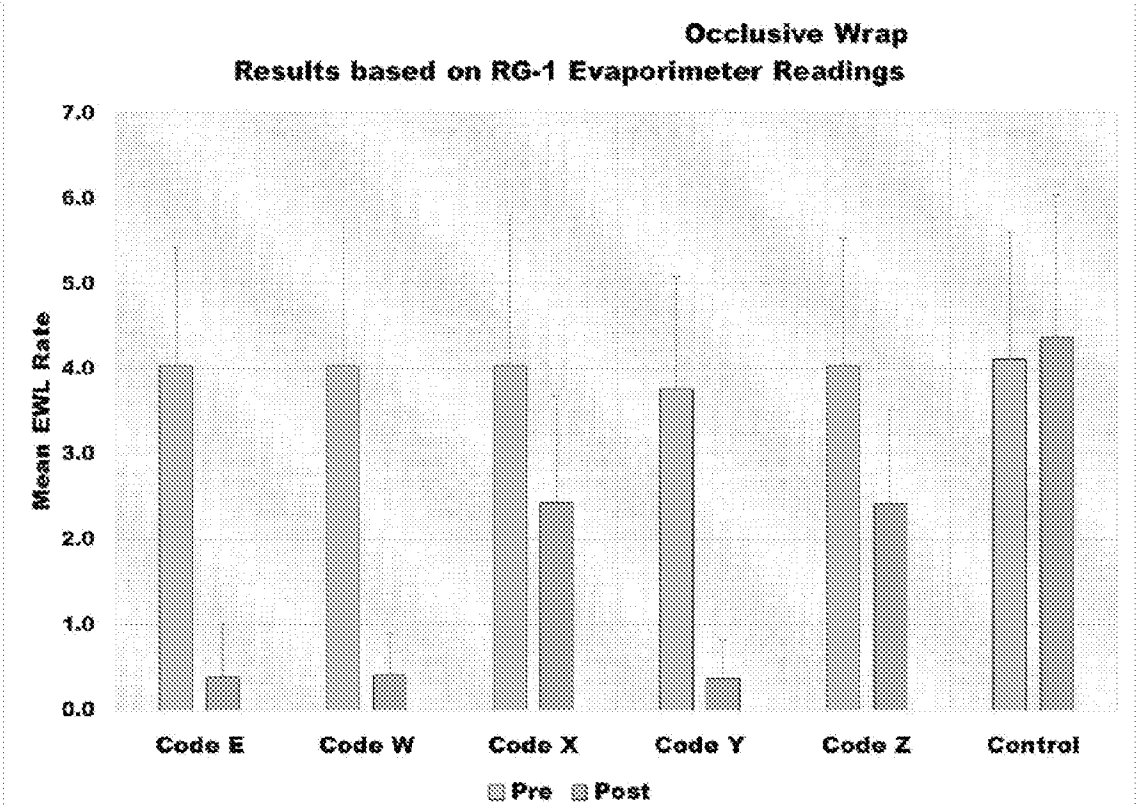

Occlusive Wrap
Results based on RG-1 Evaporimeter Readings
Mean EWL Rate
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Code E
Code W
Code X
Code Y
Code Z
Control
Pre
Post

FIG. 7

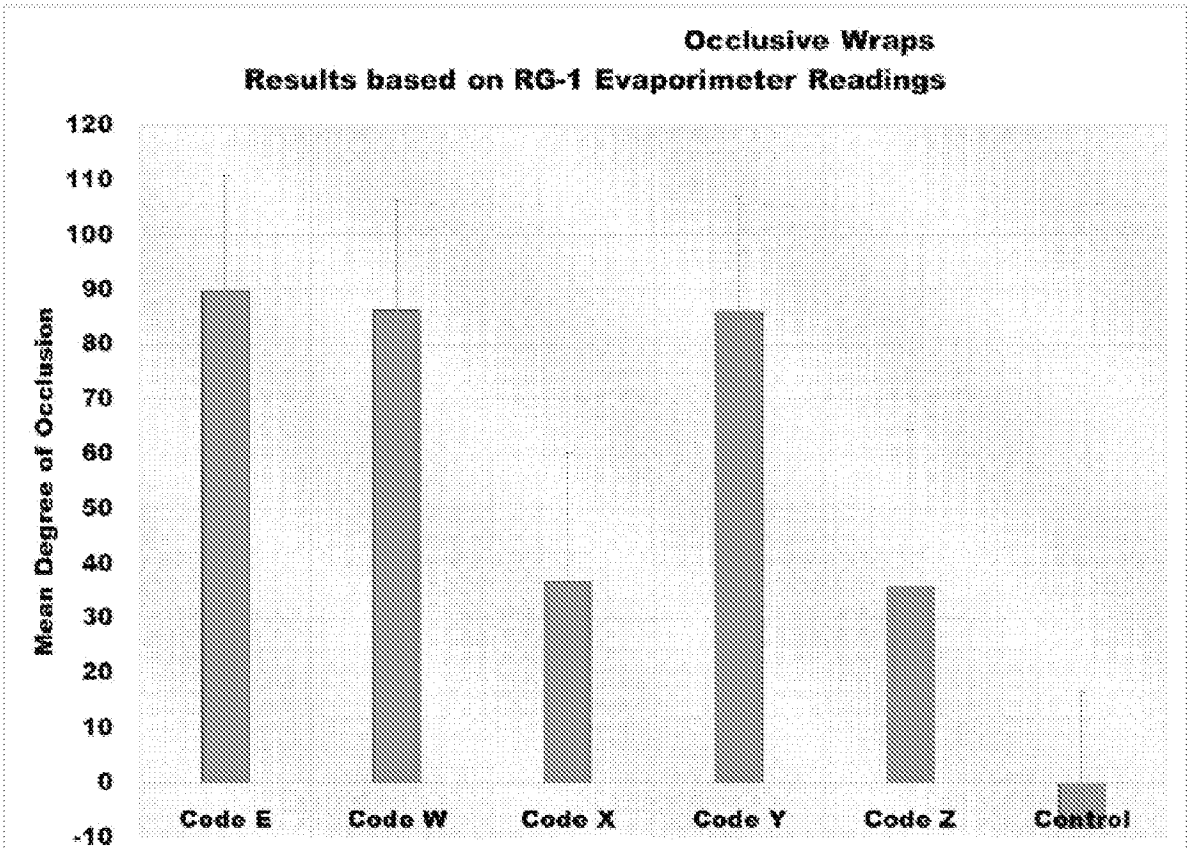

Occlusive Wraps
Results based on RG-1 Evaporimeter Readings
Mean Degree of Occlusion
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Code E
Code W
Code X
Code Y
Code Z
Control

FIG. 8

FIG. 9

Water Loss Baseline

#	SN#	A	B	C	D	E	Control
1	SN004	3.4	3.2	4.0	5.3	4.3	4.5
2	SN002	3.9	5.2	3.4	5.7	3.1	4.5
3	SN001	4.7	3.6	4.1	4.1	3.9	3.1
4	SN006	6.5	6.8	7.2	6.6	5.6	7.3
5	SN010	6.7	6.0	6.2	7.2	6.3	6.3
6	SN012	3.9	3.6	3.9	4.6	4.1	4.3
7	SN020	7.9	8.2	6.8	6.0	9.2	7.9
8	SN025	3.1	3.8	3.3	3.7	4.0	3.4
9	SN013	5.0	3.4	5.2	3.9	5.2	3.8
10	SN003	4.0	3.8	3.1	3.8	3.8	5.1
11	SN026	8.6	6.6	6.4	6.6	8.0	8.2
12	SN015	3.5	3.1	6.3	4.9	3.5	2.9
13	SN011	2.1	3.7	1.3	2.7	2.8	2.3
14	SN014	6.1	5.0	4.0	4.9	4.3	7.3
15	SN007	3.7	4.0	3.3	4.6	3.6	3.4
16	SN009	4.5	4.1	3.1	3.3	3.9	4.7
17	SN031	3.4	4.6	5.0	4.3	2.6	5.5
18	SN008	5.6	4.4	5.9	6.9	5.6	6.3
19	SN017	8.1	6.1	6.0	9.4	6.8	7.5
20	SN035	8.3	7.7	7.9	7.3	9.2	8.4
21	SN018	4.4	4.7	4.7	3.2	4.7	5.4
22	SN024	4.5	6.1	5.6	2.7	4.9	3.6
23	SN029	4.1	4.2	5.9	3.7	5.3	6.0
24	SN019	2.2	5.7	2.4	3.6	4.9	3.3
25	SN021	5.8	6.0	4.1	5.4	6.5	5.8
26	SN027	4.3	6.3	5.6	5.9	5.0	4.3
27	SN028	5.5	3.8	2.9	4.3	4.0	2.4
28	SN033	2.4	3.9	1.2	3.3	1.9	1.7
29	SN030	6.0	4.4	4.9	5.8	4.0	5.2
30	SN023	4.6	8.8	4.3	5.9	7.2	7.1
	Mean	**4.88**	**5.02**	**4.60**	**4.99**	**4.93**	**5.06**
	SD	**1.78**	**1.54**	**1.67**	**1.58**	**1.79**	**1.88**

FIG. 10

Water Loss Post 3 Hours
Wear Time

#	SN#	A	B	C	D	E	Control
1	SN004	2.7	0.4	0.6	2.7	0.5	3.6
2	SN002	3.0	1.2	1.9	1.5	0.5	4.7
3	SN001	2.8	0.1	1.2	2.7	0.3	3.3
4	SN006	2.4	1.5	0.9	4.1	0.4	5.7
5	SN010	5.1	1.8	0.5	3.8	0.2	5.5
6	SN012	2.9	0.8	0.8	2.7	0.2	4.0
7	SN020	4.6	0.3	1.8	4.5	0.7	6.0
8	SN025	0.6	0.8	1.1	2.7	0.4	3.0
9	SN013	7.0	1.8	3.3	7.5	1.2	3.6
10	SN003	1.9	0.6	0.2	1.6	0.9	2.8
11	SN026	6.5	9.1	1.3	4.5	0.2	8.3
12	SN015	0.9	0.6	1.7	1.0	0.5	5.4
13	SN011	1.6	0.6	0.6	1.2	2.5	0.6
14	SN014	3.7	0.1	0.9	2.2	0.6	2.9
15	SN007	3.5	6.0	0.9	3.7	0.0	1.7
16	SN009	2.4	0.2	0.3	4.3	0.5	4.3
17	SN031	1.1	0.4	1.9	4.4	0.5	2.0
18	SN008	3.5	0.6	1.5	1.0	0.5	6.1
19	SN017	4.1	0.3	0.8	6.1	3.8	4.8
20	SN035	1.9	0.1	0.7	5.0	0.1	3.9
21	SN018	3.5	0.6	-0.8	1.8	0.3	5.4
22	SN024	2.6	0.0	1.5	3.7	0.2	2.0
23	SN029	3.3	-0.1	0.3	2.5	1.1	5.2
24	SN019	2.8	0.2	0.1	2.3	1.1	5.6
25	SN021	3.8	1.0	0.9	3.3	0.1	6.2
26	SN027	0.9	0.7	1.0	3.4	0.9	4.0
27	SN028	4.3	0.2	1.3	3.6	0.5	3.2
28	SN033	0.9	1.9	0.4	1.1	0.7	3.1
29	SN030	4.3	0.8	0.8	4.7	0.0	3.1
30	SN023	5.5	0.8	0.3	1.9	0.7	6.8
	Mean	**3.14**	**1.11**	**0.96**	**3.18**	**0.67**	**4.22**
	SD	**1.61**	**1.88**	**0.73**	**1.57**	**0.76**	**1.69**

FIG. 11

Degree of Occlusion at Post 3 Hours Wear Time

#	SN#	A	B	C	D	E	Control
1	SN004	21.4	89.1	84.4	48.3	88.0	21.3
2	SN002	21.7	77.4	43.1	73.9	84.1	-4.9
3	SN001	39.0	97.4	71.1	35.6	93.3	-6.7
4	SN006	63.0	78.1	87.4	37.0	93.0	22.6
5	SN010	24.7	69.6	91.3	46.8	96.8	12.8
6	SN012	24.7	78.5	80.5	40.1	94.4	5.5
7	SN020	41.9	96.9	73.6	24.5	92.7	24.4
8	SN025	79.8	79.7	68.2	27.2	89.5	12.1
9	SN013	-40.4	47.7	37.0	-92.5	76.8	6.1
10	SN003	52.2	84.7	93.6	58.6	77.6	44.7
11	SN026	24.1	-37.8	79.8	32.3	97.9	-0.4
12	SN015	74.0	81.2	72.6	80.2	84.8	-82.6
13	SN011	22.5	85.2	51.5	56.0	12.3	73.5
14	SN014	39.3	98.3	77.8	55.7	85.0	60.0
15	SN007	3.7	-51.5	73.1	20.0	98.8	49.9
16	SN009	46.0	94.5	90.0	-32.0	86.8	8.3
17	SN031	66.8	91.9	62.5	-1.2	80.2	63.8
18	SN008	37.7	85.7	74.0	85.3	91.8	2.9
19	SN017	49.3	94.8	86.1	35.0	45.0	36.1
20	SN035	76.9	98.2	90.6	31.4	98.8	53.6
21	SN018	19.7	88.2	115.9	43.9	93.6	-1.0
22	SN024	42.8	100.2	73.9	-34.4	96.5	44.9
23	SN029	18.7	101.6	94.4	32.6	80.1	13.7
24	SN019	-31.4	96.4	94.3	37.7	77.4	-68.8
25	SN021	34.5	83.2	77.5	39.3	97.9	-7.9
26	SN027	78.8	88.2	82.7	41.7	82.0	7.5
27	SN028	22.4	93.9	57.0	15.7	88.3	-34.6
28	SN033	60.8	52.2	64.4	67.6	61.9	-76.7
29	SN030	29.6	80.7	83.5	18.6	99.3	40.1
30	SN023	-20.9	91.1	92.9	68.3	90.8	5.4
	Mean	**34.10**	**77.18**	**77.50**	**33.11**	**84.51**	**10.85**
	SD	**30.03**	**35.45**	**16.48**	**36.20**	**17.92**	**38.45**

FIG. 12

Water Loss Baseline

#	SN#	Code E	Code W	Code X	Code Y	Code Z	Control
1	SN007	3.6	5.6	6.3	5.8	6.0	5.6
2	SN012	5.0	4.3	3.3	4.0	4.2	3.4
3	SN001	3.5	1.4	2.1	1.3	2.5	1.1
4	SN002	2.0	1.8	2.1	1.3	2.2	4.0
5	SN008	6.1	5.8	4.1	4.4	5.8	6.3
6	SN011	5.8	3.6	3.4	2.6	4.3	3.6
7	SN006	2.5	2.6	2.1	3.2	1.2	2.0
8	SN003	3.1	4.8	2.8	3.8	2.8	2.4
8	SN005	4.7	8.0	5.8	6.2	6.4	6.2
10	SN010	4.1	4.6	4.7	3.8	3.6	4.2
11	SN016	1.8	2.1	1.2	3.4	1.7	3.0
12	SN038	2.6	2.7	2.8	3.4	3.5	3.0
13	SN013	3.5	4.7	6.7	5.1	4.1	4.6
14	SN031	2.3	1.7	1.2	2.4	2.3	2.3
15	SN024	3.5	3.5	3.3	3.8	2.6	4.0
16	SN023	7.5	7.6	8.0	5.8	7.6	7.8
17	SN025	5.3	5.0	5.1	3.8	6.1	6.5
18	SN014	4.0	2.0	2.7	5.4	3.3	3.8
18	SN026	2.4	2.4	2.7	2.3	3.4	3.1
20	SN015	2.1	1.8	2.8	1.7	2.3	2.1
21	SN037	5.3	4.8	4.2	5.8	5.1	5.4
22	SN021	4.2	3.7	4.6	3.1	4.3	4.3
23	SN022	4.0	3.0	5.2	2.3	3.3	4.0
24	SN033	5.8	5.5	4.6	4.0	4.4	5.5
25	SN018	4.1	4.2	4.6	3.6	5.2	4.4
26	SN020	3.8	5.1	4.2	4.0	4.4	3.8
27	SN034	3.3	3.6	4.1	3.6	4.8	4.3
28	SN028	5.1	3.6	6.5	5.3	5.1	4.7
28	SN027	4.7	6.1	5.6	3.3	3.8	3.4
30	SN028	5.3	5.4	3.5	4.1	4.8	4.7
	Mean	**4.04**	**4.04**	**4.04**	**3.76**	**4.04**	**4.11**
	SD	**1.38**	**1.71**	**1.76**	**1.33**	**1.50**	**1.49**

FIG. 13

Water Loss
Post 3 Hours Wear Time

#	SN#	Code E	Code W	Code X	Code Y	Code Z	Control
1	SN007	0.3	0.2	2.6	0.7	2.2	4.4
2	SN012	0.5	-0.1	1.1	0.1	0.7	4.1
3	SN001	-0.2	1.1	2.2	1.2	2.3	1.1
4	SN002	0.3	1.2	1.3	0.8	0.5	4.6
5	SN008	0.7	0.5	1.0	0.1	3.6	5.1
6	SN011	1.1	1.1	1.2	0.7	1.2	4.1
7	SN006	0.6	0.5	1.6	1.2	1.4	2.0
8	SN003	1.1	0.6	1.4	1.0	4.1	3.8
8	SN005	0.4	-0.6	2.0	-0.2	2.3	3.4
10	SN010	0.1	0.4	2.5	0.3	2.8	4.0
11	SN016	-0.2	-0.3	1.0	-0.3	1.1	2.1
12	SN038	2.5	0.5	2.2	-0.1	2.6	4.5
13	SN013	0.2	-0.1	3.7	-0.1	3.1	4.8
14	SN031	0.1	0.2	1.2	0.2	1.8	2.4
15	SN024	-0.6	0.6	2.8	-0.2	2.4	4.0
16	SN023	0.0	-0.2	5.2	0.2	3.8	7.8
17	SN025	-0.4	0.4	5.2	0.1	4.7	8.2
18	SN014	0.4	0.6	1.7	0.2	2.6	4.1
18	SN026	-0.7	0.3	1.4	0.6	2.0	2.5
20	SN015	-0.2	-0.3	1.4	-0.1	1.7	3.1
21	SN037	0.8	-0.4	3.0	0.1	2.6	7.1
22	SN021	0.7	1.0	3.0	0.8	1.8	5.1
23	SN022	0.8	0.8	1.8	0.7	2.5	3.8
24	SN033	0.0	0.8	3.8	0.2	4.3	5.4
25	SN018	1.0	0.8	1.1	0.5	2.8	4.6
26	SN020	1.2	1.2	3.5	0.6	1.2	3.8
27	SN034	0.2	0.4	3.6	-0.1	2.6	4.7
28	SN028	0.0	0.3	3.0	1.1	4.5	5.6
28	SN027	0.4	0.4	4.7	1.0	1.6	4.8
30	SN028	0.3	0.4	2.8	0.1	2.0	4.6
	Mean	**0.39**	**0.41**	**2.43**	**0.37**	**2.42**	**4.36**
	SD	**0.63**	**0.49**	**1.25**	**0.45**	**1.09**	**1.67**

FIG. 14

Degree of Occlusion at Post 3 Hours Wear Time

#	SN#	Code E	Code W	Code X	Code Y	Code Z	Control
1	SN007	81.3	86.2	58.2	88.7	62.5	22.0
2	SN012	80.3	102.7	66.4	87.6	82.7	-21.3
3	SN001	104.5	20.3	-7.5	12.4	8.8	2.8
4	SN002	85.7	35.8	38.8	40.3	78.7	-14.4
5	SN008	88.0	81.3	74.3	87.8	37.3	18.8
6	SN011	81.4	68.1	64.7	73.0	72.6	-13.0
7	SN006	77.8	81.6	23.2	63.3	-18.5	2.2
8	SN003	65.3	87.1	50.8	74.3	-41.4	-63.6
8	SN005	81.5	107.7	64.8	102.8	64.8	45.1
10	SN010	87.7	81.2	46.3	82.6	22.3	4.7
11	SN016	110.8	115.3	22.8	110.0	33.6	31.0
12	SN038	4.8	82.8	22.5	103.8	26.3	-52.8
13	SN013	84.7	101.2	45.0	102.8	24.5	-4.5
14	SN031	84.8	88.8	0.8	82.1	18.4	-3.3
15	SN024	116.7	82.7	13.1	104.1	10.3	-0.6
16	SN023	88.5	103.1	42.2	86.3	48.5	-1.8
17	SN025	106.8	81.8	-3.0	87.1	22.8	-42.4
18	SN014	81.0	71.2	38.0	87.0	20.0	-6.7
18	SN026	128.0	88.4	46.4	72.8	41.2	18.1
20	SN015	107.5	115.3	51.8	106.8	28.4	-50.5
21	SN037	84.3	108.3	28.8	88.0	48.8	-32.8
22	SN021	83.2	73.3	33.8	76.1	55.8	-18.3
23	SN022	77.2	73.1	66.3	67.8	25.5	3.8
24	SN033	88.5	85.5	18.1	84.0	3.0	2.0
25	SN018	75.2	78.7	76.5	86.5	45.3	-3.5
26	SN020	67.6	77.3	17.6	85.5	72.7	-0.3
27	SN034	82.6	87.7	12.3	101.8	46.8	-8.8
28	SN028	88.8	80.5	54.4	78.1	11.5	-18.7
28	SN027	82.3	84.1	15.5	70.8	58.4	-43.8
30	SN028	85.1	83.4	18.7	86.5	58.4	1.2
	Mean	**89.87**	**86.22**	**36.80**	**86.11**	**35.78**	**-8.39**
	SD	**21.07**	**20.06**	**23.45**	**20.97**	**28.59**	**24.95**

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