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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, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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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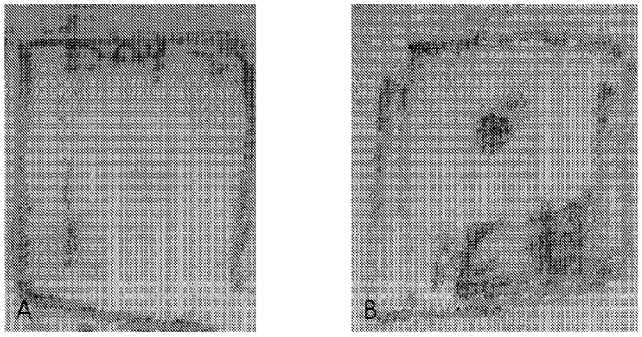
(88) Date of publication of the international search report:
1 May 2014

(54) Title: LASER ASSISTED DELIVERY OF FUNCTIONAL CELLS, PEPTIDES AND NUCLEOTIDES

FIGURE 1



(57) Abstract: Methods, uses, systems and kits for laser-assisted delivery of at least one bioactive agent to a subject. Specifically, laser light is used to create channel (s) in tissue of the subject, and the bioactive agent (s) is applied to the opening of the channel (s). The bioactive agent may be a cell, such as a functional cell, including stem cells, protein, peptide, peptide fragment, nucleic acid, nucleotide fragment, gene, pharmaceutical compound, therapeutic compound, medicament, small molecule, aptamer, or any combination of the above. Delivery may be accomplished locally or systemically, and can be used to treat local or systemic conditions or disorders. Functional reconstitution and gene therapy is also possible with the present invention. Other uses include directing bioactive agent migration, stimulating endogenous stem cell circulation, treating biofilms, and regrowth of hair. Tissue explants are also incorporated in some embodiments.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/43982

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61N 5/067 (2012.01)
USPC - 604/20, 607/89
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(8) - A61N 5/067 (2012.01)
USPC - 604/20, 607/89

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 607/88, 604/19, 22, 17, 48, 500

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, PubMed; light, laser, channel, passageway, aperture, orifice, bore , hole, borehole, perforation, delivery, medication, drug, pharmaceutical, bioactive, therapeutic, treatment, distal, expression, antimicrobial

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 2011/0130748 A1 (KELLOGG et al.) 2 June 2011 (02.06.2011) para [0006], [0018], [0020], [0026]- [0027], [0030]-[0031], [0036], [0038]-[0039], [0045], [0049], [0054], [0055], [0060]-[0117], [0123]-[0124], [0128]-[0129], [0137]-[0138], [0140]-[0141], [0145], [0146], [0152]	1-13, 17-22, 24, 29, 35, 40-44, 48-56, 58-85, 87-93, 96-97, 101-111, 114-116, 118, 120-129, 133-134 ---------- 14-16, 23, 25-28, 30-34, 36-39, 45-47, 57, 86, 98-100, 112-113, 117, 119, 130-132, 137-139, 142, 147-172
X ----- Y	US 6,527,716 B1 (EPPSTEIN) 4 March 2003 (04.03.2003) col 5, ln 15-26; col 18, ln 15-37; col 57, ln 66-67; col 60, ln 31-57; col 66, ln 33-64	94-95 ---------- 14-16, 36-39, 45-47, 86, 130-132
Y	US 2009/0285787 A1 (MINGUELL et al.) 19 November 2009 (19.11.2009) para [0006], [0011]	23, 25-28, 30-34, 57, 98-99, 117, 119
Y	US 2003/0113304 A1 (BURKHOFF) 19 June 2003 (19.06.2003) para [0006], [0008], [0009], [0011], [0012]	100, 112-113

☒ 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
12 November 2012 (12.11.2012)	14 DEC 2012
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) (July 2009)

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	WO 1999/049909 A2 (MANN et al.) 07 October 1999 (07.10.1999) abstract; pg 3, ln 2-10; pg 7, ln 11-24;	135-136, 140-141, 143 ---------- 137-139, 142, 144-146
Y	REDENTI et al. "Engineering retinal progenitor cell and scrollable poly(glycerol-sebacate) composites for expansion and subretinal transplantation" Biomaterials; July 2009, published online 9 April 2009; Vol. 30, No. 20; pp 3405-14; pg 3406, col 1, para 3; pg 3407, col 2, para 2-3; pg 3411, col 2, para 2; pg 3410, Fig 1, Fig 4	145-172
X ----- Y	US 2010/0160838 A1 (KRESPI) 24 June 2010 (24.06.2010) para [0022], [0024], [0052], [0093], [0218], [0237]	173-176, 178 ---------- 144, 177
Y	US 2007/0259087 A1 (SEGURA et al.) 08 November 2007 (08.11.2007) para [0255]	177
A	BACHAVE et al., "Effect of controlled laser microporation on drug transport kinetics into and across the skin" J. Control. Release.; 17 August 2010, published onnline 25 May 2010; Vol. 146, No. 1; pp 31-36; entire document	1-178
A	US 2008/0071258 A1 (LEMBERG et al.) 20 March 2008 (20.03.2008) entire document	1-178
A	US 2011/0077627 A1 (LEMBERG et al.) 31 March 2011 (31.03.2011) entire document	1-178

INTERNATIONAL SEARCH REPORT

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-39, directed to a method of delivering one or more bioactive agents to a subject, comprising:
a) applying laser light to a target site on the subject, wherein the target site is spaced apart from a distal site to be affected by at least one bioactive agent; b) creating at least one channel in the tissue of the target site with the laser light; and c) administering one or more bioactive agent to the target site at said channel for migration into the channel and to the distal site.

- Please see extra sheet for continuation -

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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

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Continuation of Box III: Lack of Unity of Invention

Group II: claims 40-57, directed to a method of delivering one or more bioactive agents to a subject, comprising: i) applying laser light to a target site on the subject, wherein the target site is spaced apart from a distal site to be affected by at least one bioactive agent; ii) creating at least one channel of a predetermined depth in the tissue of the target site and defining an opening of the at least one channel at a surface of the target site tissue; iii) administering one or more bioactive agents at the opening of the at least one channel for migration into the channel and to the distal site; and iv) applying laser light to the distal site, thereby creating at least one channel at the distal site so as to direct the at least one bioactive agent to the distal site.

Group III: claims 58-72, directed to a method of directing at least one bioactive agent to a particular site within a subject, comprising: 1) identifying a particular site within a subject at which to direct at least one bioactive agent present in the subject; 2) applying laser light to the identified particular site; and 3) creating at least one channel with laser light at the identified site.

Group IV: claims 73-86, and 135-146, directed to a laser-assisted method of treating a systemic condition, comprising: a) applying laser light to a target site of a subject, wherein the target site is spaced apart from a site affected by the condition to be treated; b) creating at least one channel of a predetermined depth at the target site using the laser; and c) administering at least one bioactive agent to the target site of the subject at said channel for migration into said channel and systemic delivery to the affected site, or a kit therefor.

Group V: claims 87-93, directed to use of at least one bioactive agent applied to an opening of at least one channel created by laser ablation for treating a systemic condition.

Group VI: claims 94 and 95, directed to use of at least one bioactive agent applied to an opening of at least one channel created by laser ablation for vaccination against a particular and predetermined antigen.

Group VII: claims 96-113, directed to a method of stimulating endogenous stem cell production comprising: i) identifying a target site on a subject; ii) applying laser light to the identified target site; iii) creating at least one channel at the identified target site with the laser light; and iv) administering at least one bioactive agent to the at least one channel, wherein the at least one bioactive agent includes at least one type of functional cell.

Group VIII: claims 114-134, directed to a system for delivery of a bioactive agent, comprising:
1) a laser capable of producing laser light for creating at least one channel of a predetermined depth in a target tissue at a target site, thereby defining an opening at the surface of the target tissue; and 2) at least one bioactive agent disposable at the opening of the at least one channel and capable of migration into and through the at least one channel and systemic delivery to a distal site for beneficial effect at the distal site.

Group IX: claims 147-178, directed to a method of delivering a bioactive agent to a subject, comprising: a) applying laser light to a tissue explant, creating at least one channel of a predetermined depth in the tissue explant with the laser light; b) administering at least one bioactive agent to the tissue explant to obtain a seeded tissue explant; and c) implanting the seeded tissue explant into a subject.

The inventions listed as Groups I - IX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of the claims of Groups I-IX are disclosed in the Group descriptions, above.

The only common technical element shared by the above groups is that they are related to laser light creation of at least one channel in a tissue or site, for delivery of a bioactive agent. Groups I, II IV and VIII share the common technical element wherein the treatment target is not at the site of laser channel formation and administration of the active agent. These common technical elements do not represent an improvement over the prior art of the article entitled "Effect of controlled laser microporation on drug transport kinetics into and across the skin" by Bachhav et al., which teaches a method of delivering one or more bioactive agents to a subject (drug delivery across the skin; abstract), comprising: applying laser light to a target site on the subject (laser microporation technology...pore were typically 150-200 .mu.m in diameter...fluence could be used to effectively control pore depth; abstract), wherein the target site is spaced apart from a distal site to be affected by at least one bioactive agent (transport across...skin; abstract); creating at least one channel in the tissue of the target site with the laser light (laser microporation technology...pores were typically 150-200 .mu.m; abstract); and administering one or more bioactive agent to the target site at said channel for migration into the channel and to the distal site (application of a marketed liodcaine cream...to laser-porated skin; abstract). Groups IV, V, VIII and IX share the common technical element wherein the condition treated is systemic. This common technical element does not represent an improvement over the prior art of US 2011/0130748 A1 to Kellogg et al., which discloses the use of a fractional laser to form a hole in the skin, filling the hole with a drug-containing gel, and crosslinking the gel to provide a stable drug-releasing matrix (para [0012]), further wherein the compositions administered have a systemic effect (para [0123], [0089], [0104]). Although Kellogg does not explicitly recite wherein the compositions having systemic effects may be used to treat a systemic condition, it would have been obvious to a person skilled in the art to use the method of drug delivery, wherein the drugs may have systemic effects, as taught by Kellogg, to treat a systemic condition in order to enhance compound administration.

Therefore, the inventions of Groups I-IX lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.